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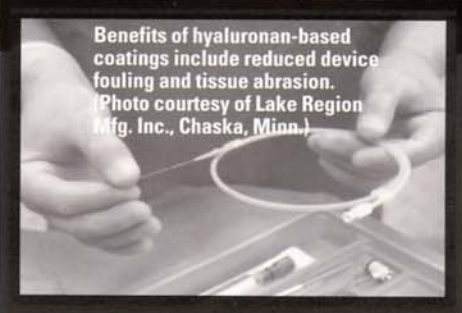
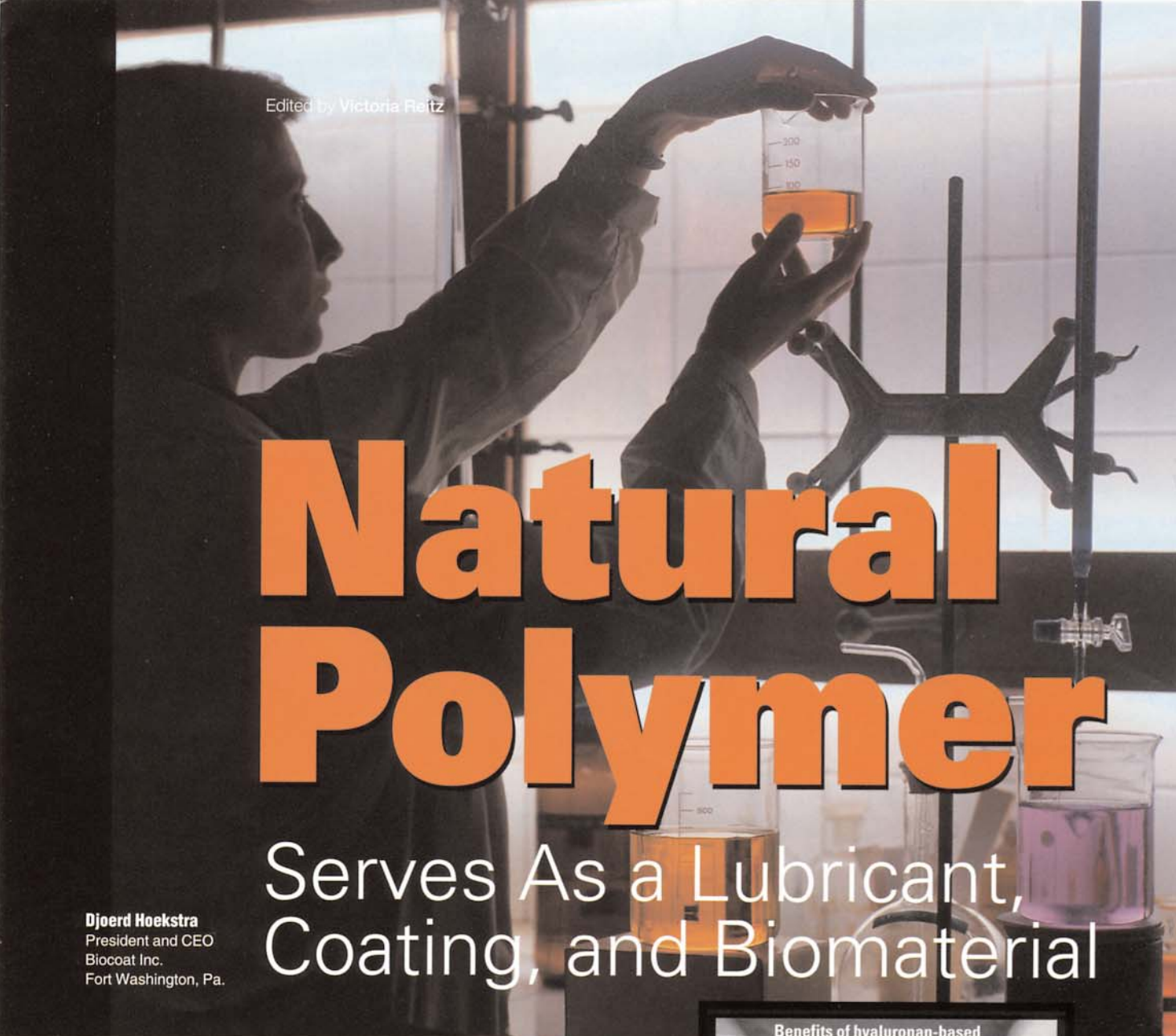
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Hyaluronan-based coatings create hydrophilic, lubricious, and biocompatible surfaces for medical devices such as guidewires and catheters.

