EPOXY TECHNOLOGY

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The Suitability of Epoxy-Based Adhesives for Use in Medical Devices

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The use of solventless adhesives in the fabrication of medical devices continues to increase in all areas of the industry due to legislation that prohibits the use of solvents and solvent-laden adhesives. This legislation has been enacted in response to concerns about the short-term toxic effects of solvents as well as the possibility that many of them may be carcinogenic.

Relatively nontoxic solvents such as cyclohexanone have been successfully utilized for bonding PVC tubing to many types of polymers in the fabrication of molded connectors, but their use is now diminishing as new adhesive systems are custom-formulated to meet the stringent requirements of medical applications. In particular, UV-cure acrylics, UV-cure epoxies, urethane adhesives, and epoxy-based adhesives are being used in increasing amounts as they demonstrate their advantages over solvents and solvent-based adhesives.

This article focuses on the use of epoxy-based adhesives for the joining of surfaces in the fabrication of medical devices. Epoxies are excellent adhesives due to their good strength, compatibility with many materials, and chemical and moisture resistance. In addition, several epoxy adhesives are nontoxic, making them especially suitable for use in implantable medical devices, where the risk of allergic reactions or long-term toxic effects are of paramount importance to patient safety.

Selection of Adhesives

The choice of adhesive must be dictated by the requirements of the application. There is no "ideal" adhesive that will be suitable for use in the manufacture of all medical devices. Properties that are important to the selection of the proper adhesive for specific applications include:

- Nontoxicity (meeting USP Class VI biocompatibility standards)
- Adhesion to organic and inorganic surfaces
- 100 percent solids before and after curing
- Rheology optimized for wetting and gap filling
- Working life suitable for high-volume production
- Compatibility with radiation, chemical and autoclave sterilization
- Fungus- and bacteria-resistant (non-nutrient)
- Ability to cross-link 100 percent with optimized cure schedule

Beyond the scope of these properties, the adhesive must be formulated for proper viscosity and thixotropic index, an optimized modulus for bonding dissimilar substrates, and cure temperature and time. Some adhesives must be rapidly cured at room temperature or using UV radiation, while others can be cured for longer periods of time, with or without heat. The optimal attributes for an adhesive to be used in a specific medical device are determined by the surfaces to be bonded, established reliability criteria, and the process to be employed in manufacturing.

For several years Epoxy Technology has been manufacturing both electrically conductive and insulating adhesives that have been successfully used in the fabrication of medical devices. The following discussion focuses on the properties and uses of some of these adhesives and concludes with a brief consideration of new materials and their potential for use by medical-device manufacturers.

Application

Epoxy Technology currently manufactures five adhesives that are used in fabrication of a variety of medical devices. All five have been tested to the requirements of United States Pharmacopoeia (USP) Class VI biocompatibility standards, and all meet or exceed these requirements. Because the FDA approves applications rather than adhesives, satisfying the USP Class VI standards does not guarantee that an adhesive will meet FDA requirements in a particular application. But passing USP Class VI testing for incutaneous toxicity, acute systemic toxicity, and implantation is strong evidence of nontoxicity and establishes the potential suitability of an adhesive for medical applications.

Each of these five biocompatible adhesives – EPO-TEK® H20E, EPO-TEK 301, EPO-TEK 301-2, EPO-TEK 353ND, and EPO-TEK 377 – will be discussed further with respect to their relevant properties and applications in the manufacture of medical devices. A specific application for EPO-TEK 301 will then be explored in greater detail, along with biocompatibility testing data.

EPO-TEK H20E

A two-component, silver-filled, electrically conductive adhesive, EPO-TEK H20E has been used successfully for years in hybrid, semiconductor and aerospace applications. Some of the features of this adhesive which make it suitable for "high-reliability" applications are:

- 100 percent solids
- Volume resistivity < 1 x 10^{-4} ohm-cm
- Electrically stable at frequencies to 100 GHz
- Current carrying capacity > 1,800 amps/cm^2
- Low outgassing and low dermatitis potential
- Long pot life and fast heat curing
- Suitable for automatic dispensing
- History of long-term reliability
- Low thermal resistance of 6-7°C/watt

