Chapter 7

MODIFICATION OF POLYESTER FOR MEDICAL USES

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7.1 Introduction/Overview

Polyester has been around for more than half a century, in which time its cost and properties have combined to make it the world's best selling synthetic fiber. As with any other manufactured fiber, it is routinely sold in many variants of diameter, cross-section, and luster. It has a number of limitations, but its ubiquity has lead to many attempts to modify the fiber to overcome them.

Among its many uses are several in the medical field: polyester is a very useful biomaterial. In routine use, however, and similar efforts to modify the fiber have been widely researched.

This chapter reviews the modifications applied to polyester in normal use, the principles by which they have their effects, and the parallel modifications used for medical applications of the fiber.

7.2 Polyester

Poly(ethylene terephthalate), PET, or most simply "polyester" was first discovered in 1941 in the Accrington, UK laboratories of The Calico Printers Association. Whinfield and Dickson demonstrated that a partially aromatic polyester based on terephthalic acid yielded a strong, resistant fiber with a high melting point and good hydrolytic stability [1]. The fiber was commercialized

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through the 1950s as Dacron™ in the United States and as Terylene™ in the United Kingdom. It entered a textile world in which nylon had been around for a decade or more, and nylon had pioneered both the replacement of natural fibers in traditional end uses and the development of novel synthetic fiber uses. The production of PET accelerated in the early 1960s when processes to produce pure terephthalic acid were improved [2]. The 1970s saw a fashion-led "polyester boom" that made consumers aware of both the good and bad properties of polyester: the latter tended to predominate and polyester acquired connotations of cheapness and tastelessness that have only recently been overcome. Meanwhile, with a growing volume of production, the lower cost of polyester allowed it to replace other synthetic fibers, especially nylon and acrylic, in many routine textile applications where these did not have an advantage in properties. Its esthetic qualities have been improved largely by the development of finer fibers, especially the so-called "microfibers", and today polyester is approaching cotton as the world's most widely used fiber: more than 24 million tons of polyester were produced in 2004.

7.2.1 Production and properties

PET is a linear macromolecular homopolymer (i.e., one repeating unit) formed from step reaction polymerization. It is nominally produced by the polymerization of terephthalic acid and ethylene glycol. These monomers are both readily available in few reaction steps from the petroleum-based feedstocks of the refinery: terephthalic acid from the oxidation of *p*-xylene, ethylene glycol from ethylene *via* ethylene oxide, and the low monomer cost contributes to the low cost of the final polymer.

In practice, terephthalic acid is converted first either to dimethyl terephthalate, or *bis*(hydroxyethyl) terephthalate, and the polymerization proceeds with the elimination (condensation) of either methanol or excess ethylene glycol as the ester interchange reaction continues. PET is predominantly produced using antimony III catalysts, about which there are on-going environmental concerns [3]. Titanium IV catalysts have superior activity to antimony III, but for many years the polymers produced using this technology have had a limited attainable molecular weight and also exhibited a yellowish tinge. However, the thrust for research into catalyst development is not founded on environmental concerns alone. The desire to increase plant capacity and improve product quality and economy by reducing the additive levels is an alternate goal. For a new catalyst technology platform to be commercially acceptable, it must possess certain basic qualities. These include, but are not limited to, good solubility in ethylene glycol as well as stability to water, phosphorus stabilizers, and other necessary additives. There are problems associated with titanium catalysts, which have to be solved, for example, the well documented tendency for hydrolysis that destroys the catalyst, causing thermal instability and haze in the resultant

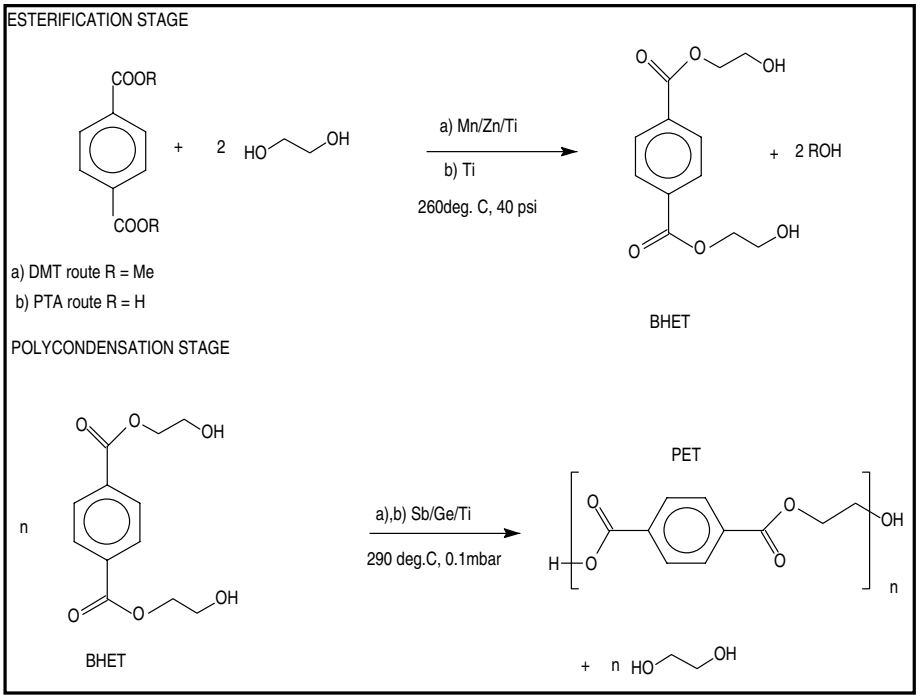

Figure 7.1. Production of polyester

polymer. The polymer should exhibit equivalent color, clarity, and stability to that of standard PET. The basic chemical pathways for PET production are shown in Figure 7.1.

The molecular weight of PET is most often described in the PET industry in terms of intrinsic viscosity (IV) in units of dL/g measured by solution viscosity in a suitable solvent such as *o*-chlorophenol at 25 °C. The range of IVs typically used depends upon the end use of the PET fibers. For example for apparel applications, an IV of 0.63 dL/g is typical but for industrial yarn applications, higher IV polymers are used in order to obtain higher tenacities. Depending upon the industrial end use, the IV range used to make these yarns will fall between 0.80 and 0.92 dL/g.

Fiber is produced by the extrusion of a polymer melt through spinnerets. The absence of solvents in the fiber spinning process is a further contributor to the low cost of the fiber. Polyester can be produced in a wide range of deniers; finer ones (below about 0.5 denier) require modified spinning methods. The fiber cross-section can be modified by changing the shape of the spinneret holes; and while a round section is usual, a myriad of other shapes have been produced, the more common of which would be trilobal or pentalobal. Most fiber is rendered semi-dull or dull by the inclusion of titanium dioxide delustrant. The fiber is solidified by cooling and drawn to encourage polymer chain orientation

and crystallinity. The fiber is produced as continuous filaments that can be texturized, or cut into staple lengths. Filaments may be partially drawn (POY) for later draw texturizing, while FOY is fully drawn at the fiber production stage.

Polyester's general properties are well established [4]. Polyester melts at around 260 °C. Its glass-transition temperature of around 100°C is high compared with other thermoplastic fibers, and this limits the action of many reagents to the fiber surface at temperatures below T_g. This is particularly apparent when the fiber is dyed: the wide use of polyester prompted the development and implementation of dyeing machines capable of dyeing at elevated pressures (and thus temperatures): suitable dyes readily penetrate the fiber at 130°C. Depending on the degree of drawing, polyester has a tenacity of 4–8 g/d and an elongation of 40–20% (higher tenacities are associated with lower elongations). The standard moisture regain is around 0.5%, and the low sorption of moisture means that elongation and tenacity vary little when the fiber is wet or dry. Fabrics of polyester have good abrasion resistance and good recovery and resilience.

Polyester's all-round good properties, and its low cost, have made it ubiquitous. It is used in all fabric styles from sheer georgette to heavy fleece, from stretch knit to canvas. It is used in all types of apparel, in home furnishings, in geotextiles, industrial applications, tire reinforcement, and so on. Somewhat like cotton among the natural fibers, the first choice for a synthetic fiber would probably be polyester, and only if that does not fit the bill would another fiber be considered.

