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Characteristics of Ethylene Vinyl Alcohol Copolymer (EVAL) Mixtures

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PURPOSE: To determine physical characteristics of mixtures of ethylene vinyl alcohol copolymer (EVAL) and metrizamide dissolved in dimethyl sulfoxide, liquid materials developed for embolization of arteriovenous malformations. **METHODS:** EVAL and dimethyl sulfoxide were mixed in various proportions and sterilized. The viscosity and density of each mixture was measured. Precipitation times were determined by dropping the mixtures into saline or human blood. The mixtures were filtered and the filtrates weighed. **RESULTS:** Densities and viscosities of the various mixtures differed significantly, proportionally to the concentration of EVAL. Precipitation times also differed significantly, in inverse proportion to the concentration of EVAL. Temperature and aqueous solution did not affect precipitation times significantly. The weight of the filtrate significantly increased with time but was constant for each precipitation time. Temperature significantly affected filtrate weight; aqueous solution did not. **CONCLUSIONS:** Because of their different physical properties, the various EVAL mixtures are suited to embolizing different types of arteriovenous malformations.

Index terms: Interventional materials, embolic agents; Interventional materials, liquids; Interventional neuroradiology, experimental; Arteriovenous malformations, embolization

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The EVAL mixtures are a combination of ethylene vinyl alcohol copolymer (EVAL) and metrizamide dissolved in dimethyl sulfoxide which have been developed as liquid materials for embolization of arteriovenous malformations (1). EVAL precipitates as dimethyl sulfoxide diffuses in aqueous conditions, and thus mechanically occludes the vessel lumen. The EVAL mixture has been reported an effective agent for cerebral (1, 2) and spinal arteriovenous malformations (3), and cerebral aneurysms (4). The purpose of the present study was to determine the physical properties of the various combination of the compo-

nents and to discuss their possible clinical applications.

Materials and Methods

One solution was prepared by dissolving 10.0 g of EVAL into dimethyl sulfoxide to make 100 ml (solution A). Another solution was prepared by dissolving 70.0 g of metrizamide into dimethyl sulfoxide to make 100 mL (solution B). The L-type mixture was made with solutions A, B, and dimethyl sulfoxide in the ratio of 1:1:1. The M-type mixture was made with solutions A and B in the ratio of 1:1, and the H-type mixture had solutions A and B in the ratio of 2:1. Each mixture was sterilized by filtration through a Millipore (Milford, Mass) filter of 0.22 μ m before the study.

The viscosity and density of each EVAL mixture and solution A were measured 10 times with a viscometer and a densitometer (Top Medical, Tokyo, Japan) at 37°C.

Each mixture was aspirated into a 1-cm³ tuberculin syringe, and a single drop slowly ejected from an 18-gauge needle 1 cm above a laboratory dish containing saline at 20°C or 37°C, or heparinized human blood at 37°C. The precipitation time was defined as the time it took the transparent mixture to become a white opaque membrane after contact with aqueous solutions. Measurements for each mixture were made five times with a stopwatch.

Each mixture was aspirated into a 1.00-mL volumetric pipet and injected into saline at 20°C and 37°C and hepa-

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rinized human blood at 37°C, each contained in a laboratory pot placed in an incubator bath. At every second after the injection for 15 seconds, the mixture was filtered five times through the nets of 100- μ m meshes. The filtrate of each mixture was gently rinsed by saline, dried, and weighed.

Analysis of variance followed by Student's *t* test for multiple comparison of means was used to compare the precipitation time and the weight of the filtrates. The result was declared significant if the *P* value was less than .05.

Results

In the Table the density, viscosity, and precipitation times are summarized. The density and viscosity of each mixture were significantly different, and the differences increased in proportion to the concentration of EVAL (Fig 1).

A single drop of the mixture dropped onto saline forms a floating transparent membrane. It becomes opaque and whitish centripetally from the rim to the center. Time for the rim to become opaque was rather constant at 1.2 to 1.3 seconds. However, time for the whole membrane to become opaque was longer. There were significant differences between the precipitation times of each mixture, which seemed inversely proportional to the concentration of EVAL. The elevation of temperature shortened the precipitation time, but not significantly. The aqueous solution, either saline or blood, did not significantly affect the precipitation time.

