Development of injectable alginate/gelatin hydrogel for proper release of tranexamic acid to control the cerebral hemorrhage in rat brain damage models

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Statement of Purpose: Postoperative bleeding is one of vital challenges in brain tumor surgeries. Tranexamic acid (TXA) is a potent drug designed to speed up blood coagulation, available for both oral and injectable use. Furthermore, innovations in injectable hydrogels present exciting possibilities for medical treatment. This research utilizes an injectable hydrogel composed of alginate and gelatin, specifically formulated to mimic brain tissue mechanical properties and, at the same time, capable for delivering TXA effectively.

Methods: In this study, alginate and gelatin, with a mole ratio of 1 were used to fabricate hydrogels according to a previous published article with some modifications [1]. First, gelatin was added to deionized water and stirred at 60°C for 2 hours at a speed of 500 rpm, then the alginate powder and TXA were added to the gelatin solution and stirred at 300 rpm for 1 hour. In the next step, the solution was transferred into a microtube, and 1 ml of calcium gluconate (1% w/v), as the crosslinking agent, was added. The microtube was immediately placed on a vortex mixer and mixed for 2 minutes. A rheology test was conducted to evaluate the properties of the hydrogels and confirm their injectability. Additionally, the drug release profile of TXA was investigated in three different formulations, presented in table 1, at pH of 7.4. Subsequently, the efficacy of the gel was evaluated on brain-damaged rat models in vivo followed by the approval of the ethical committee.

Prototype	Alginate	Gelatin	TXA
A4G4	4% w/v	4% w/v	20 mg/ml
A6G6	6% w/v	6% w/v	20 mg/ml
A8G8	8% w/v	8% w/v	20 mg/ml

Table 1. Formulations of 3 different prototypes

Results: In this research, we investigated the rheological properties of hydrogel using a rotating disk. The hydrogel developed in this study exhibits injectability at a temperature of 25°C. According to Figure 1, the viscosity of hydrogels decreases with increasing shear stress.

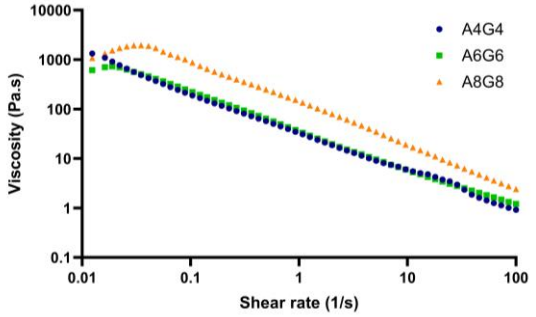

Figure 1. Rheology of hydrogel prototypes

The release of TXA from hydrogels was studied in phosphate-buffered saline (PBS) at 37°C. The results reveal a burst release, with nearly 70% drug release within 6 hours. Furthermore, almost the rest of 30% of the drug is released within 48 hours (refer to Figure 2). These findings are consistent with previous studies on releasing TXA from alginate hydrogels [2]. The A4G4 gel shows a better mechanical and drug release properties compared to the others.

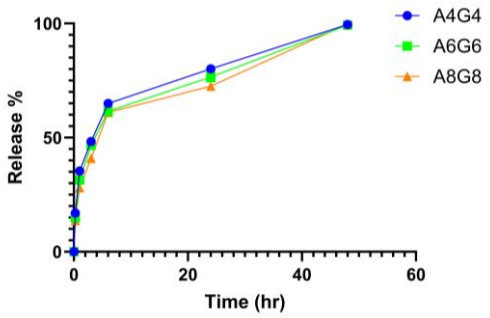

Figure 2. TXA release profile of various prototypes

An in vivo study was conducted on rat models in which an injury was intentionally caused through a specific area of the brain. After bleeding occurred, the A4G4 gel was injected into the injured area. The results prove that the gel is effective in controlling the bleeding caused by the injury.

Figure 3. Effect of hydrogel on the Brain of a rat

Conclusions: The designed alginate/gelatin hydrogel prototypes demonstrate a proper injectability property. The TXA controlled release of all prototypes exhibit a similar profile with slightly higher rate for A4G4 samples. The effectiveness of bleeding control of the A4G4 prototype is significantly determined on rat brain tissue.

References:

1. Distler T, JMBBM, 2020;111: p. 103979.
2. Halawany EL, Pharmaceutics, 2022;14(10): p. 2255.