7.3 Medical uses of polyester

The biological response of a wide range of (mostly fibrous) materials was studied in the early 1950s, and polyester's superiority was apparent. Good strength, the lack of a reaction by the body, and the inaccessibility of the fiber interior to potentially degrading materials make polyester a useful and biodurable material. There are over 13 million medical devices implanted annually in the United States, ranging from simple devices such as hernia repair mesh, wound dressings, and catheter cuffs to more complex devices such as the total implantable heart, left ventricular assist devices, and prosthetic arterial grafts [5]. When textile fibers must be left in the body for extended times, polyester is useful. In vascular grafts, polyester has been used in woven, warp, and weft-knitted structures, both smooth and texturized: in all these, the major variation is in fabric, rather than fiber structure. The initial development of vascular grafts, their structure, and performance up to the early 1980s was reviewed [6]. Structurally, little further advance has taken place since then, but the need for improvement has prompted much work on modifying the polyester from which they are constructed, as noted in what follows. An extensive review of arterial grafts, their limitations, and modifications has been published [7].

Prosthetic heart valves require a textile-based cuff that can be used to sew the valve into place. The experience with vascular grafts suggested that polyester would be an appropriate material in this use, and the suggestion has been borne out in practice. Sewing cuffs are typically knitted structures.

A hernia is an abnormal bulging of internal organs, often the intestine, through a muscular wall weakness. This complication, which can present in several areas of the body such as the stomach, groin, or throat, requires that the inner contents of the muscular wall (e.g., organs) be placed back into the cavity and the tissue repaired *via* suturing. Hernia repair mesh can be made of polyester, PTFE, or polypropylene and be designed into various shapes. This is sewn into place over the defect to add strength to the repaired tissue or can serve as a tissue substitute in the event of significant structural loss. These devices, which are not exposed to flowing blood as described for the sewing cuff, are designed to last long-term.

As with non-medical uses, other fibers (silk, nylon) are preferred where stretch/recovery is important, and these are still preferred for sutures where long-term durability is not an issue.

7.4 Limitations of polyester in routine (non-medical) use

Polyester has inherent characteristics that limit its use in some applications. Abrasion resistance, recovery, and resilience are generally better in nylon, and nylon retains its wider use in, for example, carpets, hosiery, and ropes for dynamic applications. Its hydrophobic character limits the comfort of polyester garments in warm weather and the absorption characteristics of hydrophilic fibers such as cotton mean that cotton still dominates the apparel and domestic (sheets/towels) textile market. The hydrophobicity of polyester goes hand in hand with oleophilicity, and when developed into a fabric, polyester textiles dry quickly but tend to retain oily soils once again favoring more hydrophilic materials. Polyester fabrics made from staple fibers can develop surface pills: the strength of the fiber tends to hold such pills on the fabric when a weaker fiber would allow them to break away.

7.5 Modifications of polyester in routine (non-medical) use

In routine use, polyester can be modified for a number of reasons and by several different strategies. The principles involved and the techniques based on those principles have, in many cases, given rise to parallel modifications in the medical uses of polyester. An extensive survey of such modifications is provided: if they have not yet been used to modify medical polyester, they may suggest future opportunities. Progress up to around 1980 in routine use

modifications for repellency, flame retardance, soil release, and static control was covered in an extensive review [8].

Whatever the reasons for modification, the strategies can be grouped under the following headings.

7.5.1 Include co-monomers in the polymerization process

The extent to which this can be accomplished without fundamentally changing the nature of the polymer in its definition or other properties is debatable. Some basic criteria must be met in order for the material to be satisfactory: the co-monomer must be stable during polymerization and extrusion and not lead to a polymer with markedly inferior mechanical properties.

Thus, for example, challenges in dyeing polyester have been answered in part by the development and commercialization of PET that includes a proportion of 5-sulfoisophthalic acid as a co-monomer: the resulting sulfonic acid groups provide "sites" for dyeing with cationic ("basic") dyes [9]. Co-polyesters of PET have been examined for obtaining deep dyeing material [10]. For flame retardance, bromine-containing co-monomers have been developed, such as 2,5 dibromophthalic acid [11]. More recently, phosphorus-based co-monomers have been examined [12].

In general, the use of a co-monomer as opposed to an additive in the melt results in reduced leaching tendency in later use. This may be an advantage or disadvantage. Related to the use of a co-monomer is the inclusion of some agent that affects the DP or linearity of the polymer. Thus, the inclusion of a depolymerization agent in the melt produces a PET with a lower MW (narrower weight distribution) that pills less [13], and the addition of 6–16% (by weight) of polyethylene glycol together with ca. 0.1% pentaerythritol branching agent increases the wetting and wicking behavior of the polyester fiber [14].

7.5.2 Include additives to the polymer melt before extrusion

Additives to the melt become embedded in the fiber structure after extrusion and drawing. The additive must be stable to the temperature of the melt, i.e., up to about 300°C. The additive must be readily miscible with the melt and not significantly change its rheological properties. It must also not degrade the polymer at the high temperatures. The resulting polyester should not have markedly worse physical properties. Subsequent use should also not remove the additive, unless leaching is a required property.

The prime example in this case is the routine inclusion of titanium dioxide as a delustrant. Colorants can be added as the fiber is formed, and around 5% of the total production of polyester is thus produced as "solution dyed" material. Flame retardancy has also been achieved using additives to the melt,

especially bromine [15, 16] and phosphorus compounds [17]. To avoid problems of interaction when antimony compounds are used as adjuncts, blending of melts, skin-core spinning, and microencapsulation of the additive have been suggested [18, 19]. Static may be controlled by incorporating carbon into the fiber matrix [20], and the improved compatibility of polyester with a carbon bicomponent has been described [21]. When a surface effect is required, this method, like co-polymerization, is of limited value, since the bulk nature of the fiber is being altered. It is thus not usually used to affect the hydrophilicity (hence soil release or moisture transport properties) of the fiber.

7.5.3 Topical additive treatments after the fiber is formed

Chemical additives to the solid fiber may be divided into polymeric materials that lie on the surface, and do not penetrate to any significant extent, and smaller moieties that rely on some measure of fibrophilic penetration into the polyester matrix.

7.5.3.1 Surface polymer additives

Polymeric additives that lie on the surface of the polymer may be applied as a melt, solution, or emulsion. The durability is enhanced if the polymer is cross-linked as part of a curing or fixing process. Further, durability enhancement occurs if some bonding takes place between the polymer and the fiber. Given the paucity of functionality on the surface of polyester, this may involve a pre-treatment to create functionality or occur *via* transesterification reactions.

Soil release finishes can be grafted, transesterified, or generated by sorption of surfactants at the surface [22]. Repellency from silicones has been widely studied, and increasing durability is obtained by cross-linking them or by incorporating groups that react with the substrate. They can also be grafted and linked by this reaction [23, 24]. Perfluoroalkyl acrylic polymers are increasingly common [25, 26] and provide both oil and water repellency. So-called "dual acting" fluorochemicals that additionally contain oxyethylene segments can provide both soil release and soil repellency [27]. Soil release can be obtained by the application of vinyl polymers containing acrylic acid [28]: if a cross-linker is included, durability increases [29]. The anionic hydrophilicity may be augmented by non-ionic oxyethylene moieties.

Surface polymer deposits at a PET surface can be generated by "grafting" in which a monomer is applied and polymerization induced by the generation of initiation. Grafting can be performed during the activation process (direct irradiation method) or on a pre-activated surface (post-irradiation method) [30]. UV-induced graft polymerization of water-soluble monomers has been used to

increase the hydrophilicity of PET permanently without changing its bulk properties [31]. The anti-static properties and wicking time were also improved. In a similar study, a thin functional layer was established at a PET surface by cross-linking reactive substances by irradiation with excimer UV-lamps. Dyeability was also improved [32]. Laser treatments are used in grafting: a CO_2 pulsed excimer laser in air formed peroxides that initiated graft co-polymerization of acrylamide on the surface of PET film to improve wettability [33]. Vinyl compounds containing bromine or phosphorus have been grafted onto polyester to provide flame retardance [34]. The grafting can be made deeper by pre-swelling with ethylene dichloride. Repellency requires surface treatment, and in routine use, zirconium and aluminum soaps, combined with wax emulsions, have been used for many years [35]. Durable anti-static finishes based on polyamines modified again with oxyethylene segments have been widely used [36].

