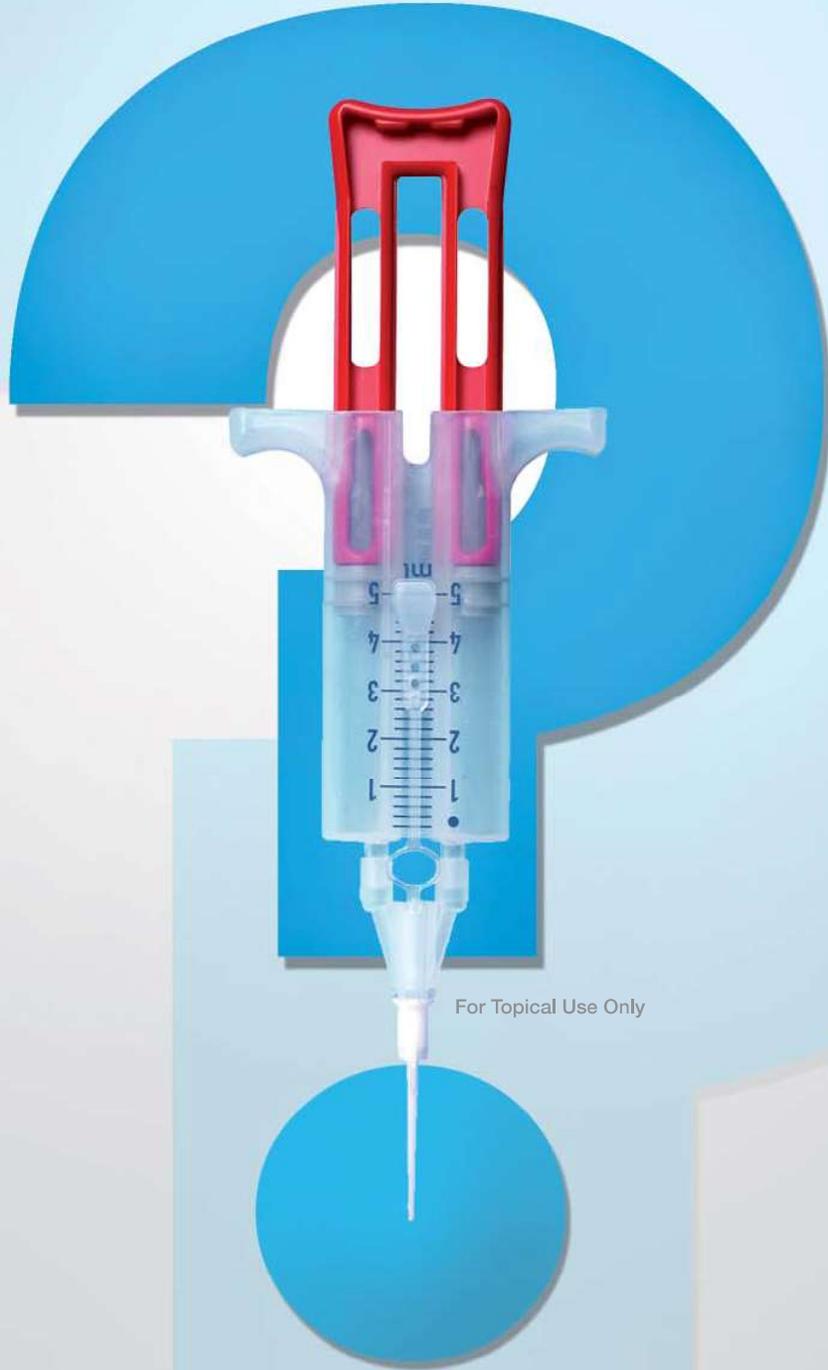




TISSEEL
[Fibrin Sealant]

do you really know it



For Topical Use Only

Evolution and Improvement

1972



Dr. Helene Matras

Reintroduction of modern tissue sealants by Helen Matras who successfully employed fibrin sealant for reuniting severed nerves in an animal model.^{6,7}

image From Redl.⁹ Used with permission.

1980

A special heating and stirring device, FIBRINOTHERM, is developed to dissolve lyophilized TISSEEL.⁹



1998

Fibrin sealant approved in the United States following TISSEEL clinical study led by Dr. John Rousou.¹⁰



Dr. John Rousou

2007



Introduction of TISSEEL VH SD (frozen).⁵

For Topical Use Only

1972

1978

TISSEEL VH (lyophilized) introduced.^{8,9}



1987



For Topical Use Only

A dual-syringe, deep frozen system for TISSEEL VH is introduced.⁹

2005, 2006

The EASYSpray application system was introduced in 2005 and the DUPLOSPRAY system was introduced in 2006.³



