Rheologically-Modified Absorbable Tissue Adhesives

D. R. Ingram, K.J. Garcia, J.T. Corbett, M.S. Taylor, S.W. Shalaby
Poly-Med, Inc., Anderson, SC

Statement of Purpose: Traditionally, wound approximation has been accomplished using staples, clamps, and various types of sutures. Because of disadvantages experienced with these devices, wound closure techniques utilizing tissue adhesives have been developed. One such family of tissue adhesives is the lower alkyl 2-cyanoacrylate family (1-8 carbon alkyl groups). Based on composition, these tissue adhesives either bioabsorb too slowly or, when rates are faster, elicit a negative tissue response due to the resultant rapid release of depolymerization byproducts. For these reasons, formulations based on alkoxyalkyl 2-cyanoacrylate were developed.[1]

The goal of the studies summarized in this communication is to develop a tissue adhesive that is spreadable on tissue, releases low amounts of heat when curing, and, when cured, forms a non-toxic, flexible, and strong polymer that promotes healing. Additionally, it should have the ability to bioabsorb.[1]

Methods: The major component, methoxypropyl 2-cyanoacrylate (MPC), was blended with ethyl 2-cyanoacrylate (ECA) and stabilizers were added. Previously described[2] polyether-ester-urethane copolymers (Table 1) were dried then dissolved into the cyanoacrylate monomer at 80-110°C.

Table 1. Compositions of Polymeric Modifiers

Polymer Name	Poly-ether-ester Composition	Inherent Viscosity[A]
OC19	PEG/TMC/ε-Cap/gly[B]	0.35 dL/g
OC9	PEG/DL-lac/gly[C]	0.33 dL/g
OC17	PEG/DL-lac/gly[C]	0.60 dL/g

[A] At 25°C in a 0.1 percent solution of polymer in chloroform,
[B] PEG/Trimethylene carbonate/ε-caprolactone/glycolide (30/36/26/8 wt.),
[C] PEG/DL-lactide/glycolide (30/58/12 molar)

The initial viscosity (Visc) of the polymers was obtained by either using u-tube viscometry or measuring the flow time through an orifice (method chosen based on expected viscosity range). Adhesive peel strength (Peel) was measured by adhering two 7.2 pH buffer soaked strips of 10 oz. cotton canvas with tissue adhesives (25 mm wide). The samples were cured then mechanically tested to determine the maximum peel load per 25 mm. After 9 weeks at room temperature, the mechanical properties were measured again to assess stability (Table 2).

The heat of anionic polymerization of select tissue adhesives was measured by DSC using a novel modified DSC method.

Results: For this family of polymers, there is a correlation between % modifier and strength, that can be modeled logarithmically (R^2=0.87). The viscosity, however, is harder to model mathematically, and appears to be a function of composition as well as modifier amount (See Table 2).

As % modifier increases, the shelf stability of the tissue adhesive formulations decreases, as evidenced by rheometric changes over time. It appears that strength changes may occur to some degree as curing occurs, especially for the high modifier formulations.

Table 2. Properties of Polymeric Modifiers[D]

Mod-ifier	% Mod./ Form. Name[E]	Initial Properties		9 Week Prop.[F]	
		Visc, cSt	Peel, N/25mm	Visc, cSt	Peel, N/25mm
OC19	2/HTA34	7.5	43.3	15.4	51.5
	10/HTA45	50	16.8	173	15.3
	20/HTA41	256	9.5	5212[4Wk]	5.5[4Wk]
OC9	2/HTA32	6.9	64.3	7.7	54.9
	10/HTA43	38.8	18.9	1103	19.1
	20/HTA47	1150	5.9	Cured[4Wk]	Cured[4Wk]
OC17	2/HTA33	8.7	51.7	10.7	53.4
	10/HTA44	95.6	31.9	206[6Wk]	22.5[6Wk]
	20/HTA40	1468	14.4	Cured[4Wk]	Cured[4Wk]

[D]Cured=Too Viscous to test [E]Percent Modifier/Formulation Name, [F]Properties, [4Wk]4 Week Removal[6Wk]6 Week Removal

The heat of polymerizations (ΔH_p) of the tissue adhesive formulations decrease for a given modifier with increasing amounts. It should be noted that all of the formulations as well as MPC release less heat than n-butyl 2-cyanoacrylate (nBCA), an accepted alkyl 2-cyanoacrylate currently is used in commercially available products, such as Indermil® (by Covidian). As expected, ECA has the highest heat of polymerization.

Table 3. Heat of Polymerization Study Data

Polymeric Modifier	Adhesive Description	ΔH_p, J/g
ECA	Monomer	308±60
nBCA	Monomer	283±7
MPC	Monomer	243±16
HTA32	2 % OC9	185±22
HTA43	10% OC9	149±3
HTA34	2% OC19	195±8
HTA45	10% OC19	175±27

Conclusions and Recommendations: Poly-Med has developed a series of tissue adhesives compositions that provide a range of handling and strength properties. Rheometric and strength properties of these tissue adhesives are largely a function of the modifier composition. Shelf stability has been shown to decrease with increasing modifier content. This may be remedied with stabilizers or increasing modifier molecular weight. The heat of polymerization for all tested tissue adhesive formulations is lower than that of unmodified ECA, nBCA, and MPC, indicating a lower possibility for tissue damage during curing.

References:
1. Shalaby, S.W., U.S. Pat. 6,299,631 (2001)
2. Shalaby, S.W., et al., U.S. Pat. App. 12/798,458 (2010)
3. Shalaby, S.W. and Burg, Karen. Absorbable and Biodegradable Polymers. Boca Raton : CRC Press, 2004 (pgs. 60-75).