Embolizing agents for endovascular therapies: characterization of mechanical and occlusive properties

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Introduction:

The development of minimally invasive procedures and tissue engineering strategies has led to a growing need for injectable materials. Injectable polymers are thus increasingly used to occlude blood flow in arteriovenous malformations (MAV), cancer therapy or endoleaks after endovascular aneurysm repair. However, current embolizing agents are far from ideal and clinicians seek for new injectable agents.

We recently demonstrated that chitosan-BGP thermogels could be used to create more biocompatible radioopaque injectable embolizing agent (1). These have several advantages (low toxicity, good control at injection, no risk of catheter entrapment, rapid loss of radiopacity, etc.) compared to the most popular embolizing agents at this stage, namely Onyx and cyanoacrylate-based glue. However, these hydrogels exhibit relatively slow gelation and need further optimization and characterization in regards to their gelation kinetic and mechanical properties, which determine their occlusive properties.

Here we report the characterization and optimization of chitosan-BGP hydrogels made radiopaque with iodixanol, an iodinated X-ray contrast medium, in regards to gelation rate, mechanical properties, and occlusive properties as determined using an in vitro bench test.

Materials and methods:

Chitosan (DDA= 94%) was purified and mixed with beta-glycerophosphate (BGP, Sigma) and Iopamidol (iodixanol, Bracco Diagnostics Inc.) at several ratios (1). Their gelation kinetic was studied by rheology on a Physica MCR301 (Anton Paar), by following the evolution of both storage (G') and loss (G'') moduli as a function of time at 37°C.

Gel occlusive properties were assessed on a custom-made embolization bench system designed to evaluate the ability of the gel to occlude blood flow by measuring the maximal pressure of liquid sustained by the gel-embolized tubular structure. The system consists in a syringe filled with water mixed with glycerol 40% to mimic blood viscosity. The syringe is pushed at a constant rate, leading to increasing pressure up to 250 mmHg, or until gel breaks or slides along (Fig 1). The maximal pressure sustained by the gel was determined at different time points after gelation (5, 10 min, 1h, 1 day and 1 week), in order to correlate with the mechanical properties (mainly G') obtained by rheometry.

Results:

Evolution of both storage (G') and loss (G'') moduli showed rapid gelation and increase of the mechanical properties with time for all radiopaque chitosan-BGP gels. Addition of contrast agent was shown to slow down gelation, but increasing BGP was able to counteract this effect. Radiopacity naturally increased with Iopamidol concentration and a minimum concentration of 20% v/v was identified for good visibility via x-rays. To conclude whether these properties are sufficient to occlude blood flow, the maximal pressure sustained by the gel in the in vitro bench test was determined, as a function of the nature of the embolization agent and embolization time.

One day after gelation, all gels supported up to the maximum pressure created by the bench system (>220 mmHg). At shorter time points, the pressure supported by the gels increased with BGP concentration. This can be explained by the strong effect of BGP on the gelation kinetic, and therefore on the storage modulus with time. Fig 2 thus presents the maximal pressure obtained for 12%BGP gels for various times of gelation. Five minutes of gelation is not sufficient to occlude blood flow at normal blood pressure (about 100 mmHg), despite a G' value of about 500 Pa.

Fig 1. Schematic representation of the bench test used to characterize gel occlusive properties

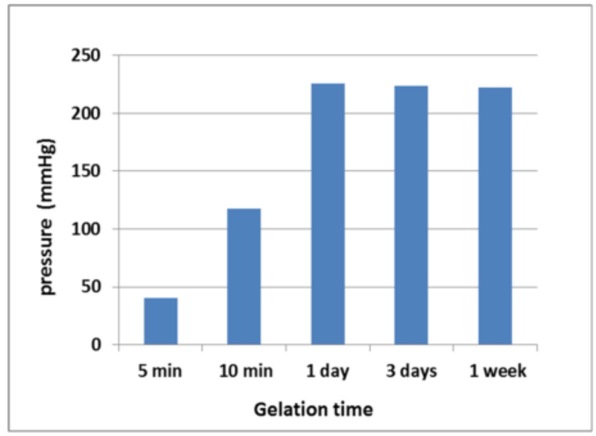

Fig. 2: Maximal pressure supported by 12% BGP gels after 5 min, 10 min, 1, 3 and 7 days of gelation.

Discussion:

Chitosan radiopaque hydrogels with a concentration of 20% or 30% v/v iodixanol appear as promising materials for embolization. However further evaluation and optimization is required to ensure that these hydrogel exhibit sufficient occlusive properties to block blood flow and prevent their migration into the blood vessels. In vitro bench tests and finite element modeling are useful engineering tools to predict the occlusive behavior of hydrogels and correlate with rheometry data.

References:

(1) Coutu et al. A new radiopaque thermogel for treatment of endoleaks after endovascular repair: Influence of contrast agent on chitosan thermogel properties. JBMR-B 2013; 101(1):153-61.

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