ADHESIVE SEALANT BIOMATERIALS

Clinical Series

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The fate of TissuePatch: Tissue response and *in vivo* degradation.

Introduction

The TissuePatch product family comprises a series of Class III implantable medical devices that were first approved for clinical use in 2007. To date in excess of 15,000 devices have been supplied to surgeons worldwide for use as adjuncts in the control and prevention of air, blood or fluid leakage in a range of surgical procedures.

Aside from product efficacy, the biocompatibility of the product family has been established in accordance with the ISO 10993 (Biological evaluation of medical devices) series of standards. These tests cover a well defined and broad range of areas including cytotoxicity, systemic toxicity, sensitisation, carcinogenicity, genotoxicity. This rigorous scrutiny provides users of the products with confidence that they have been certified safe for use.

The purpose of this technical bulletin is to provide a summary of the *in vivo* tissue response to TissuePatch (TP) and its two polymer constituents, poly(lactide-co-glycolide) (PLGA) and Tissuebond™ (formerly known as Terpolymer) – the self adhesive component of the device.

Materials and Methods

Three different materials (all sterile) were examined during the course of this study.

- Standard TissuePatch
- 10µm PLGA film
- 10µm Tissuebond™ film.

The *in vivo* method used is a well defined model for investigating the tissue response to medical devices involving subcutaneous (SC) implantation of the materials defined above. The size of material implanted into each subject (at two different sites) was proportional to the current recommended maximum human dose of 200cm^2.

Following implantation, a single 5/0 Prolene suture was inserted in the midline between both sites in order to identify the implantation site.

Subjects were recovered for 2, 6, 12 and 24 weeks.

Results

As observed with all implantable medical devices, TissuePatch and its associated components elicit a foreign body response. This response is inflammatory in nature and its magnitude declines with time.

The response to the two components, PLGA and Tissuebond™ was equivalent in respect of the type of response, namely a chronic inflammatory response, involving macrophages and in some instances giant cells which actively remove the implanted materials (figure 1).

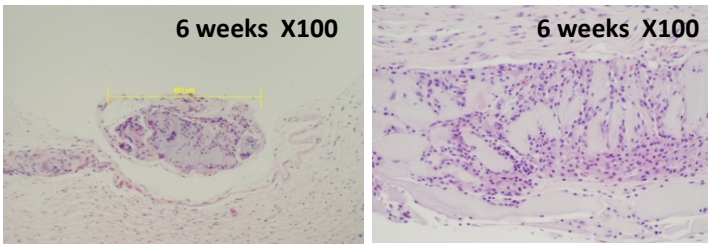

Figure 1: Photomicrographs of histological sections of PLGA *(left)* and Tissuebond *(right)* implanted subcutaneously.

After a period of 12 weeks no visible remains of PLGA were evident, the only visible signs being an area of mildly responsive tissue (figure 2).

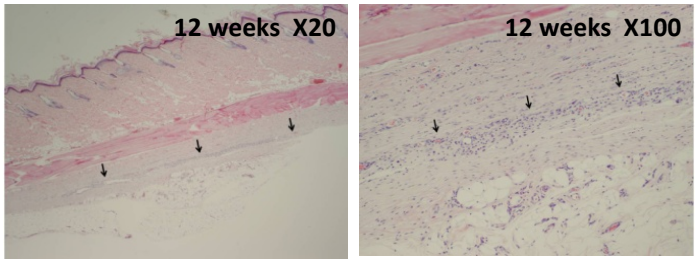

Figure 2: Photomicrographs of histological sections of PLGA implanted subcutaneously. Arrows indicate the area of responsive tissue but no visible remains of material.

In the Tissuebond™ group remains of material and/or what is likely to be associated crosslinked proteins were evident at each time point, both in subjects treated with Tissuebond™ alone and those receiving TissuePatch. The amount of material remaining and the response to these remains declined as a function of time following implantation. These changes are summarised in low and high power micrographs in figures 3 and 4.