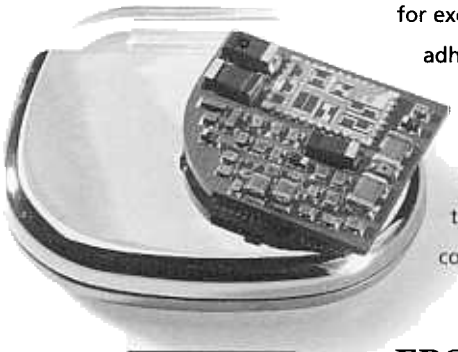

FIGURE 1

While EPO-TEK H20E has multiple uses in the field of medical electronics, it is especially noted for exceptional performance in the fabrication of heart pacemakers (Fig. 1). The conductive adhesive is used for bonding critical components in hybrid circuits within pacemakers. EPO-TEK H20E has been consistently shown to provide superior electrical and thermal performance over other electrically conductive adhesives in this application. In addition, its low outgassing in the hermetic enclosure ensures that no residues cause corrosion that can compromise reliability. EPO-TEK H20E is also used extensively for bonding components in hearing-aid assemblies.

EPO-TEK 301-2

EPO-TEK 301-2 is a two-component, optically clear epoxy that offers excellent adhesion to a variety of plastics and other surfaces. Its properties include:

- Low viscosity (< 300 cps)
- Solvent-free for low outgassing
- Curing at room temperature or with heat
- Low levels of mobile ions
- Excellent chemical and moisture resistance
- Excellent adhesion to plastics and metals
- Long pot life (24 hours) for ease of manufacturing
- Survives autoclave, ETO and chemical sterilization

This epoxy is generally used for bonding optical fibers (fiber bundles) into plastic tubing to make catheter assemblies. Its low viscosity and clarity also make it suitable for molding housing for medical implants.

EPO-TEK 353ND

EPO-TEK 353ND is a two-component, high-temperature adhesive that can be snap-cured with heat. This makes it possible to fixture and align components, then quickly cure them in place while still in the fixture. It is possible to cure the epoxy in less than one minute at 175°C. EPO-TEK 353ND is used extensively for manufacturing medical devices using fiber optics. This high-performance adhesive has a balance of properties that make it an excellent candidate for fiber-optic applications as well as bonding optical components:

- Quick cure
- Survives autoclave, ETO and chemical sterilization
- High tensile strength
- High glass transition temperature
- Low viscosity for excellent wetting
- Low outgassing

In addition to meeting USP Class VI requirements, EPO-TEK 353ND has excellent dimensional stability over a wide temperature range. This assures low dB losses of light in fiber assemblies and eliminates fiber pistoning that leads to failures.

EPO-TEK 353ND has an excellent reliability record for use across a wide spectrum of medical-device applications. It is used extensively for bonding and coating applications and has proven itself one of the most versatile and effective adhesives for medical-device fabrication. Applications where this adhesive is currently being used successfully include:

- Terminating fiber optics in laser angioplasts
- Fiber-optic bundling in 3D endoscopes
- Fiber-optic bundling in dental hand tools
- Fiber-optic bundling in otoscopes and laryngoscopes
- Bonding balloon to catheter for balloon angioplasty
- Coating ultrasonic transducer (bonded with H20E) in a device that simplifies prostate cancer surgery
- Bonding diamond scalpel blades for coronary bypass surgery

EPO-TEK 377

Like EPO-TEK 353ND, EPO-TEK 377 is a low-viscosity, high-temperature adhesive useful in medical fiber-optic applications. Its uses include fiber-optic terminating and bundling in laryngoscopes, endoscopes and other devices. Key properties of EPO-TEK 377 include stability at high temperatures, sterilizability by most techniques, and significant optical clarity (in thin films) at high temperatures. Although this adhesive requires a longer cure (at temperature) than EPO-TEK 353ND, it has a longer pot life and can be used at higher operating temperatures. In addition, EPO-TEK 377 is the most moisture-resistant and chemical-resistant adhesive in Epoxy Technology's line of medical-grade adhesives.

EPO-TEK 301

EPO-TEK 301 is a clear, low-viscosity epoxy that has found many uses in the fabrication of medical devices. It has compiled an extensive record of high reliability and provides a blend of properties that make it suitable both as an adhesive and a potting material. Besides low viscosity (< 100 cps), EPO-TEK 301's key attributes include room-temperature curing, adherence to a variety of plastics and metals, and excellent moisture and chemical resistance. This adhesive can be sterilized by autoclave, ETO and chemical methods. Its applications include:

- Bonding lenses to fiber-optic termini in endoscopes
- Bonding plastic tips to tubing in disposable catheters
- Coating access ports for long-term tissue implants
- Prism and lens bonding for instrumentation
- Coating implantable neural prosthetic devices
- Potting fiber optics in catheters
- Molding housings for titanium injection access ports

Sample Application: Access Ports

EPO-TEK 301 has proven itself highly suitable for use in the fabrication of access ports that are implanted beneath the skin of patients requiring multiple injections. By preserving access for subsequent treatments, the ports enhance patient comfort and reduce complications. In combination with a catheter assembly, access ports are used to direct medicines to specific areas of the body. As shown in Figure 2, they can be used for venous, arterial, peritoneal or intraspinal access.

