SRPe Scottish Research Partnership in Engineering

NMIS National Manufacturing Institute Scotland

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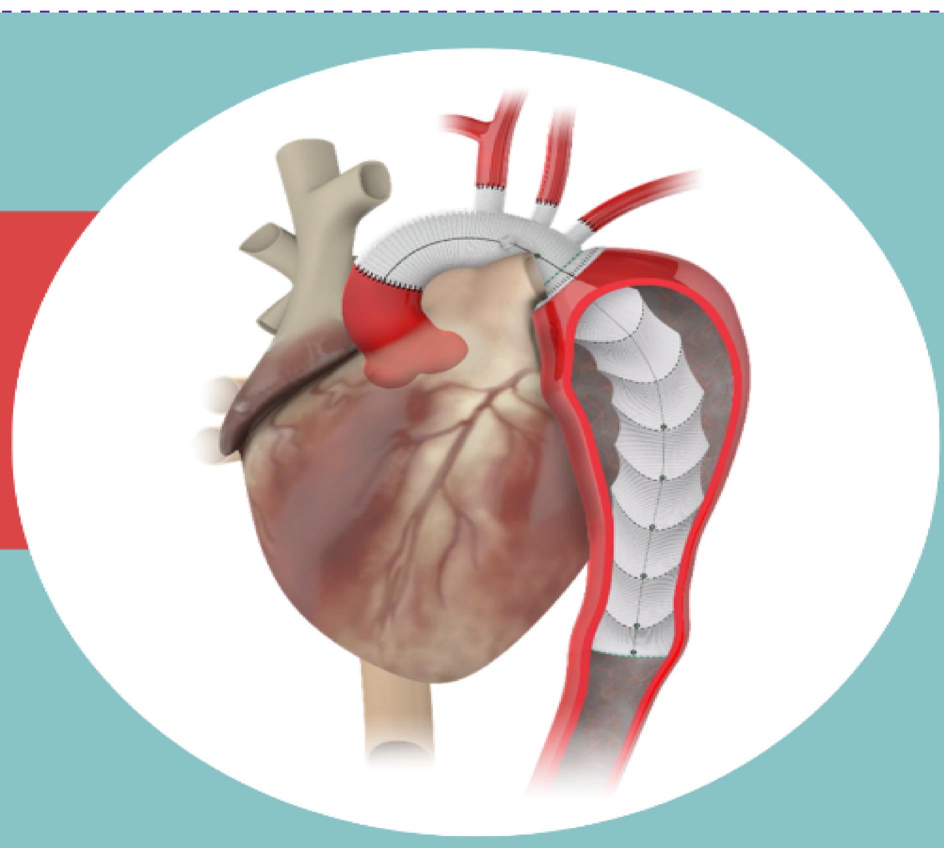
TERUMO Aortic

Advanced Manufacturing for Vascular Graft Sealant Technology

Kirsty Goudie/ Terumo Aortic / Prof. John J. Liggat

ADVANCED MANUFACTURING FOR VASCULAR GRAFT SEALANT TECHNOLOGY

Terumo Aortic (TA) is a global leader in the design and manufacture of vascular grafts for open surgery, currently producing 120,000 synthetic grafts per year for life-saving arterial replacement to treat patients with aortic disease. A key component of the market sucess of these products is the gelatin impregnation sealing technology which makes the grafts impermeable to blood leakage when implanted but which degrades over a period of approximately 14 days in-vivo to allow unimpaired tissue incorporation into the matix of the graft.