2012

Introduction of TISSEEL VH SD (frozen) with synthetic aprotinin.³

2012





What Makes TISSEEL Fibrin Sealant Different

The Only “4 in 1” Fibrin Sealant¹

- Hemostasis
- Sealing
- Adherence
- Healing

Unique Formulation

- Fibrinogen content determines clot strength⁷
- Lower thrombin supports adhesion and spreading of NHEKs¹²
- Aprotinin promotes clot stabilization²

Component	TISSEEL ²	EVICEL ¹¹
Fibrinogen	67-106 mg/mL	50-90 mg/mL
Thrombin	400-625 IU/mL	800-1,200 IU/mL
Aprotinin	2250-3750 KU/mL	---

Benefits of High Fibrinogen Concentration

- Fibrinogen concentration is directly related to:
 - Elasticity of the fibrin clot⁹
 - Increased tensile strength⁷
 - Increased adhesive strength⁷
- The TISSEEL fibrin clot contains:
 - 30 times the fibrinogen concentration in blood²⁰
 - 5 times the strength of a normal, healthy clot²¹



Image from RedP. Used with permission.

The physiologic fibrin clot formed by TISSEEL Fibrin Sealant has a high elasticity.⁹

Benefits of Low Thrombin Concentration

- Normal human epidermal keratinocytes (NHEK) play a key role in wound healing of the skin as they re-epithelialize the wound area¹²
- A lower thrombin concentration⁹ supports adhesion and spreading of NHEK *in vitro*¹²
- A lower thrombin concentration provides a more uniformly polymerized, stronger adhesive bond¹³

Morphology of NHEK on fibrin clots prepared with low, medium, and high concentrated thrombin solutions. Cells were seeded on top of fibrin clots with different thrombin contents: 505 IU mL (left); 820 IU mL (right) were incubated for 24 hours (top) or 48 hours (bottom). Cells were stained to visualize cell nuclei (blue stain).¹²

Striking differences in cell morphology were observed between fibrin clots made with low, medium, and high concentrated thrombin solutions. With increasing thrombin concentration cell morphology became more and more deteriorated.¹²

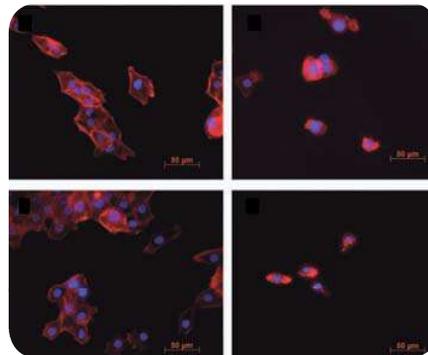


Image from Gugerall et al.¹² Used with permission.

What Makes TISSEEL Fibrin Sealant Different

In Vitro Comparison of Clot Lysis Under Highly Fibrinolytic Conditions¹⁴

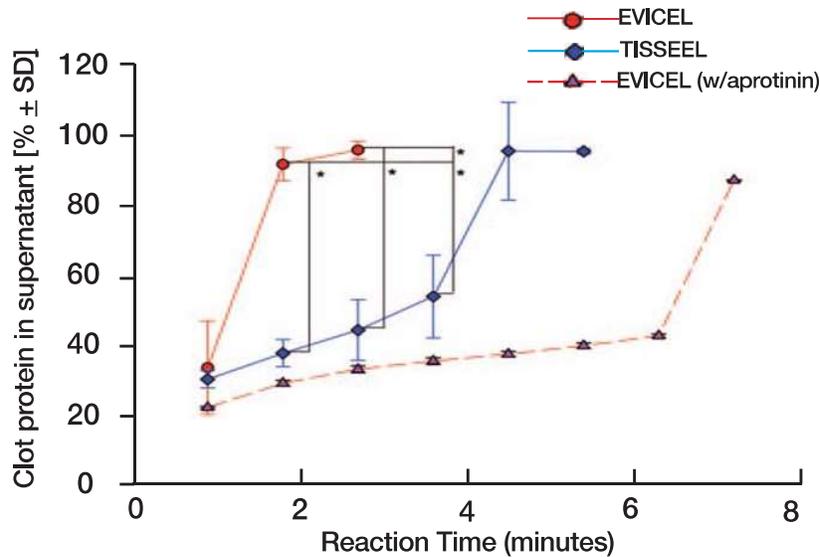
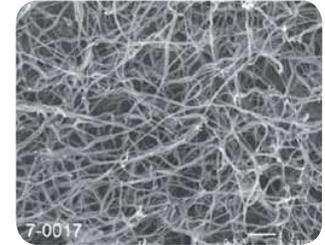


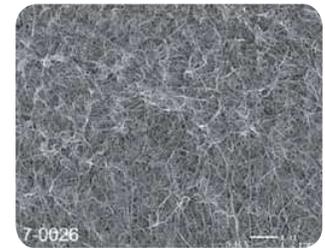
Image adapted from Hedrich et al.¹⁴ Used with permission.

