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Fibrin hydrogel as a novel delivery agent for local anesthetics: issues in demonstrating its efficacy at in vitro level

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ABSTRACT

There is an identified need within the field of pain management to optimise the delivery of local anaesthetic agents as slow release formulations. Fibrin gel has shown huge potential for the local delivery of drugs including antibiotics, vasodilators, and chemotherapeutic agents however its potential for the delivery of local anaesthetic drugs has not, as yet, been fully investigated. Early randomized controlled trials have demonstrated efficacy, but to date, these have been relatively few and report the gross effect rather than specific kinetics. 1-3 The authors designed an in-vitro study aiming to evaluate sustained release of a local anesthetic agent from loaded fibrin gels over time.

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Some approximation was necessary in the methodology, as fibrin delivery of local anesthetics had not previously been investigated in vitro. Previous studies have addressed either local anaesthetic release from other delivery agents [4] or other drug release from fibrin gels. [5] Shemash et al. investigated controlled release of bupivacaine and ibuprofen from manufactured hybrid structures. [4] As part of their study bupivacaine loaded disc-shaped hybrids were immersed in vessels of phosphate buffered saline (PBS). At designated time intervals samples were withdrawn for analysis and the PBS medium replaced. Bupivacaine concentrations within the samples were assessed with high performance liquid chromatography (HPLC). HPLC has been validated as a rapid,

sensitive and reproducible method of measurement of bupivacaine in plasma using a reversed- phase method. [6-7] The use of ultraviolet detection at 254nm enabled a limit of detection of 25ng/l to be achieved with a retention time of 3.8 minutes.

In this study fibrin gels loaded with bupivacaine and a control of fibrin gels without bupivacaine were immersed in phosphate buffered saline (PBS) and incubated at 37 degrees C. Loaded fibrin gels were prepared by mixing one part of a solution (250 ul) containing bupivacaine, with one part (1:1) of fibrinogen solution (91mg/ml fibrinogen and 3000KIU/ml synthetic aprotinin). Gels were obtained by the addition of 250 ul thrombin solution (4IU/ml diluted in 40 µmol/ml calcium chloride) and letting the reaction proceed for 30 min at 37 °C. At designated time intervals samples were withdrawn for analysis and the PBS medium replaced. Bupivacaine concentrations within the samples were assessed with HPLC. Preliminary testing with bupivacaine estimated a similar retention time and limit of detection comparable to previous studies. There was a single large peak at retention time of 3.53 minutes in the generated HPLC chromatogram from injection of a standard solution of 0.25% w/v bupivacaine (Figure 1a), assumed to represent bupivacaine. However the control in the experiment showed multiple peaks of a similar response and retention time. The baseline of the generated chromatogram from the control samples at 2 hours, predicted to be flat line as the sample contained no bupivacaine, showed multiple peaks are seen at retention times 2.13 to 3.27 minutes suggesting detection of another compound, assumed to be fibrin (Figure 1b). It had a similar peak response and retention time to bupivacaine. The chromatogram from samples taken from fibrin gel loaded with bupivacaine had multiple peaks at 2.52 to 3.44 minutes assumed to be from detection of both fibrin and bupivacaine (Figure 1c). Simultaneous detection of fibrin and bupivacaine resulted in multiple closely relate peaks that were unable to be separated for analysis.

During the experiment it was expected the fibrin gels would undergo fibrinolysis and would therefore be present in samples withdrawn. However it was not expected that fibrin would be detectable by HPLC at the wavelength selected for bupivacaine, or that this wavelength would produce a similar peak response and retention time as bupivacaine. This had not previously been described in the literature. Alternative methods of determination were considered and the following are suggested for further in vitro testing. Ultrafiltration of collected samples, using a semi-permeable dialysis membrane suitable for low molecular weight compounds, could allow separation of fibrin degradation products from bupivacaine. Similarly, coupling HPLC with mass spectrometry could separate compounds in collected samples, basic on their ionic charge. The resulting extracted ion chromatograms could then be analyzed.

Manufactured fibrin gels are hugely desirable drug delivery systems. Fibrin delivery of local anaesthetic remains an area of development with potential to translate into positive clinical outcomes. This study is the first to investigate its efficacy at an in vitro level. Although results yielded were not suitable for analysis it has provided important recommendations for future testing in this field.