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INTRODUCTION

Gelatin is utilised in the medical field due to a number of favourable properties:

- Biodegradable & biocompatible
- Temporary scaffold for cell attachment
- Abundant & inexpensive
- Non-immunogenic
- Can be easily modified

Patient healing is influenced by the rate of tissue incorporation into the matrix of the graft. Therefore, the sealant properties are extremely important. Hydrogels are held together by weak interactions that are easily broken down above 30 °C. To improve the material properties, chemical crosslinking is often carried out. This allows these hydrogels to be used at body temperature (37 °C). A balance must be achieved as an overly crosslinked sealant would be brittle, influencing handling and permeability. The extent of crosslinking can be controlled by chemically modifying the gelatin. TA use a mixture of modified (succinylated) and unmodified gelatin to achieve the optimum sealant. Succinylation is the reaction between succinic anhydride and the lysine residue. Lysine is involved in chemical crosslinking reactions so blocking this group allows the extent of crosslinking to be controlled.

FURTHER INFORMATION

Gelatin hydrogel properties are influenced by the charges located on the amino acids of gelatin.

The isoelectric point (IEP) is the pH at which the protein is electrically neutral. If the pH is above the IEP, the surface charge of gelatin is negatively charged. If the pH is lower than the IEP, the surface charge of gelatin is positively charged.

Understanding the influence of pH is essential as it effects the properties of the material i.e. how the protein structure packs and ultimately determines the accessibility of amino acid sites for modification and crosslinking.

OBJECTIVE

To develop a better understanding of the succinylation process and the parameters that influence the reaction success. To identify any key factors and optimise the procedure in order to maintain supply of this critical raw material.
To study material properties pre- and post-modification.
Finally, to investigate and understand the transition from lab scale to commercial production with focus on repeatability and quality control.

OPTIMISATION WORK

Strict pH control ⩾ pH 7 is essential for reaction success.

100% modification can be achieved by using reactant in excess.

The degree of modification can be relatively easily controlled by altering the mass of reactant added (Fig 1).

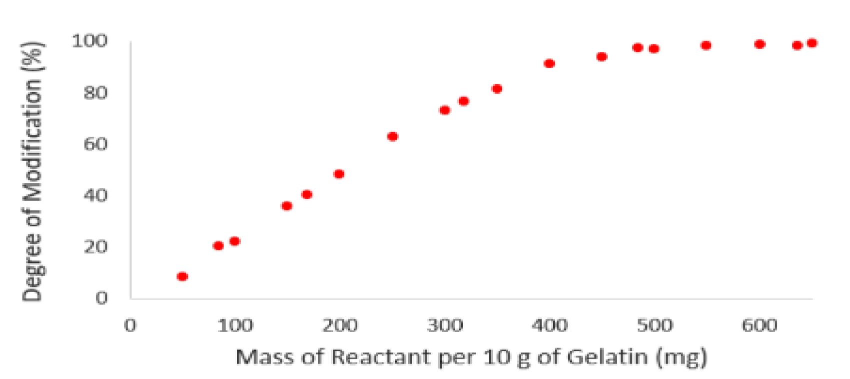


Fig 1: Degree of modification vs mass of reactant added

PH WORK

Functional group changes as a function of pH can be probed using NMR spectroscopy (Fig 2).

At acidic pH values charged amino acids such as aspartic and glutamic acid become protonated. This changes the electronic environment and causes the associated peaks to shift to higher ppm values.

This is also observed in peaks associated with the succinylation modification.

Additionally, changes in peak intensity are observed in the amide region of the spectra. At acidic pH the signals are the most intense as the amide protons are more strongly bound. However, as the pH increases the amide signals get less intense due to changes in the electronic environment which result in the protons being less tightly bound to the gelatin meaning they can exchange with the solvent (hydrogen-deuterium exchange).