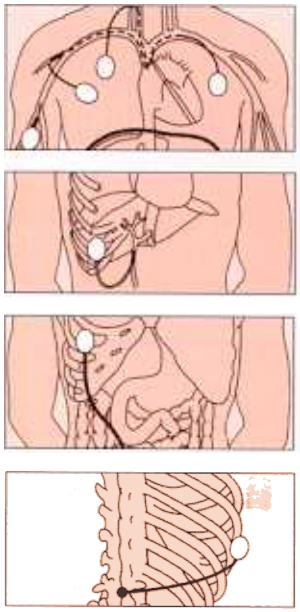

FIGURE 2

The access port assembly is completed by encapsulating (potting) the titanium or stainless steel access port with EPO-TEK 301 epoxy. The mixed and degassed epoxy is poured into a mold that holds the access port in place. The outer connection (for the catheter) and the silicone surface (for needle punctures) are not covered by the epoxy. The epoxy is cured at room temperature for 24 hours, and the surface is polished after removal from the mold to yield a completed access port with a pinhole-free, hard and durable finish, as shown in Figure 3.

The access port is attached to tissue just below the patient's skin using sutures threaded through a hole in the epoxy. The catheter is then directed to the target blood vessel or area of the body. The catheter is connected to the access port, and a needle is inserted through the silicone septum to administer doses of medicine.

This in-vivo medical application requires the epoxy used to encapsulate the access port to be completely nontoxic and meet FDA requirements for the application. EPO-TEK 301 satisfies both of these needs. The data presented in Tables 1 through 5 show the test results of USP Class VI testing and cytotoxicity tests performed on EPO-TEK 301.

FIGURE 3

As the "certificate of compliance" indicates, EPO-TEK 301 passed all phases of USP biocompatibility testing and is therefore a suitable epoxy candidate for medical-device applications. As previously mentioned, compliance with this testing does not guarantee FDA approval of the epoxy in all applications. But passing these critical toxicity tests demonstrates the nontoxic nature of the epoxy and therefore its potential suitability for use in medical applications.

TABLE 1

CERTIFICATE OF COMPLIANCE USP BIOLOGICAL TESTS
CLASSIFICATION VI

ACUTE SYSTEMIC TOXICITY (USP):
The saline, alcohol in saline, polyethylene glycol 400 and cottonseed oil extracts of the test article injected into mice did not produce a significantly greater systemic reaction than the blank extractant.

INTRACUTANEOUS TOXICITY (USP):
The saline, alcohol in saline, polyethylene glycol 400 and cottonseed oil extracts of the test article injected intracutaneously in rabbits did not produce a significantly greater tissue reaction than the blank extractant.

IMPLANTATION TEST (USP):
The macroscopic reaction of the test article implanted 7 days was not significant as compared to the USP negative control plastic.

The sample of test article extracted at a ratio of 4 g/20 ml and at a temperature of 121 degrees C for 1 hour met the requirements of a USP Class VI Plastic.

TABLE 2

ACUTE SYSTEMIC TOXICITY - T12

Extracting Conditions: A 7.7 gram portion was added to 39 ml of vehicle(s) and extracted at 121 degrees C for 1 hour. Control solutions (extracts without test article) were prepared in a similar manner.

Condition of Extracts: CSO test extract cloudy; others clear.

Procedure: Healthy, young albino mice ranging in body weight from 17 to 23 grams were used as test animals. The animals, identified by fur marking, were group housed in stock cages and offered food and water ad libitum.

Two groups, each consisting of five mice, were used for each extract. One group was injected with the extract of the test article, while the other group was injected with the control solution. After injections, the animals were observed immediately and at 4, 24, 48 and 72 hours. The initial and final body weights were recorded as well as mortalities and/or reactions. If, during the observation period, none of the animals treated with the test article extract showed a significantly greater reaction than the animals treated with the control solution,then the test article met the requirements of the test.