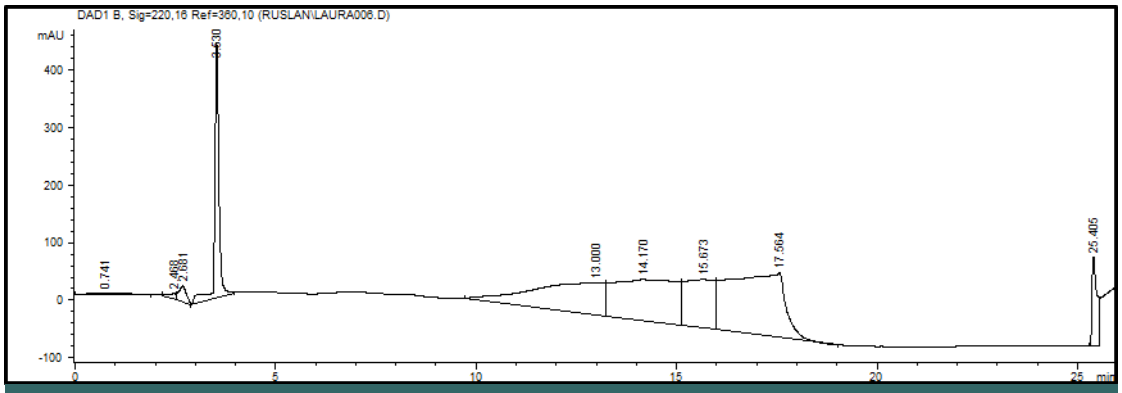

Figure 1(a) - HPLC chromatogram of standard solution of 0.25% bupivacaine

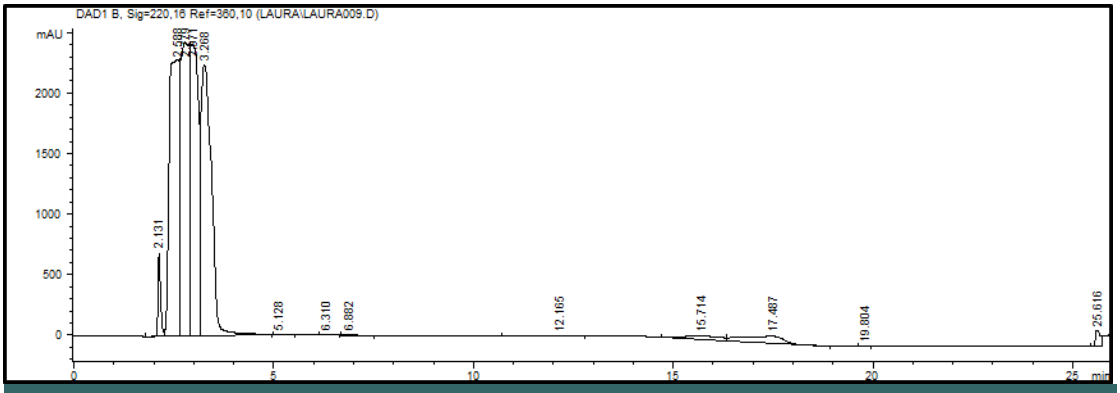

Figure 1(b) - HPLC chromatogram of control sample

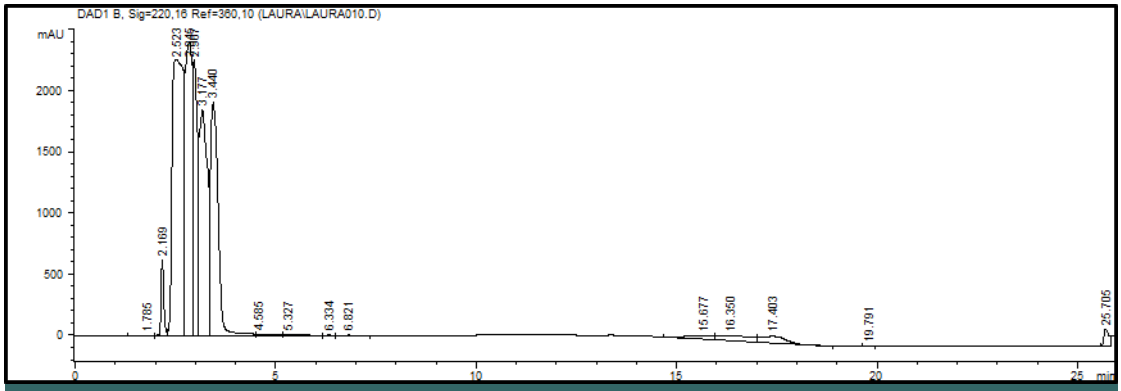

Figure 1(c) -HPLC chromatogram of sample from bupivacaine-loaded fibrin gel

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