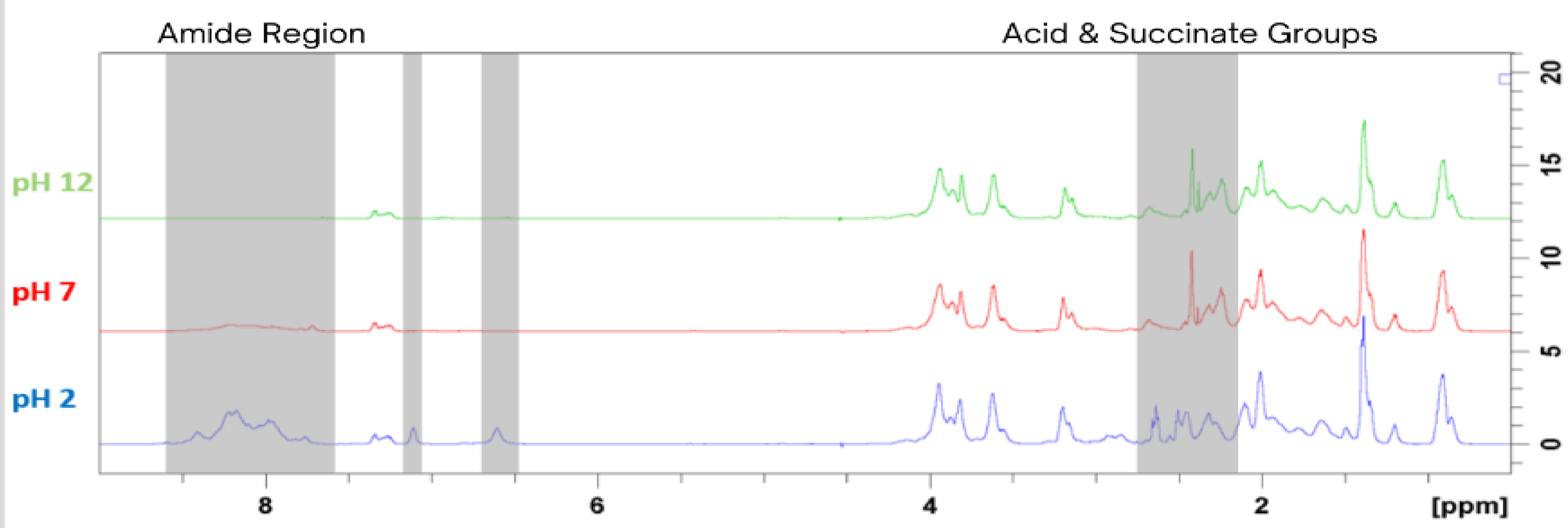


Fig 2: Proton NMR spectra of succinylated gelatin at different pH values

CONCLUSION

The succinylation process is now well understood with the ability to control the extent of modification.

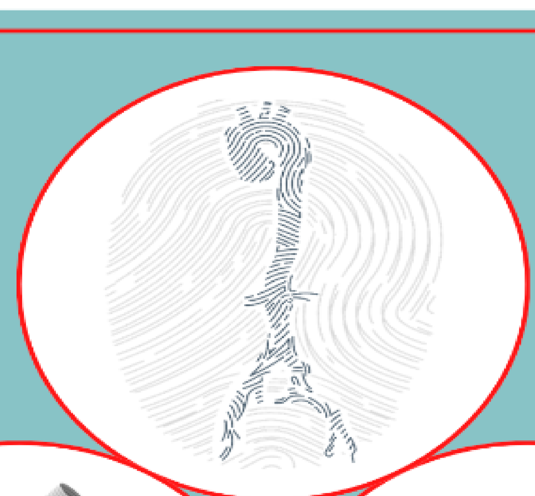
Materials can be well characterised by NMR spectroscopy and the chemical shift changes can be tracked as a function of pH.

Scale up development has also been carried out with third party companies, where we have successfully modified gelatin at 100 litre scale and developed purification solutions.

FUTURE WORK

To study how factors such as pH and impurities influence the properties of gelatin i.e. swelling, mechanical and relaxation behaviour and relating back to changes observed at the molecular level.

To research alternative modifications and crosslinking chemistry.



ACKNOWLEDGEMENTS

I would like to thank my academic supervisor J. J. Liggat and my industrial supervisor G. Clarke for their help throughout my research. I would also like to thank the rest of my research group and the R&D department at Terumo Aortic for all of their helpful inputs into my research.

Scottish Funding Council
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