7.5.3.2 Fibrophilic, "dyeing" additives

The modifying substance, usually non-polymeric, or at least a low polymer, may be diffused into the polymer matrix. This is akin to dyeing and relies on a measure of substantivity. The dyeing may be achieved by exhaustion from an aqueous bath or by a pad heat ("thermosol") technique. Effects may be confined to the surface by adjustment of the application conditions, especially if the molecular make-up of the diffusing substance has "fibrophilic" and fibrophobic portions: the fibrophilic part sinks into the matrix while the active, non-fibrophilic part remains at the surface. The diffusion into the polymer matrix can also be limited by the time and temperature at which the diffusion takes place.

Thus for flame retardancy, the now discredited "tris" (*tris*-2,3-dibromopropyl phosphate) was exhausted or dyed to give 4% add-ons [37]. Soil repellency is similarly a surface phenomenon and is important in the case of polyester. In an elegant piece of work [38], increasing the temperature of application increased the sorption of the finish to anchor a lipophile and leave a hydrophilic segment protruding from the surface. A polyester emulsion co-polymer with some ethylene, and some oxyethylene segments can be pad heated to provide soil release [39]. Other oxyethylene moieties can be applied together with dyestuffs in an exhaust procedure [40]. Non-ionic surfactants cloud up at high temperature and deposit on the fiber surface, or are absorbed in a dye-like manner.

7.5.4 Physical/non-additive chemical modifications

Several other approaches do not involve the use of finishes *per se*, but instead rely on chemical reactions to modify the polyester itself. The foremost of these, alkaline hydrolysis, has been widely studied. Aminolysis is less widely known. The use of solvents as swelling agents or that other wise promote diffusion into

the fiber has been widely studied for improving the dye uptake of polyester, but other than that has been comparatively little studied. Steam explosion is in its infancy, and laser treatments have been examined in several studies. More esoteric but better established are modifications based on electrons, ions, and other transient reactive species that are present in plasmas, flames, and coronae.

7.5.4.1 Alkaline hydrolysis

Polyester may be made more hydrophilic by alkaline hydrolysis. This has been widely studied and the work extensively reviewed [41–43]. Hydrolysis of PET can occur under acidic conditions or under alkaline conditions. Acid hydrolysis is not a useful or practical process for modification of polyester. Under alkaline conditions, the carbonyl oxygen atom of the ester group is attacked by the hydroxyl anion to produce one hydroxyl and one carboxylate end group (see Figure 7.2). The rate of diffusion of the alkaline reagent determines the rate of hydrolysis. The hydrolysis of polyester groups initially causes (surface) chain shortening, and the generation of hydrophilic/functional carboxylic acid and hydroxy groups. As the chains become shorter, continued reaction will result in the loss of material and a reduction of fiber diameter, but the overall molecular weight remains largely unchanged. This is used commercially as the so-called "denier reduction". If carried out extensively, hydrolysis results in

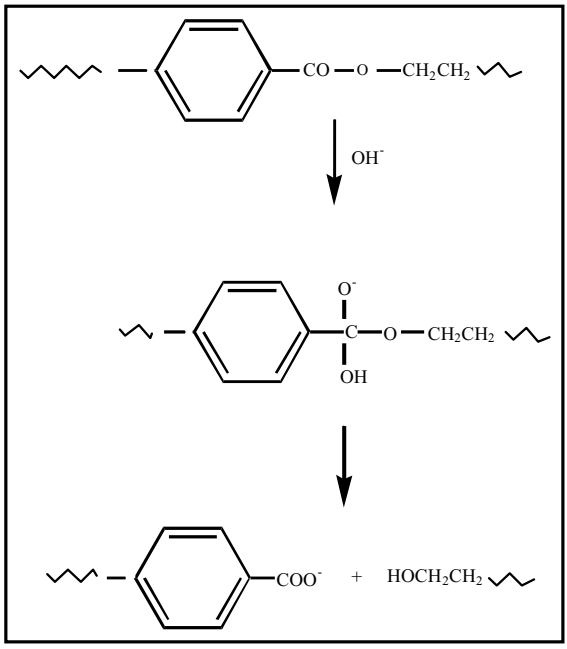

Figure 7.2. Alkaline hydrolysis of PET

loss of strength and weight, and care is needed to make sure that maximum strength is retained. The use of enzymes for this hydrolysis has recently been suggested [44].

The use of a quaternary ammonium salt to augment the alkali has been widely suggested: one recent example has examined its use for modifying the strength of non-woven materials [45].

7.5.4.2 Aminolysis

Several studies have assessed the effects of amine interaction with polyester. Early studies assessed the aminolysis of polyester as a means of examining fiber structure without regard to maintaining the integrity of the polymer [46, 47]. The degradation effects on polyester of a monofunctional amine versus alkaline hydrolysis have been studied [48]. These studies, which again involved high levels of fiber degradation, demonstrated that alkaline hydrolysis has a more substantial effect on fiber weight without extensive strength loss. In contrast, aminolysis had less effect on fiber weight but decreased fiber strength, indicative of a reaction within the polymer structure rather than simply at the surface. It was later demonstrated that bifunctional amine compounds could be reacted with the polymer with minimal loss in strength while generating amine groups at the fiber surface [49]. The early stages of the reaction were largely confined to the fiber surface and the resulting fiber had modified wetting properties and improved adhesion with the matrix when used in composites.

A recent paper by our research group has re-examined the interaction of untreated and alkali hydrolyzed polyester with a range of aliphatic diamines [50]. 1,6-Hexanediamine, 2-methylpentamethylene diamine, 1,2-diaminocyclohexane, tetraethylenepentamine, and ethylene diamine were applied to untreated polyester. Ethylene diamine was also applied from a range of solution concentrations in toluene. The treatment generated amine groups on the fiber surface and was revealed by staining with anionic dyes under conditions in which the amine group was protonated. Unexpectedly, the reaction resulted in the simultaneous formation of carboxylic acid groups in a manner similar to alkaline hydrolysis, revealed by staining with Methylene Blue (Figure 7.3). The reaction thus resulted in a bifunctional polyester surface. The ratio of amine and carboxylic acid groups differed with unhydrolyzed and hydrolyzed starting materials (Figure 7.4). Strength loss was somewhat greater than with alkaline hydrolysis.

7.5.4.3 Solvent swelling

Before the widespread introduction of pressurized dyeing machines, emulsified solvent-type materials were widely examined and the better ones widely used as “carriers” to allow satisfactory polyester dyeing [51]. These materials

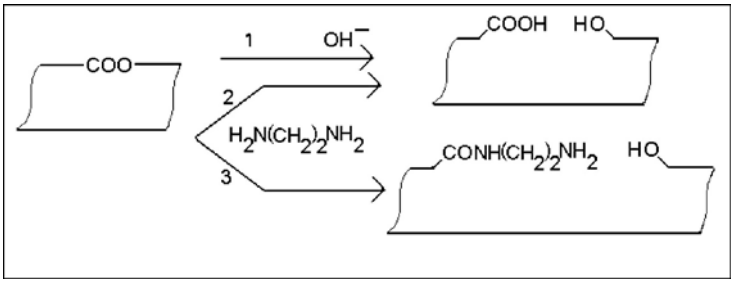

Figure 7.3. Hydrolysis and aminolysis of polyester

effectively lowered the glass transition temperature of the fiber. The range of more general solvent-type pre-treatments that produce improved dyeability has been reviewed, and the effect on a range of fiber properties is included [52].

