Resorbable Temperature-Responsive Hydrogels Are Biocompatible Controlled Release Vehicles

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Statement of Purpose:

Previously, we have reported on the novel controlled release properties of temperature-responsive hydrogels based on copolymers of *N*-isopropylacrylamide and Jeffamine® M-1000 acrylamide (1,2). Benchtop data shows that these hydrogels are viscous, provide sustained release of antimicrobials over 1-7 days, and undergo degradation in 9-40 days. We are now investigating the potential of these materials as controlled release carriers for antimicrobial delivery in orthopaedic applications, such as total joint arthroplasty. Delivery of antimicrobial to prevent infection will require gel degradation and replacement by healthy tissue during the healing process. In this study, we investigated the biocompatibility of these hydrogels with 2 degradation times in soft and hard tissue sites at 2 and 6 weeks.

Methods:

Polymers (abbreviated PNDJ) were synthesized by radical polymerization of NIPAAm, DBLA, and JAAm with either 15 or 22 wt% JAAm relative to NIPAAm in the feed. Properties of the polymers are summarized below.

	PNDJ15	PNDJ22
NIPAAm (mol%)	92.2 %	91.7%
DBLA (mol%)	6.6%	6.3%
JAAm (mol%)	1.2%	1.9%
Mw (Da)	36890	35920
Initial LCST	21°C	24°C
Deg. Time (37°C)	40 days	15 days

Sprague Dawley rats (~300 g) were injected with 100 uL of gel in 4 sites each (2 intramedullary femur percutaneously from the knee, 18G needle, 2 intramuscular quadriceps, mid-thigh, percutaneous, 18G needle). Methyl cyanoacrylate (MCA) and saline were used as positive and negative controls, respectively. The table below shows the experimental enrollment. Each number corresponds to one quadriceps and one marrow space injection.

	pNDJ 15	pNDJ22	MCA	Saline
2 week	4	4	2	2
6 week	2	2	2	2

Upon sacrifice, the legs were dissected, preserved in 10% formalin and then decalcified. After decalcification, specimens were mounted in paraffin and sectioned. Sections were taken 1 cm in each direction from the mid-thigh injection point at 2 mm intervals. Sections were stained with hematoxylin and eosin and supplied to the pathologist (AD) for interpretation. The pathologist was blinded to the identity of the sample analyzed and samples were presented in random order. ASTM F-981 was used as a guide in interpreting the pathologist report on each specimen.

Results:

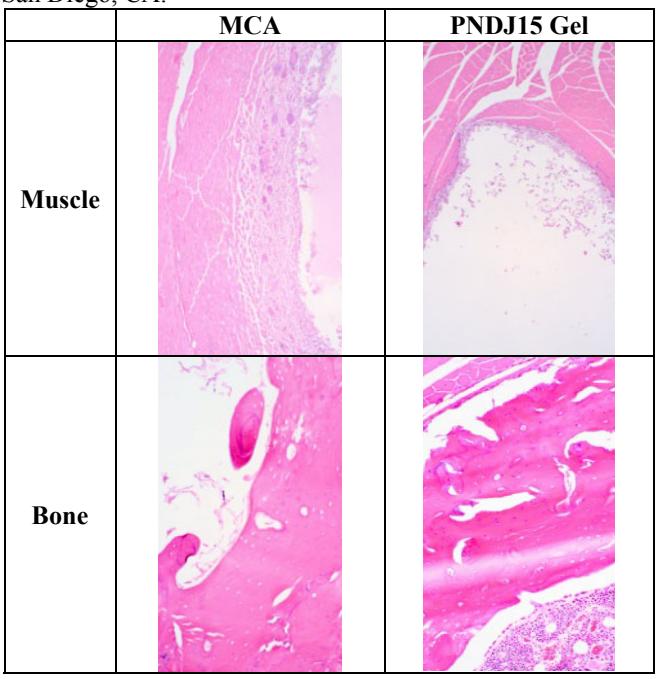

Figure 1: Representative Histological Sections at 2 wk.

For MCA (positive control), material was found in 10/10 slices upon sacrifice at 2 weeks in both soft and hard tissue sections. For PNDJ15, material was found in 3/10 slices in soft tissue and in 0/10 slices in hard tissue. Bone and marrow exposed to MCA showed large areas of dead bone (Fig. 1), with some areas of osteogenesis. Bone exposed to PNDJ15 had live bone in all sections, and by 2 weeks, most of the space had been re-filled with healthy bone marrow. Muscle exposed to MCA had large areas of lymphocytic activation, banding, and apoptotic muscle cells. Muscle exposed to PNDJ15 had a thin layer of foamy macrophages present, but little evidence of scar formation or swelling. Results were similar for across all formulations of PNDJ gels, excepting degradation time.

Conclusions:

PNDJ hydrogels were well-tolerated following injection in both soft and hard tissue sites, leading to minimal tissue reaction upon in vivo implantation. There is minimal tissue reaction and foreign body response to the polymer, similar to many other biomaterials. The desirable swelling properties identified *in vitro*, and short degradation time of the material are maintained in the *in vivo* setting. This study provides reliable evidence that PNDJ hydrogels are likely to be biocompatible for intramedullary and soft tissue drug delivery.

References:

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2. Overstreet D, Hyunh R, Jarbo K, McLemore R, Vernon B. In situ forming, resorbable graft copolymer hydrogels providing controlled drug release. J Biomed Mater Res A. 2012 Oct 31. [Epub ahead of print]