ADHESIVE SEALANT BIOMATERIALS

Technical Bulletin

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A Review of the Composition and Constituent Materials of TissuePatch™

TissuePatch™ Product Family

Tissuemed has spent over 20 years at the forefront of technical innovation within medical devices. The TissuePatch™ product family was CE Mark approved and launched in 2007 as a general surgical sealant. The scope of indications was subsequently expanded to neurosurgery use in 2008:

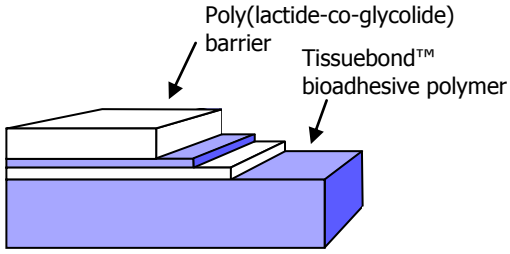
TissuePatch™	general/thoracic sealant
TissuePatchDural™	dural sealant
Obex Neurofilm™	dural sealant*

*Marketed by Medtronic Inc.

Formulation of TissuePatch™

The components of TissuePatch™ are selected from materials already in widespread use in medical applications. The device is fully synthetic and contains no materials of animal origin. PLGA provides a barrier layer and strength whilst a proprietary polymer provides the tissue adhesive characteristics.

Tissuemed have designed every single aspect of this unique device. This includes the synthesis of a proprietary adhesive polymer, purification processes and the optimisation and validation of manufacturing processes.



TissuePatch™	w/w
Tissuebond™ bioadhesive	**61.0%**
- Poly(vinyl pyrrolidone)	(28.2%)
- Poly(acrylic acid)	(18.2%)
- N-hydroxysuccinimide	(14.6%)
Poly(lactide-co-glycolide)	**33.5%**
Water	**5.5% max**
Methylene blue	**0.15% max**

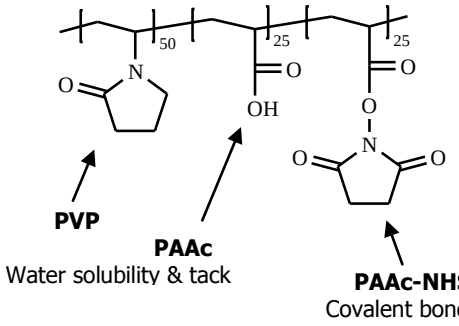
Safety Testing of TissuePatch™

TissuePatch™ has been subjected to an extensive range of biocompatibility tests in accordance with ISO 10993-1 prior to achieving the CE Mark. Each batch of product is tested to ensure strict regulatory compliance.

Tissuebond™ Bioadhesive Polymer

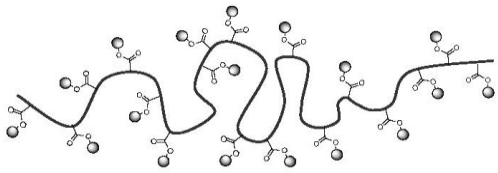
Tissuebond™ is based on a 50/50 copolymer of N-vinyl pyrrolidone and acrylic acid. This is prepared by a free radical polymerisation. The acrylic acid component is then partially functionalised with N-hydroxysuccinimide. The final terpolymer contains three different components which impart water solubility, electrostatic tack and covalent bonding potential. The proportions are shown below:

Tissuebond™	w/w
Poly(vinyl pyrrolidone) (**PVP**)	46.2%
Poly(acrylic acid) (**PAAc**)	29.9%
N-hydroxysuccinimide (**NHS**)	23.9%



TISSUEBOND
bioadhesive technology

Tissuebond™ is a polymer chain containing a random mixture of the three components. The adhesive strength of the material is derived from the polymer chain being long (many hundreds of repeat units). To further improve adhesive strength the polymer is lightly crosslinked during production.



Poly(vinyl pyrrolidone) (PVP)

PVP is the largest component of Tissuebond™ and imparts a number of different features:

- Water solubility
- Film forming characteristics
- Electrostatic adhesion ('tack')

Polymers and copolymers of vinyl pyrrolidone have widespread medical applications. It is used as a binder in pharmaceutical tablets; being completely inert to humans, it simply passes through the GI tract. PVP has multiple uses as a food additive and medically as a substitute for blood plasma (Sheftel, 2000).