7.5.4.4 Steam explosion

The process of steam explosion involves exposing a sample to conditions of high pressure and temperature for a certain period or residence time, and then explosively discharging the product to atmospheric pressure [53]. The rapid expansion of any water molecules present in the material occurs over a very short time and hence causes changes at the morphological level only [54]. These two effects increase the specific surface area, accessibility, and hence, the reactivity of the material [55]. The application of steam explosion technology to PET has recently been examined [56]. Steam-exploded PET fabrics were

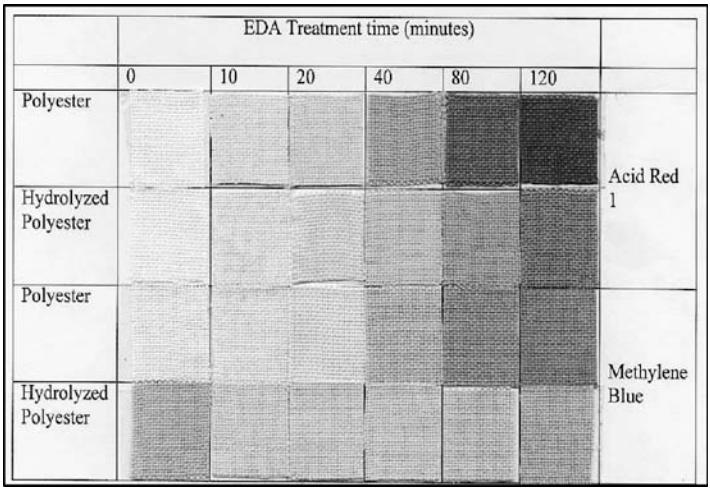

Figure 7.4. Staining of EDA-treated, hydrolyzed, and unhydrolyzed polyester

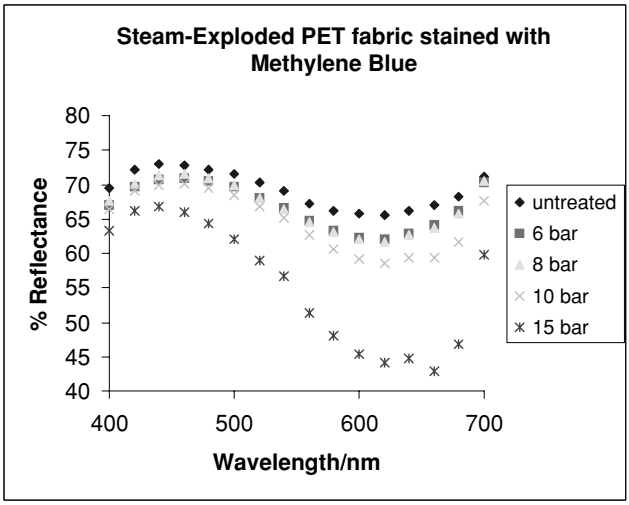

Figure 7.5. Reflectance values of steam exploded PET fabric, stained with methylene blue

stained with Methylene Blue (C.I. Basic Blue 9) dye to determine the presence of acidic functional groups on the surface of the fabric as a result of treatment. The reflectance values of the stained fabrics and of the unstained equivalent are illustrated in Figure 7.5. The decrease in reflectance at ca. 600 nm corresponds to increased staining. There is a gradual increase in the effect of treatment with increasing pressure up to 10 bar: at 15 bar, there is a much larger increase in the effect of treatment.

7.5.4.5 Corona treatments

A corona discharge is generated by applying a high frequency voltage, under atmospheric pressure to electrodes that are separated by a narrow gap. Ozone, radicals, and electrons are formed in the corona discharge [57]. Background radiation generates a small number of electrons that cause the formation of these highly active species [58]. "Corona" is the term given to this mixture of gas molecules, excited molecules, electrons, radicals, and positive ions that are formed between the electrodes, and coronae will modify polymer surfaces passed through the electrode gap. This is a useful technique since it can be operated in air at atmospheric pressure [59]. The changes that occur are both chemical and physical. Polar functional groups are introduced to the surface by oxidation, increasing the wettability of the polymer. Changes in surface morphology of polymeric films, caused by electron bombardment, improve the adhesion properties of certain polymers. Corona treatment has been evaluated for olefin [58] and wool [59], but the method has received little attention for use on PET.

7.5.4.6 Excimer laser treatments

Pulsed excimer lasers first became commercially available in the late 1970s [60]. The name excimer was derived from the term "excited dimer", referring to a group of diatomic molecules that are chemically stable in the excited state rather than the ground state. The surface of synthetic fibers can be modified by irradiation with a pulsed excimer laser. Laser irradiation penetrates only a few micrometers of the surface without interfering with the interior structure. Photodissociation and ablation of the polymer occur as a result of treatment with a UV pulsed excimer laser [61].

Such UV irradiation has been carried out on PET fabric [62]. The UV irradiation penetrated the top layer of the surface only. SEM micrographs showed the rippled structures on the surface of the fabrics due to laser treatments. A decrease in surface oxygen content and the formation of a thin carbonaceous layer on the PET surface increased the contact angle of PET treated with a high-energy dose, i.e., the treated PET was more hydrophobic. Lower energy pulses caused a decrease in contact angle. The effect was stable for at least 1 month.

Compared to these conventional excimer lasers, frequency-doubled copper vapor laser (FDCVL) systems are cheaper and safer for modifying polyester fibers and films. The pulse energies obtained from FDCVLs are less than those obtained from excimer lasers, but repetition frequencies of up to 20 kHz result in higher average power levels and minimal peripheral damage. FDCVLs also possess a relatively high spatial coherence and low divergence. An experiment used an FDCVL to scan a beam across the surface of warp knit PET microfiber fabrics and films repeatedly at different speeds and scan times. Even short exposure times improved the surface functionality of PET fabrics and films [63].

7.5.4.7 Flame treatments

Flame treatments were developed initially in the 1950s to increase the wettability of polyolefin films. More recently, flame treatments have been used in the modification of paperboard and of thicker polyolefin materials, for example, automobile body parts [64]. Corona treatments have generally played the major role in modification of films due to the ease of operation. Flame treatments are currently being revived in the modification of films, as concerns about safety and efficiency of the technique have been improved. Another advantage of flame treatments is that the improved properties of the flame-treated surfaces, such as increased wettability do not wear off over reasonable times, whereas corona-treated surfaces deactivate quite rapidly [65]. As with corona treatments, this technique remains open to exploration on polyester.

7.5.4.8 Plasma treatments

Plasma is a result of ionization, fragmentation, and excitation processes. Electrons colliding with gaseous molecules form excited molecules, ions, and energetic photons [66, 67]. These excited species react further to form charged particles, radicals, and UV photons. This mixture of charged particles is extremely reactive with surfaces that are exposed to the plasma [68]. Ions generated in the plasma are accelerated to energies of 50–1000 eV, causing sputtering or etching of thin films [69]. Given a continuous supply of energy to maintain the plasma state, the highly energetic, active species within the plasma will create new macromolecular surface structures [70]. They do so while having minimal or no effect on the bulk properties [70]. The increase in surface energy brought about by plasma treatments results in an increase in wettability and can improve dyeing, moisture uptake, and fabric handle.

Non-polymerizing plasma, such as oxygen or nitrogen, etches and chemically modifies the surface of the polymer substrate. The extent of the modification depends on the substrate, the type of gas used, the treatment time, gas pressure, and RF power. Fibers or fabrics experience a mass loss due to the etching of the topmost layer of the surface by bond scission, and etching or sputtering [71]. Such etching occurs preferentially in the non-crystalline regions of the polymer surface. An examination of the ultimate dyeability of PET and nylon 66 fibers of varying crystallinity exposed to plasma etching confirmed that the attack was concentrated on the non-crystalline regions [72]. Oxygen plasma can increase the wettability of the fabric by introducing polar functional groups onto the surface. Nitrogen plasmas introduce -NH_2 groups that provide extra dyesites onto the fabric, increasing its dyeability. A hydrogen/nitrogen plasma mixture generates free carbon radicals on the surface that form carbon–carbon cross-links on the surface and reduced dyeability. An inert gas such as argon can cause sputtering on the material being treated. Chemical etching during plasma can occur when using an oxidative gas, such as oxygen [73]. Nitrogen and oxygen plasmas have been shown to provide PET with reduced wetting times and the most durable wettability by the production of fine micropores on the surface, whereas ammonia plasmas did not [74].