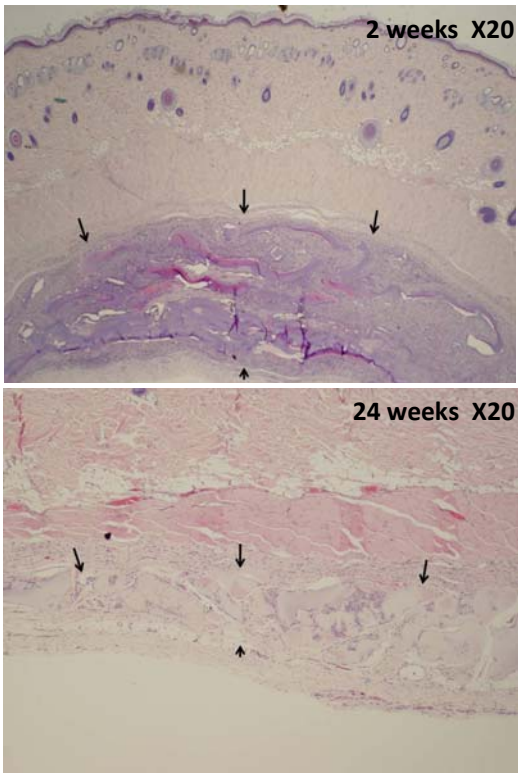

Figure 3: Photomicrographs of histological sections of TissuePatch implanted subcutaneously.
Arrows indicate the location of material remains.

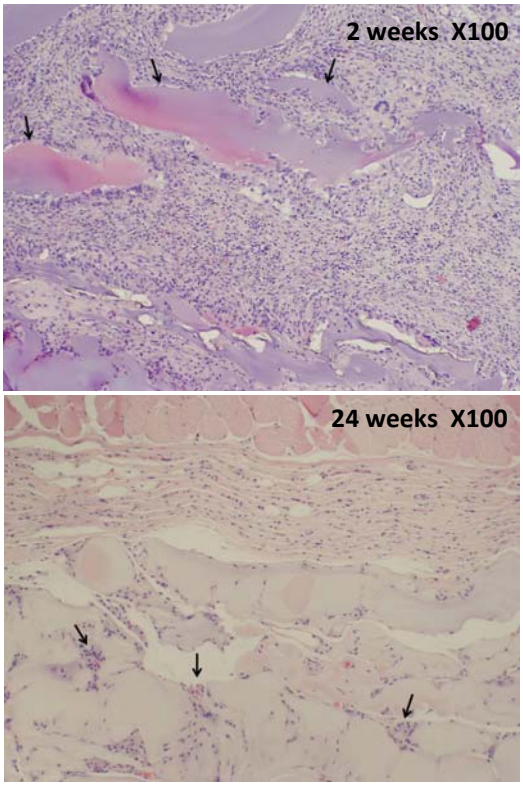

Figure 4: Photomicrographs of histological sections of TissuePatch implanted subcutaneously.
Arrows indicate the location of material remains and active removal by macrophage activity.

Discussion

This review details the fate of TissuePatch and separately its constituent materials by observing histological findings in a preclinical model.

PLGA is a well characterised biodegradable polymer and various blends are used in a number of medical devices, including degradable sutures such as Vicryl™ and Polysorb™, the absorption of which are reported to be complete between 56 and 70 days. The findings of this study are consistent with the expected absorption profile.

Tissuebond is prepared by the co-polymerisation of vinyl pyrrolidone and acrylic acid monomers, and the subsequent functionalisation of half of the acrylic acid groups with N-hydroxysuccinimide (NHS). This component of TissuePatch does not incorporate the same hydrolysable ester bonds that are present in PLGA. Consequently, the mode and rate of degradation of Tissuebond differs from that of PLGA. In addition to facilitating adhesion to tissue surfaces, the NHS active chemistry present on Tissuebond crosslinks proteins that are present at the site of application. Therefore, the material remaining at the site includes a combination of the Tissuebond polymer and crosslinked proteins, the latter of which results in an apparent swelling of the material, although the very thin nature of the implanted film means this is unlikely to have clinical significance.

Conclusion

The tissue response following implantation and during degradation/resorption of TissuePatch (and its constituent materials) has been examined. In summary:

- The response is characterised as a typical foreign body reaction, mildly inflammatory and fibrotic in nature;
- The intensity of the tissue response declines with time and is classified as mild to minimal over the duration of the study;
- The response to TissuePatch is defined by that of the Tissuebond adhesive;
- PLGA degrades at a faster rate than Tissuebond, with all traces removed by week 12, leaving a small area of responsive tissue;
- The residual material at the site of implantation represents Tissuebond that has not yet degraded, together with proteins crosslinked by Tissuebond.

TissuePatch is a fine, synthetic, absorbable, self-adhesive film designed to act adjunctively to sutures and other closure methods to minimise undesirable leakage of air, blood or other fluids from bodily tissues. This study investigated the fate of the material over time following implantation and concludes that histologically the response of tissues to the presence of this particular foreign body is typical, mild and predictable.