The very earliest use of PVP in medicine was during World War II when a 3.5% solution of PVP was infused into patients as a synthetic blood plasma volume expander. This use recognized such valuable properties of PVP as water solubility, viscosity, and osmotic activity and demonstrated that the material appeared to be biologically inert and safe. The toxicity of PVP in a variety of species including humans is extremely low order (Middleton and Tipton, 1998; Lin et. al., 2001). PVP is metabolically inert in rat, dog, and man as shown by experiments using 14C- or 131I-labelled PVP (Ravin et al., 1952).

The copolymerisation of PVP and PAAc allows for a new material containing the properties of the individual homopolymers.

Poly(acrylic acid) (PAAc)

Polyacrylic acid is the primary adhesive component of Tissuebond™ and imparts a number of different features:

- Water solubility
- Electrostatic adhesion ('tack')
- Covalent bonding (via NHS-ester)

Acrylic acid polymers, copolymers and derivatives ('**acrylates**') are widely used as bioadhesives, mucoadhesives, bone cements. They are also used as coatings for catheters, intrauterine devices and sensor electrodes; in contact lenses, burn wound dressings, orthopaedic prostheses, synthetic cartilage and haemodialysis membranes; as drug carriers in ocular, nasal, oral, gastro-intestinal, rectal, dermal, and vaginal delivery; as pharmaceutical excipients; in skin, hair and body lotions; and in a wide range of consumer, industrial and medical products

Acrylic acid polymers and copolymers have low toxicity. The fully polymerised macromolecular products, free from residual monomers, are regarded to be non-toxic and highly biocompatible.

N-Hydroxysuccinimide (NHS)

NHS activates the acrylic acid functionality rendering it adhesive towards surface proteins, via the formation of an amide bond between the polymer backbone and primary amines present within tissues. When the bonding process has been completed the NHS molecule is liberated. NHS is strongly water soluble and once the reaction has completed it will be quickly removed from the surgical site.

NHS is used to promote the cross-linking and tissue adhesion in a number of regulatory approved surgical sealants and barriers that are currently available for clinical use. These are typically based on polyethylene glycol (PEG) materials:

- Duraseal™ (Covidien)
- VascuSeal™ (Covidien)
- Coseal® (Baxter)
- ProGEL™ (NeoMend)

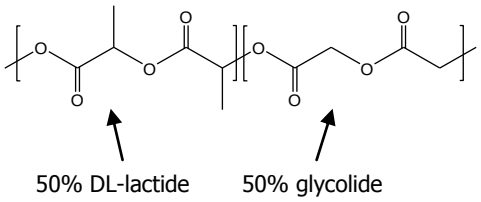
Poly(lactide-co-glycolide) (PLGA)

PLGA (sometimes called PDLG) is a polyester copolymer used in a variety of Food and Drug Administration (FDA) approved devices, owing to its useful material properties and biodegradability-biocompatibility. PLGA is one member of a large family of biodegradable homopolymers and copolymers (comprised of glycolide, lactide and caprolactone), many of which have been successfully developed for many device and drug delivery applications (Muthu, 2009).

Chemical Properties

PLGA is synthesized by means of random ring-opening copolymerization of two different monomers, the cyclic dimers of glycolic acid and lactic acid.

The grade of material used in TissuePatch™ has a 50/50 mole ratio of DL-lactide and glycolide. The molecular weight of the copolymer is 150,000 Da, it has a glass transition temperature (Tg) of 45ºC and an *in vivo* degradation time of approximately 3 months.



The properties of copolymers of PGA and PLA may be fine-tuned according to the ratio of monomer units in the final material. The ratio is used to adjust the degree of crystallinity and degradation rate, and this influences the mechanical strength and application of the material

Toxicological Profile and Degradation

The rate of degradation of PLGA-based products after performing their *in vivo* function is significant in determining their usefulness. The factors determining this phenomenon are, among others, the degree of their crystallinity, molar mass, porosity, pH and the environment temperature (Cieslik et al., 2009).

The biological safety of PLGA has been extensively investigated and established (Jin et al., 2000; He et al., 2009; Yang et al., 2009). Investigations have shown that intramuscular or subcutaneous injections of PLGA demonstrated biological safety without side effects including toxicity, irritation of conjunctiva and

muscle, pyrogenicity, haemolysis, and allergic reaction.