The introduction of functional groups onto a plasma-treated surface is known as implantation. Activated gas molecules from the plasma interact with the polymer surface to implant new functional groups at the polymer surface. The type of functional group introduced depends on the type of gas used [71], whereas the number of free radical species generated in the plasma will depend on the substrate. Various low-temperature plasmas, including O_2, N_2, H_2, and Ar, were applied to cotton, linen, PET, nylon, wool, and silk [75]. The free-radical yield was greatest for the cotton fabric, followed by wool, silk, nylon, and PET. More stable free radicals were formed in the natural fibers. Various

studies have been carried out to introduce hydrophilic functional groups onto the surface of PET, *via* plasma irradiation, to improve its wettability and dyeability [76]. RF-plasma-generated sillylium cations can be used to activate inert polymeric surfaces [77, 78]. The $SiCl_3^+$ ions generated in the plasma are readily converted into $Si(OH)_x$ functionalities when in contact with moisture, allowing PET to be dyed with basic dyestuffs.

The immediate effects of plasma treatments wear away over time. The adsorption of contaminants from the atmosphere occurs very rapidly. Surface reorganization occurs slowly over time, and low molecular weight material formed from the plasma treatments can diffuse into the bulk material: as it does so the surface properties of the plasma-treated material will change [79].

Comparison of various gas-phase processes for the surface modification of polymers

Corona, flame, and plasma treatments are all used to generate very fast surface oxidation. UV and ozone treatments oxidize the surface at a much slower pace. The treatments on the surface of PP and PET films have been compared [64].

Corona, plasma, and flame treatments oxidized the polymer surface to the target level in <0.5 s, but much longer times were required to oxidize the polymer surface using UV/ozone treatments. The researchers also discovered that the contact angle measurements for each technique varied suggesting that the surface chemistry derived from each technique is slightly different. Flame-treated samples were the most wettable, as most of the oxidation occurs in the outermost 2–3 nm. FTIR analysis shows that UV/ozone treatments can modify the polymer surface to a greater depth.

Long exposure corona treatments of PE films reduce the peel strength of the film being treated due to an increased formation of low molecular weight oxidized material: this is not the case for plasma treatments [80]. Obviously, long exposure treatments are not an option for flame treatments. Corona treatments have been more widespread in industry than plasma treatments because industrial scale plasma equipment is more expensive and requires a vacuum. However, corona treatments are limited to one-dimensional material, whereas plasma treatments can modify three-dimensional material readily. Flame treatments can also modify three-dimensional materials but are limited to treating materials that cannot be thermally damaged. Plasma, however, is capable of modifying heat-sensitive polymeric materials [64].

Plasma-induced grafting

Grafting was referred to earlier. Plasmas can be used to induce polymerization of monomers at the fiber surface. Monomers can be pre-selected to

produce the desired surface property onto the treated polymer, and the treatment is stable over time. Peroxide-initiated grafting occurs on immersing an oxygen- or air-plasma-treated polymer into a solution of monomer, with a high yield of grafted monomer on the surface [81]. Among the many reports on this technique is included the modification of polyester [82]. Graft fluorination of PET fiber was used to produce oil-resistant and water-repellent materials [83]. The authors found that a hydrophobic surface was reached at a grafting yield of 3.65%. Exposure of a PET film to argon plasma, followed by the introduction of acrylic acid vapor into the plasma chamber, generated a more wettable surface than a liquid-phase grafting [84].

7.6 Limitations of polyester in medical use

Polyester in medical use has undoubtedly improved the quality of life for an aging patient population. However, all implantable devices are prone to three major complications: surface thrombus formation, post-surgical/wound bleeding, and incomplete/non-specific cellular healing.

Surface thrombus formation is the result of the interaction of blood with the relatively thrombogenic biomaterial surface. This problem is evident in medium/small-diameter vascular grafts as well as stents and catheters, which can fail early after implantation due to occlusive thrombus formation within the blood-contacting surface of the device.

A complication of all implantable biomaterials is incompatibility between flowing blood and the biomaterial surface. Thrombin, a pivotal enzyme in the blood coagulation cascade, has been implicated as the primary agent responsible for thrombus formation. The initial interaction of blood and the foreign surface results in a myriad of responses: platelet activation and adhesion [85], activation of the intrinsic pathway of the coagulation cascade resulting in formation of active thrombin [86], leukocyte activation [85], and the release of complement and kallikrein [87]. If unregulated, these responses lead to mural thrombus formation with subsequent occlusive thrombosis and failure of the implanted biomaterial.

Uncontrolled post-surgical/wound bleeding is directly related to the limited interaction of blood with the foreign surface as well as the physical construct (i.e., porosity, weave design) of the material. For hernia repair mesh and wound dressings, the problem arises in that the overall time to create surface thrombus is extensive, thereby delaying hemostasis and compromising the patient.

Lastly, incomplete/non-specific cellular healing affects various medical devices. Since biomaterials are composed of foreign polymeric materials, cellular components normally present within native tissue are not available for the reparative process. These complications are evident in medical devices such as vascular grafts, hernia repair mesh, wound dressings, and catheter cuffs [88–90].

Common to these complications is that currently available biomaterials do not emulate the multitude of dynamic biologic and reparative processes that occur in normal tissue. Thus, development of a novel biomaterial that would emulate some of the normal healing processes of native tissue would improve patient morbidity and mortality upon implantation of various medical devices. Exhaustive studies have been aimed at creating a novel biomaterial surface by either non-specific binding of a biologically active agent, covalent linkage of an agent with a broad spectrum of activity, or altering the biomaterial surface. Thus far, none of these technologies have resulted in a clinically used biomaterial surface.

7.7 Efforts to combat limitations in medical use

A survey of the broad range of attempts to overcome these shortcomings for vascular grafts has been published, and the reader is referred to that publication [91]. What follows extends and complements that work.

Medical limitations have some direct correlations with limitations in normal use. Where a surface interacts with a biological system, many factors relating to the nature of the surface can modify the biological response. In many cases, the interaction is unpredictable, and there is much still to learn about the effect of the physical and chemical nature of the surface on these interactions. The techniques for modification in normal use discussed earlier thus form a rich basis for exploratory work in providing better materials for medical use. More specifically, the modifications that generate surface functional groups allow covalent binding of specific proteins. Where more than one functional group is present, the possibilities exist for the binding of more than one bioactive moiety. Our research group has been much involved in producing a more successful medical polyester material. Using the techniques outlined in section 5.3.2, we have "dyed" polyester with antibiotics [92]. We have also looked to link bioactive proteins to the surface of polyester and have found that carboxylic acid groups generated by alkaline hydrolysis (section 5.4.1) are useful in such covalent linking [93]. We have linked clot-preventing proteins and a growth factor to promote cellular ingrowth and demonstrated that they retain their activity when linked [94, 95].

7.7.1 Combating surface thrombus formation

Many attempts to create a more biocompatible surface have been based on establishing a new biologic lining on the luminal surface that would "passivate" this initial clotting reaction. These have ranged from non-specifically binding albumin to the surface followed by heat denaturation [96] to non-specifically cross-linking albumin [97], gelatin [98], and collagen [99]. Covalent or ionic binding of the anti-coagulant heparin alone [100], in conjunction with other

biologic compounds [101] or with spacer moieties [102], and covalent linkage of thrombomodulin [103] have also been performed. Other studies have focused on modifying the composition of the biomaterial by either increasing hydrophilicity *via* incorporation of polyethylene oxide groups [104] or creating an ionically charged surface [105].

The success of these approaches has been limited: (1) thrombin is not directly inhibited, therefore fibrinogen amounts remain constant on the material surface permitting platelet adhesion; (2) heparin-coated biomaterials may be subject to heparitinases limiting long-term use of these materials; (3) non-specifically bound compounds are stripped from the surface under the shear stresses of blood flow, thereby re-exposing the thrombogenic biomaterial surface; (4) rapid release of non-specifically bound compounds may create an undesired systemic effect; and (5) charge-based polymers may be covered by other blood proteins such that anti-coagulant effects are masked.

7.7.2 Post-surgical/wound bleeding

Incompatibility between blood and the biomaterial surface complicates the use of all implantable biomaterials. The initial interaction of blood and surface results in a myriad of responses: platelet activation and adhesion [106], activation of the intrinsic pathway of the coagulation cascade resulting in formation of active thrombin [107], leukocyte activation, and the release of complement and kallikrein [108]. While this response is desirable for hernia repair mesh, wound dressings, and catheter cuffs, the intensity and overall rate at which this occurs are limited. Additionally, the physical construct (i.e., porosity, weave design) of the material affects the rate and the extent at which thrombus formation occurs. For hernia repair mesh and wound dressings, if the overall time to create surface thrombus is extensive, hemostasis is delayed and the patient may be compromised.