The mixture injected into saline formed a sinking mass with a whitish semitransparent membrane almost instantly after contact with the saline. With filtration, the semitransparent membrane was torn but did not pass through the filters; the initially contained liquid did. The

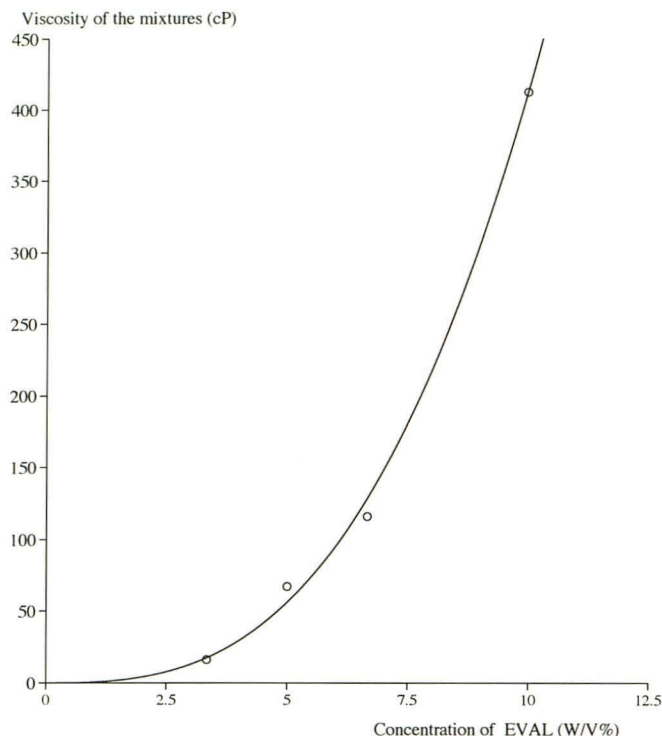


Fig. 1. The viscosity of the EVAL mixtures. The viscosity of the mixtures increases in proportion to the concentration of EVAL.

weight of the filtrate significantly increased as a function of time but was constant for each precipitation time (Fig 2). The elevation of temperature significantly increased the weight of the filtrate. The aqueous solution, either saline or blood, did not significantly affect the weight of the filtrate.

Discussion

The lower the pressure required to push a liquid material through a thin catheter the less risk there is of migration of the catheter, catheter rupture, and unexpected embolization. Hence, a liquid material with a lower infusion pressure may be more desirable. The infusion pressure versus the arterial pressure of the feeders can be expressed as $\Delta p = \mu \times (8L/\pi a^4) \times Q$ by modifying the Hagen-Poiseuille equation, that is $Q = (\pi a^4/8 \mu) \times (\Delta p/L)$. This modified equation means that the infusion pressure versus the arterial pressure (Δp) is directly proportional to the viscosity (μ) of the liquid and the infusion rate (Q), because the middle term is a constant determined by the radius (a) and the length (L) of the catheter to be used. Lower viscosity seems more desirable. Compared with other liquid embolic materials, the viscosity of the EVAL mixtures is more than that of *N*-butyl cyanoacrylate, which is about 10

Characteristics of EVAL mixtures

	Type			
	L	M	H	A
Concentration, wt/vol%	3.3	5.0	6.7	10.0
Density, g/cm ³	1.2088	1.2519	1.2953	1.3813
±SD	0.0004	0.0004	0.0006	0.0006
Viscosity, cp	16.2	67.2	116.0	412.6
±SD	0.05	0.06	0.07	0.06
Precipitation time(s)				
Saline (20°C)	11.22	10.00	7.80	6.11
±SD	0.136	0.159	0.199	0.149
Saline (37°C)	11.07	9.88	7.66	5.96
±SD	0.125	0.154	0.165	0.135
Blood (37°C)	11.05	9.87	7.66	5.98
±SD	0.130	0.155	0.178	0.138

Note.—There are statistically significant differences between the density, viscosity, and precipitation time of each mixture, but higher temperature and differences of the aqueous conditions do not significantly affect the precipitation time.