The degradation of PLGA polymers has been studied extensively both *in vitro* and *in vivo*. Degradation of PLGA was monitored by changes in molecular weight of the PLGA subcutaneously implanted in rats. After two weeks of implantation, the copolymer showed a large decrease in molecular weight (approximate 110,000 to 20,000) compared to the material before implantation. After 4 weeks of implantation, the copolymer was highly degraded. The degradation was faster *in vivo* than *in vitro*. The researchers concluded that the accelerated rate of degradation was most likely due to foreign body giant cells and/or several enzymes in the body as well as autocatalytic effect of the acidic degradation products accumulated locally in the medium surrounding the implant (Oh, Kand and Lee, 2006). There are various stages in the degradation process:

- Hydration
- Hydrolysis
- Reduction of molecular weight
- Loss of physical strength and integrity
- Absorption
- Elimination and excretion

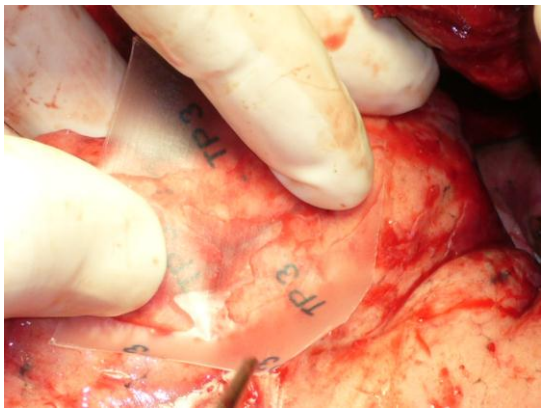
Common Poly(lactide-co-glycolide) Products

Use	**Product**
Sutures	Vicryl™ (Ethicon) Polysorb™ (Covidien)
Hernia and soft tissue mesh	Vicryl™ mesh (Ethicon) Vypro™ mesh (Ethicon) Sepramesh™ (Bard)
Dura repair	Codman® Ethisorb™ Dura Patch™ (Ethicon)
Bone void filler	Polygraft Trufit™ BGS (Smith & Nephew)
Wound healing scaffold (ulcers)	Dermagraft® (Advanced Biohealing Inc.)
Fixation	Rapisorb and Rapisorb Cranial Clamp (Synthes)
Drug delivery	Lupron Depot® for treatment of prostate cancer (Abbot Labs)

For suture use, where high tensile strengths are required for primary wound closure, polymers with a high ratio of glycolide units are typically used, for instance Ethicon's Vicryl™ 9010 (90% glycolide 10% L-lactide) (Middleton and Tipton, 1998). This ensures that the material contains a high level of crystallinity to give sufficient strength. In fact this material retains strength slightly longer that pure PGA yet has a shorter degradation time. L-lactide is selected for this particular application due to the shrinkage characteristics of DL-lactide in this application.

Methylene Blue

Methylene blue is a heterocyclic aromatic dye used extensively in medicine and is an active pharmaceutical ingredient (API).



A surface marking logo is used in TissuePatch™ to differentiate the adhesive and non-adhesive surfaces of the device; critical for an otherwise transparent film. The dye is incorporated into TissuePatch™ by a screen printing process during manufacture. The logo is sandwiched between the inner layers of the device. Each batch of TissuePatch™ is subjected to a UV spectroscopic assay to measure the quantity of methylene blue. The specification limit is 0.015%. The absolute quantity is very low, equating to 0.4mg for a maximum dose of 200cm² of TissuePatch™.

Methylene blue is used in a variety of medical treatments and is usually supplied as a USP sterile solution. Applications include:

Methemoglobinaemia
At low pharmacological doses (1-2mg/kg) methylene blue is used to treat methemoglobinaemia. This is a condition when the blood cannot deliver sufficient oxygen. Methylene blue acts to chemically reduce methemoglobin to haemoglobin.

Surgical Stain
Methylene blue is also used as a dye to stain certain parts of the body before or during surgery. It may also be used make certain body fluids and tissues easier to view during surgery or on an x-ray or other diagnostic exam. Typical diagnostic solutions are 1-2mg/ml.

Methylene blue is used in endoscopic polypectomy as an adjunct to saline or epinephrine, and is used for injection into the submucosa around the polyp to be removed. This allows the submucosal tissue plane to be identified after the polyp is removed, which is useful in determining if further tissue needs to be removed, or if there has been a high risk for perforation.

Urinary Tract Infections
Methylene blue is also used to treat urinary tract infections. It works as a mild antiseptic to kill bacteria in the urinary tract and is generally given with an antibiotic medication to treat infection.

Tissuemed® surgical sealant films CE 0088