Mortality and Body Weight Data

Extract, Route and Dose	TEST ARTICLE Animal Number	Weight (g) Day 0	Day 3	#Dead/ #Tested	CONTROL Animal Number	Weight (g) Day 0	Day 0	#Dead/ #Tested
Sodium Chloride Injection (SC) (I.V.; 50 ml/Kg)	1	18	19		1	17	18	
	2	17	18		2	17	18	
	3	17	16	0/5	3	19	20	0/5
	4	20	23		4	18	19	
	5	17	18		5	18	19	
Alcohol in Sodium Chloride Injection (1:20) (AS) (I.V.; 50 ml/Kg)	1	17	17		1	18	19	
	2	18	18		2	17	19	
	3	17	19	0/5	3	18	19	0/5
	4	17	19		4	17	18	
	5	18	20		5	20	21	
Polyethylene Glycol 400 (PEG) (I.P.; 10 g/Kg)	1	18	19		1	17	18	
	2	18	19		2	17	17	
	3	18	19	0/5	3	20	22	0/5
	4	17	19		4	17	19	
	5	17	18		5	17	17	
Cottonseed Oil (CSO) (I.P.; 50 ml/Kg)	1	19	19		1	19	19	
	2	17	19		2	19	21	
	3	17	19	0/5	3	20	22	0/5
	4	17	20		4	18	20	
	5	17	21		5	19	20	

TABLE 3

NTRACUTANEOUS TOX C TY T13

Extracting Conditions: A 7.7 gram portion was added to 39 ml of vehicle(s) and extracted at 121 degrees C for 1 hour. Control solutions (extracts without test article) were prepared in a similar manner.

Condition of Extracts: CSO test extract cloudy; others clear.

Procedure: Two healthy New Zealand white rabbits free of significant dermal blemishes were used as test animals for each extract or pair of extracts. Animals were housed individually, fed daily, and allowed water ad libitum. Prior to injection, the hair was closely clipped from the back and flanks of each rabbit. Exactly 0.2 ml of the test article extract was injected intracutaneously into five separate sites on the right side of the back of each animal while 0.2 ml of the control solution was injected into five separate sites on the left side. Injection sites were examined 24, 48 and 72 hours after injection for erythema and edema. The average tissue reaction to the extract of the test article was compared with the control. The requirements of the test were met if no significant differences were noted.

Extract	Rabbit No.		24 HR ER	24 HR ED	48 HR ER	48 HR ED	72 HR ER	72 HR ED
Sodium Chloride (SC)	52121	Test	0	0	0	0	0	0
		Control	0	0	0	0	0	0
	52122	Test	0	0	0	0	0	0
		Control	0	0	0	0	0	0
Alcohol in Sodium Chloride 1:20 (AS)	52121	Test	0	0	0	0	0	0
		Control	0	0	0	0	0	0
	52122	Test	0	0	0	0	0	0
		Control	0	0	0	0	0	0
Polyethylene Glycol 400 (PEG)	52123	Test	0	0	0	0	0	0
		Control	0	0	0	0	0	0
	52124	Test	0	0	0	0	0	0
		Control	0	0	0	0	0	0
Cottonseed Oil (CSO)	52123	Test	1	2	1	2	1	2
		Control	0	0	0	0	0	0
	52125	Test	1	2	1	1	1	1
		Control	1	1	1	1	1	1

Key

ER = ERYTHEMA
0 = None
1 = Barely Perceptible
2 = Well Defined
3 = Moderate

ED = EDEMA
0 = None
1 = Barely Perceptible
2 = Well Defined
3 = Raised 1 mm
4 = Raised > 1mm

RATING (Test Control)
0 - 0.5 Acceptable
0.6 - 1.0 Slight
> 1.0 Significant

Mean Test - Mean Control = Difference		Passes	Fails
SC = 0.0-0.0	0.0	X	
AS = 0.0-0.0	0.0	X	
PEG = 0.0-0.0	0.0	X	
CSO = 1.3-0.5	0.8	X	

TABLE 4

IMPLANTATION TEST (T14)

Preparation: The test article was cut and trimmed to 1 x 10 mm. Sterilized by ETO.

Procedure: Two healthy (minimum), adult New Zealand white rabbits weighing at least 2.5 kg were used as test animals. The back of each animal was clipped of fur on both sides of the spinal column. Loose hair was removed by alcohol wipe after clipping and the paravertebral muscles were anesthetized. Four strips (minimum) of sterile test article were introduced into the right paravertebral muscle of each rabbit.

The animals were euthanatized 7 days after implantation and the entire paravertebral muscle on each side of the vertebrae removed. Cross sections of the muscles were made to locate the implants. The tissue surrounding the implant were examined macroscopically.