7.7.3 Promotion of cellular adhesion/growth

The development of a uniform cellular layer on the implanted biomaterial has been proposed to enhance biocompatibility. These cells, while providing structural stability *via* material incorporation into the surrounding tissue, maintain hemostasis, prevent infection, and synthesize bioactive mediators. This type of cellular incorporation does not occur in actuality, thereby predisposing these biomaterials to infection [109, 110] and thrombosis [111, 112]. Thus, failure of appropriate cell-type growth and development to these biomaterials significantly limits their expanded use.

Cellular adhesion to biomaterials using cell-seeding techniques has been extensively employed [113, 114]. Adhesive proteins such as fibronectin,

fibrinogen, vitronectin, and collagen have served well in graft-seeding protocols [115]. The cell-attachment properties of these matrices can also be duplicated by short peptide sequences such as RGD (Arg-Gly-Asp) [116]. These adhesive proteins, however, have several drawbacks: (1) bacterial pathogens recognize and bind to these sequences [117]; (2) non-endothelial cell lines also bind to these sequences [118]; (3) patients requiring a seeded material such as a vascular graft have few donor endothelial cells, therefore cells must be grown in culture [119]; and (4) endothelial cell loss to shear forces from flowing blood remains a significant obstacle [120].

Modification of the surface has also been employed to modify host response to the foreign body, serving as an approach for improving cellular adherence. Cells that have been seeded have been shown to attach and grow better on a variety of protein substrates coated onto the biomaterial [121]. Bioactive oligopeptides [122] and cell-growth factors [123] have been immobilized onto various polymers and shown to effect cell adherence and growth. Additional studies have described the incorporation of growth factors into a degradable protein mesh, resulting in the formation of capillaries into the material [124]. Utilizing these techniques to incorporate growth factors, however, does have limitations: (1) growth factor is rapidly released from the matrix; (2) matrix degradation re-exposes the thrombogenic surface, thus endothelialization is not uniform; and (3) release of non-endothelial specific growth factor is not confined to the biomaterial matrix, thereby exposing the "normal" distal artery to the growth factor.

7.7.4 Use of functional groups for protein attachment

Many of the modification methods discussed (hydrolysis, aminolysis, plasma, laser, etc.) generate surface functional groups in much larger amounts than are present on original polyester. These functional groups can be the basis for covalent attachment of a variety of bioactive agents. Earlier work to bind proteins to the functional groups created by alkaline hydrolysis has been referred to earlier. This work demonstrated that bound bioactive proteins maintain their activity once bound. More recent work has examined the use of functional groups derived from those other modification techniques and also has begun work to generate a multifunctional surface *via* the binding of different proteins or a combination of protein binding with infection resistance derived from the "dyeing" of antibiotics.

Covalent linkage of a protein to a biomaterial surface in order to create a "basecoat" layer has numerous advantages. Such a layer has been shown to "passivate" a surface that is relatively thrombogenic, thereby decreasing adhesion of blood products such as platelets, red blood cells, and fibrinogen [96]. Proteins incorporated as a basecoat layer have been used as "scaffolding"

in order to promote a specific response such as linkage of RGD peptides to promote cell adhesion [125]. Additionally, Park et al. [126] demonstrated that increasing the angstrom distance between a biologically active molecule and the surface *via* polyethylene oxide groups reduced steric hindrance on the target molecule, thereby maintaining activity. Covalent linkage of a protein "basecoat" layer would serve as the spacer between the biologically active moiety and the surface. Albumin, which is in natural abundance in circulating blood, has shown numerous beneficial results *in vitro* and *in vivo* in earlier studies [127, 132] and was used in this study. Utilization of a basecoat layer could also permit significant amplification of potential binding sites for secondary protein attachment *via* heterobifunctional cross-linkers, creating a biomaterial surface with distinct properties for a specific application. This BSA surface has been shown to possess numerous binding sites for other biologically active proteins such as recombinant hirudin (rHir) [128].

7.7.4.1 Protein binding to hydrolyzed polyester

In work in our laboratories, BSA was radiolabeled using ^{125}I. Following iodination, bound ^{125}I was determined. These values were then utilized to derive a specific activity that was used to determine protein bound to the material surface. Samples of polyester were scoured with and without hydrolysis. BSA was then bound to the hydrolyzed polyester surface using heterobifunctional carbodiimide cross-linker EDC. Control and another set of hydrolyzed segments were reacted under the same parameters without EDC cross-linker. Control and test segments were then reacted with the ^{125}I-BSA solution for 2 h at room temperature. The specimens were sonicated three times in detergent solution to remove any weakly adherent ^{125}I-BSA, then gamma counted to determine the amount of ^{125}I-BSA covalently bound. The amount of ^{125}I-BSA covalently bound to the hydrolyzed segments *via* EDC was significantly greater than both control and hydrolyzed controls at all solvent concentrations evaluated (Figure 7.6).

7.7.4.2 Protein binding to a bifunctional polyester surface

A similar technique was used to immobilize protein to a bifunctionalized polyester surface. Scoured control and hydrolyzed segments were reacted with ethylenediamine. The EDA-exposed segments were then removed and placed into distilled water overnight at room temperature (C-EDA or Hyd-EDA) [134]. Staining with Methylene Blue and with C.I. Acid Red 1 was used to quantify the two functional groups present. The C-EDA segments were then assessed for ^{125}I-BSA binding *via* a range of commercially available heterobifunctional cross-linkers (Traut's reagent, sulfo-SMCC, and sulfo-SPDP). These

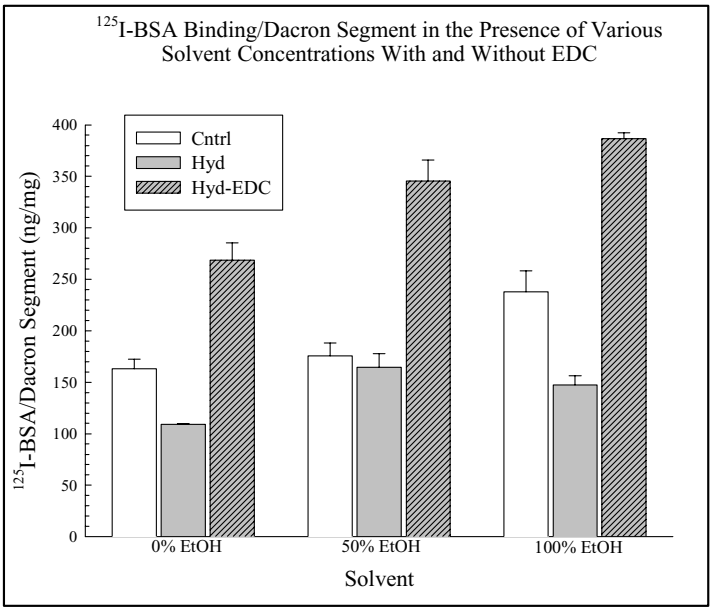

Figure 7.6. Protein binding to hydrolyzed polyester

cross-linkers react specifically with primary amine groups, but vary in solubility and chain length. EDA-treated PET was reacted with the various cross-linkers and washed. Sulfo-SMCC was added to ^{125}I-BSA solution and reacted for 20 min at 37°C in a water bath. The ^{125}I-BSA–SMCC intermediate was then purified *via* gel filtration. The ^{125}I-BSA–SMCC solution was then added and reacted for either 3 or 20 h at room temperature on an orbital shaker (150 r.p.m.). After incubation, control and test segments were removed and washed four times in PBS with Tween 20. Segments were then gamma counted. Using protein concentration determined *via* Lowry assay and gamma counts of a set ^{125}I-BSA volume (i.e., specific activity), the amount of ^{125}I-BSA/Polyester segments was determined. C-EDA segments incubated with the various cross-linkers had significantly greater ^{125}I-BSA binding when compared with C-EDA exposed to protein only (non-specifically bound segments) materials (Figure 7.7). The linking combination of Traut's reagent with sulfo-SMCC resulted in the binding of 604 ng ^{125}I-BSA per 1 mg polyester, regardless of the cross-linker reaction (surface reaction versus protein reaction). Reaction of SPDP (surface) with sulfo-SMCC (protein) resulted in lower protein binding than the Traut's–sulfo-SMCC reaction. Increasing the reaction time from 3 to 20 h not only increased total protein binding, but also significantly increased non-specific binding. Reaction of the surface with sulfo-SPDP (surface) with Traut's (protein) for 20 h had the greatest ^{125}I-BSA binding. Non-specific binding also increased.