Hyaluronan is a naturally-occurring biopolymer which lends itself to cross-linking and immobilizing in ways that produce hydrophilic, lubricious, and biocompatible surfaces. The coating gives surfaces anti-thrombogenic (anticoagulating) and antibacterial properties. In addition to its use in coatings, hyaluronan is finding growing applications in ophthalmology, treating degenerative joint disease, and adhesion prevention.

What is hyaluronan?

Hyaluronan, a polysaccharide, has large linear polymer chains in solution that take on the form of expanded random coils. These chains entangle with each other which may contribute to the unusual rheological properties. Solutions



Benefits of hyaluronan-based coatings include reduced device fouling and tissue abrasion.
(Photo courtesy of Lake Region Mfg. Inc., Chaska, Minn.)

An introduction to hyaluronan

Hyaluronan is a polysaccharide and unique biopolymer. It was first isolated from the vitreous body of the eye by Karl Meyer who called it hyaluronic acid in 1934. The term hyaluronan was proposed by Endre A. Balazs in the 1980's to encompass the different forms the molecule can take: the acid form, hyaluronic acid, and the salts, such as sodium hyaluronate, which form at physiological pH.

Now 70 years after Meyer's initial publication, a lot more is known about the structure of the hyaluronan molecule, how it behaves, its occurrence in different tissues and body fluids, how it is synthesized by cells, metabolized and cleared from the body, and some of its functions.

In the human body, hyaluronan is present in cell structure, body fluids, mucous membranes, joints, and spinal disks. Hyaluronan is synthesized by many types of cells and extruded into the extracellular space where it interacts with other constituents of the extracellular matrix to create a supportive and protective structure. It lubricates joints and separates surfaces that slide over each other such as tendons and sheaths. The highest reported concentration in mammals is found in the umbilical cord.

As one might expect for a material that is ubiquitous in the body, the biocompatibility of hyaluronan has been well established. It is found in every mammalian species and in microorganisms and in every tissue in humans. It is interesting that the hyaluronan molecule is identical in all species and all tissues and therefore never recognized as foreign by the immune system. The only requirement for medically usable preparations is to remove inflammatory fractions, for which there are several processes.

An important factor is that large quantities of hyaluronan are metabolized in the human body, on the order of grams per day in a healthy adult. The high capacity for hyaluronan turnover implies that small applied quantities do not add significantly to the metabolic burden.

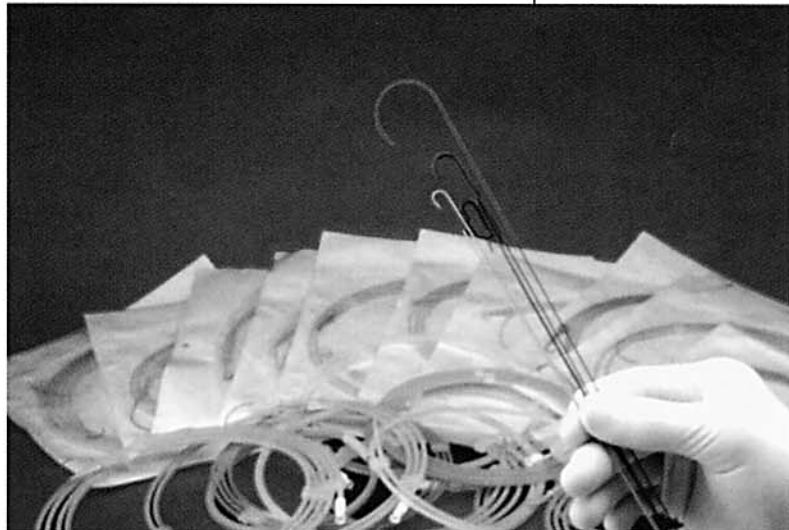
Various published and unpublished *in vitro* and *in vivo* tests conducted over the years by Biocoat Inc. and other researchers have demonstrated the biocompatibility of hyaluronan coatings. Coated surfaces exhibit a marked reduction or absence of cellular attachment and fouling and of bacterial growth, compared with uncoated surfaces. Hyaluronan-coated surfaces are as effective as heparin-coated surfaces in preventing acute thrombosis and does not activate platelets. They are most effective in preventing the adsorption of proteins, preventing adhesion of fibroblasts, and reduce the adhesion of bacteria by several orders of magnitude.

have an extremely high but shear-dependent viscosity. For instance, a 1% solution is like jelly. But under pressure, it moves easily and can be administered through a small bore needle. For this reason it has been called a "pseudo plastic" material.