Precipitating rate

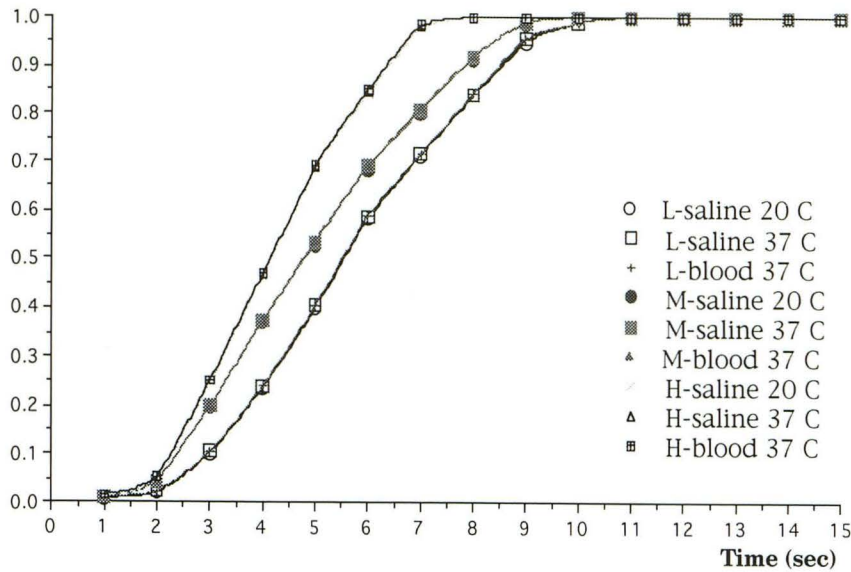


Fig. 2. Formation of precipitates. The weight of the filtrate of the EVAL mixtures significantly increases with time after contact with the aqueous conditions.

cP, but far less than that of Ethibloc, which is 200 cp (5, 6).

The suitable range of viscosity for avoidance of transvenous passage of liquids under conditions of vascular stasis has ranged from 120 to 220 cp, and the limiting viscosity for capillary transport has ranged from 300 to 350 cp (6). Liquid materials may pass the target site into the venous side with viscosities below these values. These viscosity values may define the safety range of liquid materials when used for embolization of arteriovenous malformations. A liquid with viscosity higher than these values may not reach the nidus and only occlude the proximal arteries. The viscosity of the mixtures is adjustable by changing the concentration of EVAL. Because the viscosity of the mixture increases as the dimethyl sulfoxide diffuses in the aqueous condition, and therefore, changes its viscosity within the vessel lumen, the initial viscosity of the mixture determines the extent of transport. This ability to adjust the viscosity may be an advantage of this mixture.

The precipitation time of the EVAL mixtures seems to be longer than the polymerization time of *N*-butyl cyanoacrylate (5), measured in a similar fashion. However, the concept of the precipitation time seems different from that of the polymerization time. The polymerization time is a time for the monomer of *N*-butyl cyanoacrylate to react and form the polymer. This may accurately indicate the time for *N*-butyl cyanoacrylate to function as an embolic material. The precipitation time is the time for already polymerized EVAL once dissolved in dimethyl sulfoxide to

lose its solubility. In reality, a part of the mixture begins to lose its solubility and become solid at the moment it contacts the aqueous conditions.

We have now developed three types of the EVAL mixtures and have been using them for various types of lesions (1–4). With shorter precipitation time and higher viscosity than the original EVAL mixture or the M type, the H type is not expected to flow through the lesion and to occlude more proximal vessels. H-type EVAL has been used for embolization of arteriovenous malformations with large fistulas (2) and cerebral aneurysms (4). With longer precipitation time and lower viscosity, the L type is expected to reach more distal vessels. It has been used for arteriovenous malformations with tiny fistulas (2).

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