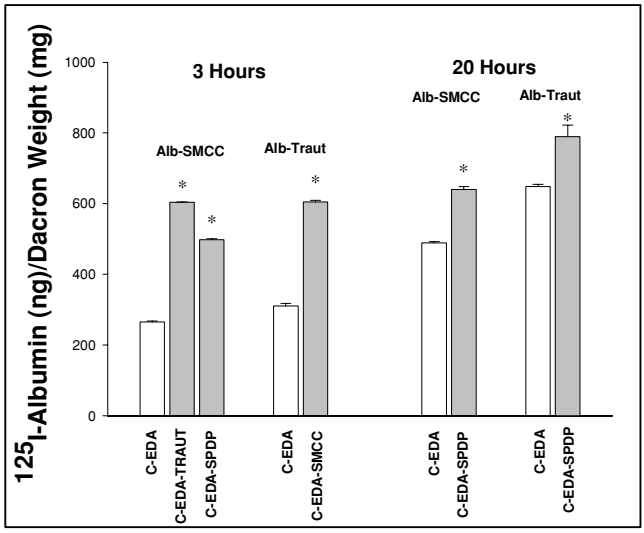

Figure 7.7. Protein binding to a bifunctional polyester surface

7.7.4.3 Protein binding to laser-treated polyester

The linking of protein to carboxylic acid groups created *via* laser exposure was assessed. Laser hydrolysis permits localized formation of carboxylic acid groups, whereas sodium hydroxide hydrolysis forms carboxylic acid groups through the entire material. The laser treatment was varied: the control software was set up to scan knitted polyester segments (30 mm × 30 mm) at a scanning speeds of x (mm/s) for a total scan cycle time of y (s). After scanning, the samples were washed in a mild detergent solution, rinsed, and air-dried. As before, methylene blue staining was used to quantify carboxylic acid group formation. Knitted and woven polyesters, scoured or scoured and sodium hydroxide-hydrolyzed, were used as controls. Polyester specimens were immersed into EDC solution in 100% ethanol for 30 min at room temperature, then removed, shaken, and placed into a ^{125}I-BSA solution for 2 h at room temperature. The segments were removed then sonicated in PBS containing Tween 20 for 5 min. The amount of ^{125}I-BSA bound (ng) per 1 mg polyester was calculated for each segment.

Carboxylic acid formation was evident from the uptake of Methylene Blue, with formation increasing with increasing laser exposure time. Modification was limited to the specific area exposed to the laser. EDC reaction with all materials containing carboxylic acid groups resulted in significantly greater ^{125}I-BSA binding (Figure 7.8). For the laser-treated knitted polyester, ^{125}I-BSA binding was slightly less than the knitted hydrolyzed polyester (740 ng ^{125}I-BSA per 1 mg polyester) but is significant given the limited area of the material modified. Non-specific ^{125}I-BSA binding to the laser-treated and hydrolyzed

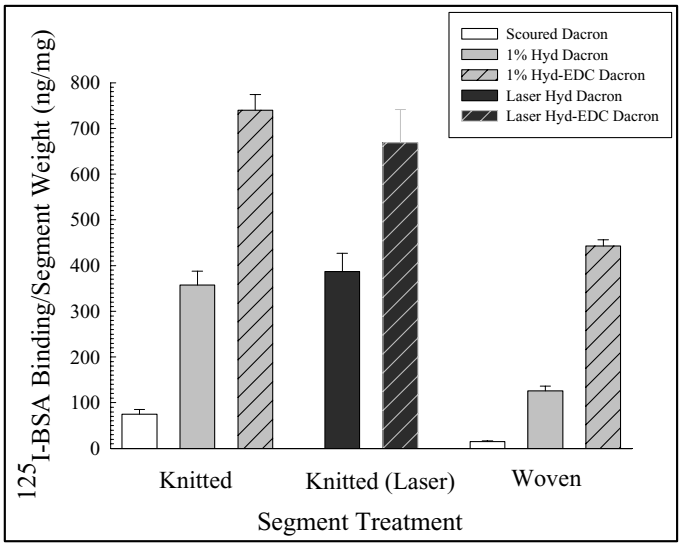

Figure 7.8. Protein binding to a laser-treated polyester surface

polyester surfaces was similar. ^{125}I-BSA binding to the woven segments was comparable to that observed in the earlier studies.

7.7.4.4 Development of an anti-microbial bioactive polyester surface

The earlier-mentioned studies evaluating protein immobilization to the various functional groups served as the foundation for creating a multifunctional surface. In our previous studies using unmodified polyester, broad-spectrum fluoroquinolone antibiotic Ciprofloxacin (Cipro) uptake into the fibers was unsuccessful using exhaust dyeing, with anti-microbial activity lasting <4 h after extensive washing [129–131]. Pad heating, a high temperature technique that opens the fiber structure, was used, and treated polyester demonstrated anti-microbial activity for >50 days. While this technique was successful for incorporating Cipro, the elevated temperatures are not conducive to maintaining the bifunctional groups created on the material surface (data not shown). In order to develop infection resistance within a modified polyester material, exhaust dyeing of the Cipro onto this more hydrophilic surface was re-examined. EDA-treated polyester segments were placed into a Cipro "dyebath" of liquor ratio 20:1, 5% owf Cipro pH $= 8.0$, dyeing for 2 h at 70°C. After air-drying overnight, Cipro-dyed segments were autoclaved for 15 min (10 min dry). Control segments were treated in a similar fashion; however, no heating or autoclaving was performed. Segments were also stained to determine the presence of the functional groups post-dyeing. Macroscopically, a yellowish hue was evident after Cipro-dyeing into the C-EDA segments. C-EDA segments dipped into

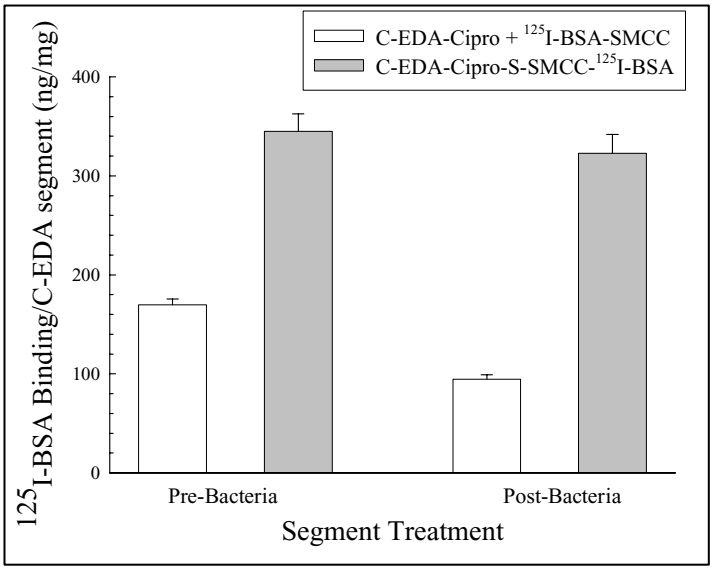

Figure 7.9. Protein binding to an antibiotic-modified polyester pre- and post-exposure to bacteria

Cipro but not heated had no gross color change. Exposure of pre- and post-dyed C-EDA segments to staining had no visible difference in dye uptake demonstrating that the functional groups were not affected by the low-temperature dyeing.

Cipro-dyed C-EDA and control segments were treated with Traut's reagent for 1 h and then washed twice with bicarbonate buffer. Sulfo-SMCC was added to a ^{125}I-BSA solution and reacted for 20 min at 37°C. The ^{125}I-BSA–SMCC intermediate was purified *via* gel filtration then added reacted for 3 h at room temperature with the C-ED-Traut's segments. Segments were removed and washed in PBS with Tween 20 for 5 min. Using protein concentration determined *via* Lowry assay and gamma counts of a set ^{125}I-BSA volume (i.e., specific activity), the amount of ^{125}I-BSA (ng)/bD-PU-AB segment (mg) was determined.

