

# Development of a Local, Sustained Delivery Vehicle for Zoledronic Acid to Treat Osteolysis

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## Introduction

Osteolysis (bone destruction) and the related pain negatively impact the quality of life for cancer patients with skeletal metastases.<sup>1</sup> Zoledronic acid (ZA) is a third-generation bisphosphonate that inhibits bone resorption and has been successful in reducing morbidity in several cancers.<sup>2,3</sup> IV delivery, however, is inefficient and is associated with devastating side effects, such as osteonecrosis of the jaw.<sup>4,5</sup> The purpose of this study was to improve delivery of ZA to the local tumor environment to inhibit osteolysis and cancer-related pain.

## Methods

ZA monohydrate was mixed into poly(methyl methacrylate) (PMMA) powder by hand and subsequently polymerized by addition of methyl methacrylate monomer. The weight ratios of drug to polymerized bone cement used were 0, 1, 2, 5, and 10%. For release studies, the PMMA dough was pushed into cylindrical molds that were 3 mm radius and 10 mm height. After 1 day, the cylinders were immersed in 5 mL phosphate-buffered saline at pH 7.4, and left to incubate at 37°C. Supernatant was collected and replaced every day for 1 week, and subsequently once a week for two months. Drug release was detected through HPLC at 220 nm wavelength, with a peak retention time of 4.4 minutes.<sup>6</sup>

Compression testing used PMMA molded into cylinders of 2.25 mm radius and 9 mm height, a ratio chosen for its proportionality to the ASTM F451-08 standard (3 mm radius, 12 mm height).<sup>7</sup> The same drug loadings as above were used. One day after preparation, samples were compressed at 25 mm per minute until failure on a Bose ELF 3300 mechanical testing system. Compressive modulus was calculated from this data.

## Results and Discussion

Lower amounts of ZA did not significantly compromise the compressive modulus of PMMA (Figure 1). Specifically, at 1, 2, and 5% (w/w), no significant change in the compressive modulus of PMMA was observed. At 10% (w/w), however, ZA significantly decreased the compressive modulus of PMMA ( $p < 0.001$ ). These data indicate that low weight percentages of ZA do not significantly change the mechanical properties of PMMA.

Figure 2 shows loading-dependent release of ZA from PMMA over the first week of incubation. Bisphosphonate concentrations measured at 3 days were larger than those at 1 week, with the effect was more pronounced at higher drug loadings. These first order release kinetics are similar to what is observed for antibiotic-loaded bone cement.

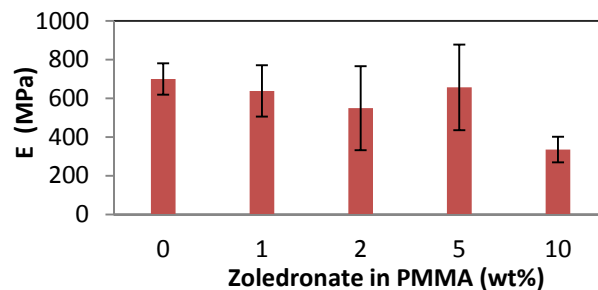


Figure 1: Compressive modulus vs. loading of ZA in PMMA. Data are mean  $\pm$  SD, n = 6.

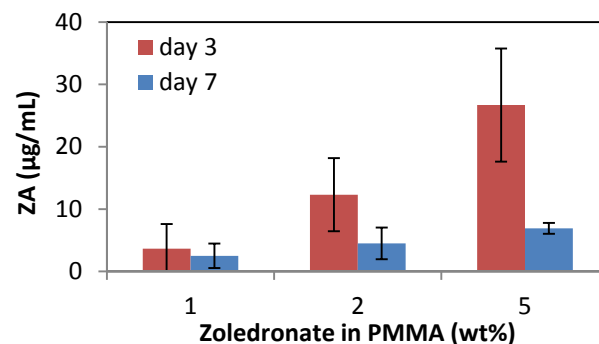


Figure 2: ZA release over 1 week vs. loading of ZA in PMMA. Data are mean  $\pm$  SD, n=3.

## Conclusion

ZA loading into PMMA between 1 and 5 w/w% did not alter the compressive modulus of the bone cement and resulted in sustained release of the drug at 1 week after polymerization. Therefore, ZA addition to PMMA may provide an improved delivery system to areas of cancer-related osteolysis.

## References

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## Acknowledgements

This research was funded by a Peter and Carmen Lucia Buck Clinical and Translational Research Grant from the Markey Cancer Center, University of Kentucky.