In highly fibrinolytic conditions, the TISSEEL clot is more stable than a clot prepared from plasminogen-depleted and aprotinin-free fibrin (EVICEL). When EVICEL was supplemented with aprotinin, it had a stabilizing effect on the clot.¹⁴

Statistically significant difference $p < 0.001$



TISSEEL



EVICEL

Images from Hedrich et al.¹⁴ Used with permission.

Ultrastructure of TISSEEL (top) and EVICEL (bottom). TISSEEL clots are formed of thick fibrin fibers. EVICEL is formed of thin fibrin fibers with a dense, less homogenous structure.¹⁴

Key Study Conclusions¹⁴

- When comparing TISSEEL and EVICEL *in vitro*, there were differences in ultrastructure and alpha-chain cross-linking rates as well as the rate of fibrinolysis which may explain the significantly enhanced sealing efficacy of TISSEEL *in vivo* (in an animal model)
- Total clot lysis occurred within two days in the EVICEL clots and five days in the TISSEEL clots
- Interestingly, when aprotinin was added to EVICEL it had a stabilizing effect on the clots; time to achieve clot lysis was prolonged from 2 days to 8 days
- There was a statistically significant higher leakage pressure with pooled lots of TISSEEL than with pooled lots of EVICEL (two-sided $p < 0.0001$)
- In Hickerson et al,¹⁵ the authors reported higher tensile strength and higher levels of factor XIII in EVICEL; investigations in this study contradict both of these findings

*TISSEEL demonstrated statistically significant enhanced efficacy as compared to EVICEL.*¹⁴



TISSEEL
[Fibrin Sealant]

TISSEEL Fibrin Sealant vs. EVICEL

Ease of Use

- Unlike EVICEL, after thawing TISSEEL (frozen) is ready-to-use with no additional preparation required^{2,16}

TISSEEL *2	Thawing Time*	Prep. Personnel	EVICEL ¹⁶	Preparation Time	Prep. Personnel
2 mL	5 minutes	Scrub nurse	1 mL	10 minutes + prep. time	Scrub & circulating nurse
4 mL	5 minutes	Scrub nurse	2 mL	10 minutes + prep. time	Scrub & circulating nurse
10 mL	12 minutes	Scrub nurse	5 mL	10 minutes + prep. time	Scrub & circulating nurse

*TISSEEL Frozen: quick thawing performed by immersion in a sterile water bath. Maintain product at 33-37°C until use.²

Coverage and Application - when applied using a spray device

Total Volume	TISSEEL ²	EVICEL ¹⁶
2 mL	100 cm ²	20 cm ²
4 mL	200 cm ²	40 cm ²
10 mL	500 cm ²	100 cm ²

2mL TISSEEL when dripped cover 10cm²

TISSEEL provides 5x more coverage



For Topical Use Only

TISSEEL (frozen) is ready-to-use²



Easy as 1-2-3



For Topical Use Only



TISSEEL Fibrin Sealant vs. TACHOSIL

Coverage and Application - when applied using a spray device

- Unlike TACHOSIL, TISSEEL can be sprayed and used with a wide variety of application devices, thus it is ideal for minimally-invasive as well as open procedures^{1,2,17,18}
- TACHOSIL is only provided as a sponge that may stick to instruments or gloves¹⁹

Size	TISSEEL ^{1,2}	Size	TACHOSIL ¹⁹
2 mL	100 cm ²	3.0 cm x 2.5 cm (1 sponge)	7.5 cm ²
4 mL	200 cm ²	3.0 cm x 2.5 cm (5 sponges)	37.5 cm ²
10 mL	500 cm ²	9.5 cm x 4.8 cm (1 sponge)	45.6 cm ²
10 mL	500 cm ²	4.8 cm x 4.8 cm (2 sponges)	46.1 cm ²

2mL TISSEEL when dripped cover 10cm²

TISSEEL provides (at least) 5x more coverage

Wide Variety of Applicators Available^{2,17,18}

DUPLOCATH 25 APPLICATION CATHETER — (A)

[length = 25 cm]

DUPLOTIP APPLICATOR 318 — (B)

[length = 318 mm]

DUPLOSPRAY M.I.S. APPLICATOR — (C)

[20 cm / 30 cm / 40 cm]

TISSEEL [FIBRIN SEALANT] PRE-FILLED — (D)

[2 mL / 4 mL / 10 mL]

DUPLOTIP APPLICATOR 267 — (E)

[267 mm]



Spray application precaution: Any application of pressurized gas may be associated with a potential risk of air embolism, tissue rupture or gas entrapment with compression, which may be life threatening. Be sure to take appropriate measures to address these risks by observing the recommended minimum spraying distance and the maximum pressure provided in the appropriate spray set instructions for use.