Incubation of the Cipro-dyed C-EDA segments with Traut's reagent resulted in two-fold greater ^{125}I-BSA binding compared with controls without Traut's (Figure 7.9). Even after exposure to bacteria, ^{125}I-BSA remained bound to the C-EDA surface. Sonication is typically used to remove non-specific protein binding. However, a combination of the wash buffer and sonication was shown to remove Cipro from the material (data not shown). Therefore, only detergent washing was employed, which may have resulted in higher non-specific binding to the controls.

Cipro-dyed C-EDA segments with covalently immobilized ^{125}I-BSA had comparable anti-microbial activity to Cipro-dyed C-EDA segments that were not exposed to protein and Cipro-dyed C-EDA segments that had

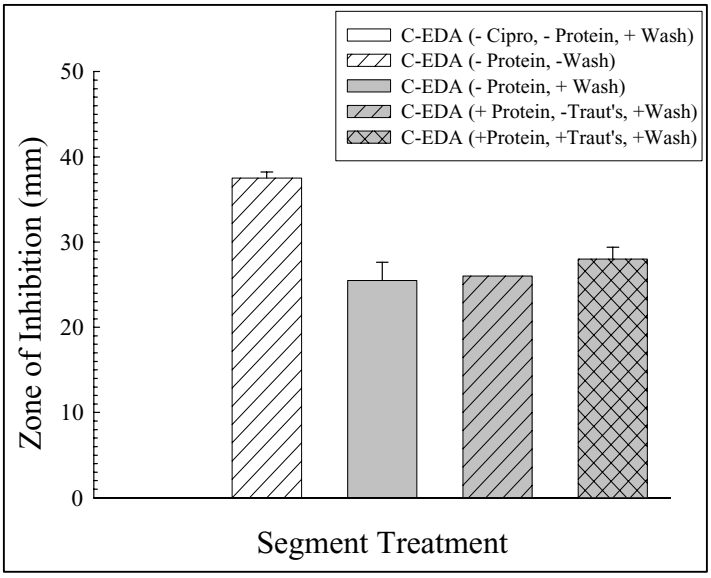

Figure 7.10. Anti-microbial activity of polyester with bound protein

non-specifically bound ^{125}I-BSA (Figure 7.10). Untreated C-EDA segments had no anti-microbial activity. Anti-microbial activity from the unwashed Cipro-dyed C-EDA was greater than these three Cipro-dyed C-EDA segment treatments, which were exposed to various solutions throughout the experimental procedure. Thus, although Cipro concentration is decreased with the various solution incubations, protein attachment does not further decrease anti-microbial activity. The anti-microbial activity of the Cipro-dyed C-EDA segments with covalently bound ^{125}I-BSA is still significant.

Untreated C-EDA, unwashed Cipro-dyed C-EDA, Cipro-dyed C-EDA segments that underwent all solution processes without protein exposure, Cipro-dyed C-EDA segments with non-specifically bound ^{125}I-BSA, and Cipro-dyed C-EDA segments with covalently bound ^{125}I-BSA were evaluated for anti-microbial activity against *Staphylococcus epidermidis* and were thawed at 37°C for 1 h. Control and test segments were embedded into streaked Trypticase Soy Agar (TSA) plates and incubated overnight. Standard 5 μg Cipro Sensi-Discs were used as a positive control. The zone of inhibition each piece was determined, taking the average of three individual diameter measurements.

7.7.5 Potential uses for various modified polyester materials

A majority of the previous and current biomaterial modifications continue to focus on a "magic bullet" approach for biomaterial healing. This unidirectional approach has yet to produce a clinically acceptable bioactive material,

potentially due to the simplistic approach taken for such a complex phenomenon. The native tissue that these materials are implanted into possesses a multitude of functions that undergo various responses upon injury such as controlling thrombus formation and orchestrating controlled cellular regrowth. Therefore, the next generation of biomaterials must also possess several characteristics in order to better mimic some of the key functions inherent to native tissue. These individual functions, when incorporated into a single biomaterial surface, will act synergistically, resulting in a novel biomaterial with localized biologic activity to stimulate complete healing of the biomaterial.

Two essential areas will need to be addressed when designing a novel biomaterial: material design and surface biologic characteristics. Material design will permit simulation of the physical characteristics of the native tissue such as compliance and durability. The material must also be easy to handle, as well as to implant (suturability). For the base material, polyester could still be utilized due to the biodurability of the fiber and the potential for creating numerous variations in the material design (i.e., knitting, weaving). Additionally, polyester can be chemically modified, creating functional groups within the polymer structure [132–134]. For these reasons, polyester would be the ideal candidate for the base material due to its proven clinical history as well as the various knitting procedures that are available.

Creation of a polyester material that possesses specific biological properties directly at the material surface can be created *via* immobilization of various proteins. For example, prevention of surface thrombus formation could involve covalent linkage of the potent anti-thrombin agent rHir. Thrombin is a pivotal enzyme in the blood coagulation cascade that is primarily responsible for cleavage of fibrinogen to fibrin [135]. During clot lysis, enzymatically active thrombin is released rendering the vessel susceptible to prompt rethrombosis [136, 137]. Even within a clot, thrombin functions as a smooth muscle cell mitogen [138] are chemotactic for monocytes and neutrophils [139, 140] and an aggregator of lymphocytes. Thus, thrombin that goes unregulated within a clot or pseudointima may lead to cellular infiltration and uncontrolled smooth muscle cell proliferation. rHir is the most potent direct inhibitor of thrombin [141], inhibiting the enzymatic, chemotactic, and mitogenic properties of thrombin [142, 143]. Additionally, rHir has also been shown to inhibit clot-bound thrombin [144]. Thus, immobilization of rHir provides an attractive strategy to controlling surface thrombus formation prior to cellular healing.

Another example is a surface that propagates hemostasis and stimulates wound healing is a desired property for hernia repair mesh as well as wound-dressing materials. Activation of the coagulation cascade in order to promote thrombus formation in an effort to control excess bleeding at the injury site is the first step. Thrombin is a pivotal enzyme in the blood coagulation cascade that is primarily responsible for cleavage of fibrinogen to fibrin [145]. During clot

lysis, enzymatically active thrombin is released rendering the vessel susceptible to prompt rethrombosis [146, 147]. Even within a clot, thrombin functions as a smooth muscle cell mitogen [138] are chemotactic for monocytes and neutrophil [139, 140] and an aggregator of lymphocytes. Thus, immobilization of thrombin to hernia repair mesh or a wound dressing could expedite hemostasis by directing enzymatic fibrinogen cleavage at the biomaterial surface/injury interface as well as by activating additional clotting factors within the wound (e.g., platelets).

For cellular attachment and proliferation, VEGF, a 42 kDa homodimeric glycoprotein, has been shown to be a potent endothelial cell mitogen and vasopermeability factor [148]. VEGF, which is produced by many different cell types both in tissue culture and *in vivo*, binds to plasma membrane receptors on endothelial cells only with an extracellular transmembrane glycoprotein linked to an intracellular tyrosine kinase domain [149]. This mitogen has also been implicated as a necessary component of wound healing [150, 151]. VEGF in these studies was being released from either a protein scaffold or a viral vector. Thus, covalent linkage of VEGF or another growth factor such as basic fibroblast growth factor to a vascular graft, hernia repair mesh, or a wound dressing would promote initial cellular growth followed by complete healing at the site of injury.

7.8 Conclusion

Polyester is a widely used and useful material. Its usefulness extends into the medical field, where its strength is maintained in implanted devices and materials: it is biodurable. In both medical and non-medical use, it has properties that are less than desirable. A large volume of research has been aimed at modifying the fiber, to make it more dyeable, less soil-retentive, more comfortable, less flammable, and so on. The modifications have been achieved with a wide range of techniques of several different types. These techniques, both in principle and practice, can be used to overcome the limitations that polyester faces in medical use, principally its clotting behavior, lack of infection resistance, and incorporation into body tissue.

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