Results of Macroscopic Examination:

Rabbit#	Article	Test	Control
51925	1	0	0
	2	0	0
	3	0	
2.7 kg	4	0	
51978	1	0	0
	2	0	0
	3	0	
2.5 kg	4	0	
Average:		0.0	0.0

Scoring Key

Score	Capsule Formation
0	None Noted
1	Up to 0.5 mm
2	0.6 to 1.0 mm
3	1.1 to 2.0 mm
4	>2.0 mm

Reaction Index

Average (test) - Average (control) = 0.0

0-0.5	Not Significant
0.6-1.0	Trace
1.1-2.0	Slight
2.1-3.0	Moderate
>3.0	Marked

Macroscopic: The reaction was <u>not significant</u> as compared to the negative control implant material.

TABLE 5

CYTOTOXICITY - MEM ELUTION MT023

Test Article Size Used: 7.7 grams

Procedure: A monolayer of L-929 mouse fibroblast cells was grown to confluency and exposed to an extract of the test article prepared by placing the test article in 39 ml of Minimum Essential Medium (Eagle) and bovine serum (5%) and extracting at 37 degrees C for 24 hours. An MEM aliquot was used as a negative control. After exposure to the extract, the cells were examined microscopically for cytotoxic effect (CTE). Presence (+) or absence (-) of a confluent monolayer, intracellular granulation, cellular swelling and crenation and the percentage of cellular lysis were recorded.

CTE was scored as either Nontoxic(N), Intermediate(I), or Toxic(T).

N = Indicates a negative or nontoxic response.

I = Indicates an intermediate response, a subjective assessment of the extent of cellular response.

T = Indicates a positive or toxic response consisting of greater than 50% cell death.

	Confluent Monolayer	Intracellular Granulation	Swelling	Crenation	% Lysis	CTE Score
24Hours						
Test Extract	(+)	(-)	(-)	(-)	0	N
Negative Control	(+)	(-)	(-)	(-)	0	N
48Hours						
Test Extract	(+)	(-)	(-)	(-)	0	N
Negative Control	(+)	(-)	(-)	(-)	0	N
72Hours						
Test Extract	(+)	(-)	(-)	(-)	0	N
Negative Control	(+)	(-)	(-)	(-)	0	N

Positive control, SCG-2, was toxic at a dilution of 1:16 at 24 hours.

Conclusion: <u>Nontoxic</u>

Comments: The test extract and control solution were clear.

New Biocompatible Epoxies

Besides the epoxies discussed above that are currently being used in medical devices, Epoxy Technology has developed additional epoxy formulations that are now under consideration for medical applications. These newer formulations, and their intended applications, are:

- EPO-TEK 302-3M (optical, general adhesive)
- EPO-TEK 353ND-4 (optical, general adhesive)
- EPO-TEK CF6-2 (high-temperature bonding)
- EPO-TEK 715 (bonding difficult plastics)
- EPO-TEK UVO-114 (UV-curable, command cure)

In addition to testing for specific applications, USP Class VI biocompatibility testing is being conducted for each of these epoxies. Of particular interest are EPO-TEK 715 and EPO-TEK UVO-114. EPO-TEK 715 will bond well to most nonpolar plastics that are normally very difficult to adhere to without special surface preparation. EPO-TEK UVO-114 is a single-component epoxy that can cure in 60 seconds or less in ultraviolet light. In addition to this snap cure, EPO-TEK UVO-114 offers important advantages over the UV-acrylic adhesives that have been in use for some time, including superior adhesion, moisture resistance, and high-temperature performance.

Summary

The use of epoxies in the field of medical-device fabrication is extensive and continuing to grow at a rapid pace as solventless adhesives replace older solvent-bonding systems. Compliance to USP Class VI standards has been achieved with several epoxies, and new formulations continue to be developed in response to the challenges of new technological developments in the medical field. Epoxy Technology has extensive expertise in formulating adhesives to meet the demands of medical-device manufacturers. In addition, Epoxy Technology will custom-formulate medical-grade adhesives to meet customer-specific requirements in this field.

About the author

Richard H. Estes received his degree in Chemistry from the University of Massachusetts in 1975. He was a chemistry instructor for six years prior to taking a position at Epoxy Technology, Inc. in February 1981. Mr. Estes has held the positions of Quality Control Manager, Technical Service Manager, and is currently the Vice President of Technical Operations at Epoxy Technology. Areas of responsibility include technical services and quality control, as well as supervising R&D in the development of new materials and processes for applications in the semiconductor and hybrid microelectronics industries and the optoelectronics/fiber optics industries. Mr. Estes has authored several technical papers on the technology of adhesives, is a member of ISHM, SEMI and IEEE, and holds patents in the field of flip chip technology.

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