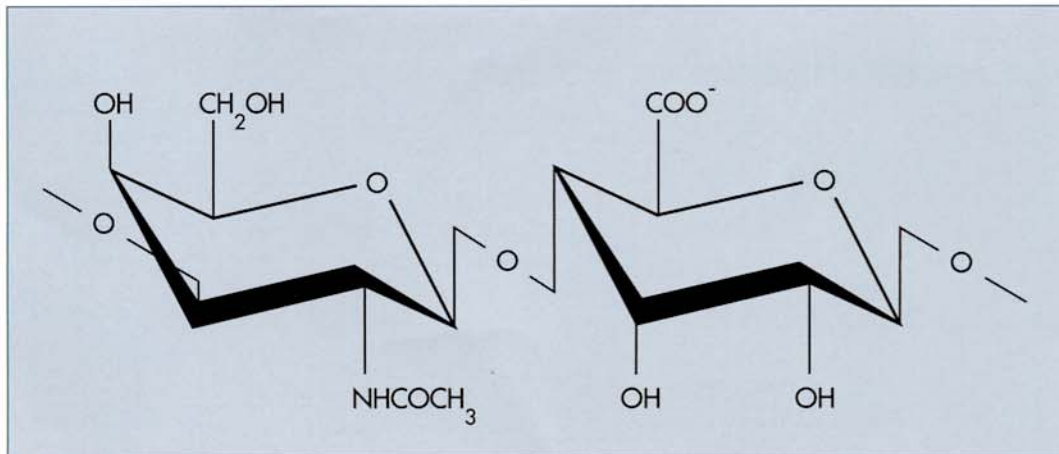
The unusual rheological properties of hyaluronan solutions make it a very slippery hydrophilic material. The coil structure traps about 1,000 times its weight in water.

Medical Applications

The major application of the material has been as a viscoelastic in ophthalmic surgery, mainly the implantation of intraocular lenses in people with cataracts. It is also used as an injectable for degenerative-joint disease. Drug release is another promising application and formulation of hyaluronan. Derivatives have been developed as topical, injectable, and implantable vehicles for the controlled and localized delivery of biologically active molecules.



Hyaluronan-based coatings are used on a variety of medical devices such as guidewires. (Photo courtesy of Lake Region Mfg. Inc., Chaska, Minn.)



A hyaluronan molecule consists of alternating glucuronic acid and N-acetylglucosamine units, which is repeated over and over to form long chains. Each repeating disaccharide unit has one carboxylate group, four hydroxyl groups, and an acetamido group. Hyaluronan differs from the other major glycosaminoglycans in that it does not have sulfate groups.

Hyaluronan is also used in hydrophilic coatings for a variety of medical devices, including catheters, guidewires, and sensors, to improve biocompatibility, lubricity, and to reduce fouling and tissue abrasion. By allowing devices to glide more smoothly it's easier for physicians to manipulate and steer devices around bends and through narrow passages while minimizing trauma and tissue damage.

Hydak coatings from Biocoat are based on hyaluronan. Applying the coatings is a relatively simple process using conventional dip-coating equipment and curing ovens. Coatings are applied in two stages. The base coat is an adhesive synthetic polymer which prepares the substrate for grafting of the top coat. The second coat, the immobilized hyaluronan, makes the surface hydrophilic and lubricious.

Devices coated this way are more hydrophilic than those coated by synthetic chemical substances. This reduces or eliminates thrombus formation and cellular attachment, without having to use bioactive substances such as heparin. Coatings can be very thin without losing effectiveness, leaving substrate materials highly flexible. This is especially important in interventional devices that have to be guided or flow-directed through narrow, twisting passages.

Hydak coatings show superior abrasion resistance because the hyaluronan is immo-

bilized with covalent chemical bonds. This allows using catheters and guidewires during longer procedures with no loss of effectiveness.

Crosslinking, derivatives, and composite forms

Crosslinking the hyaluronan molecule enhances its rheological properties and creates solids and gels that are less soluble in water. The biocompatibility of cross-linked hyaluronan is almost identical to that of hyaluronan.

In addition to cross-linking, various chemical modifications of the hyaluronan polymer have been reported over the years. According to one researcher, the earliest synthesized derivative of hyaluronan was its sulfate ester, which shows resistance to hyaluronidase and anticoagulant activity. More recently, a group of researchers at the University of Siena report that introducing sulfate groups in the hyaluronan molecule converts it to a heparin-like material with anti-thrombogenic properties and makes it resistant to enzymatic digestion.

Hyaluronan also lends itself to compounding or complexing with other materials to produce biomedically useful composites. Several patents on hyaluronan-modified polymeric articles describe how materials such as polyHema, polyurethanes, polyesters, and polyolefins are rendered biocompatible with a coating of hyaluronan. ■

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