Dual Drug Loaded UHMWPEs for the Development of Antibacterial Implant Materials for Joint Replacement

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INTRODUCTION: Total joint replacement surgeries are pivotal for improving the musculoskeletal function and the quality of life of patients. Complications include severe pain and peri-prosthetic joint infection (PJI), which can be burdensome for the patient. Ultra-high molecular weight polyethylene (UHMWPE) is used in most of the total joint replacement as a load bearing component due to its optimized wear resistance[1]. UHMWPE can be loaded with analgesics, antibiotics and non-steroidal inflammatory agents[2,3]. In this study, we hypothesized that the incorporation of both analgesic and antibiotic drugs inside UHMWPE could be beneficial for addressing common complications of these surgeries and for providing a combined antibacterial activity of the implant material based on additive drug combinations.

METHODS: Dual drug loaded UHMWPEs were prepared by blending and compression molding. The antibiotic gentamicin sulfate and the analgesic bupivacaine hydrochloride (melting point >250 °C) or bupivacaine free base (melting point ~108 °C) were incorporated into UHMWPE by mechanical mixing at various drug loading (from 0.5 to 7 wt.%). The blends were compression molded (170 °C for 10 or 20 min depending on the thickness, under 20 MPa, cooling under the applied pressure). Blocks were obtained either as homogeneous drug loaded UHMWPE or as layered composite with various ratios of a virgin UHMWPE layer and a drug loaded one. Prior to molding, selected blends were dehydrated for 18-24h at 90 °C under vacuum. Tensile test was performed according to ASTM D638-10 at a crosshead speed of 10 mm/min. Double notched coupons (6.35×12.7×63.5 mm^3) were tested for Izod impact strength (ASTM F648-14). The antibacterial activity of samples (3×5×10 mm^3, n=3, control: virgin UHMWPE) was investigated by incubating them with 1.35ml of 10^5 CFU/ml *Staphylococcus aureus* (ATCC 12600) in Mueller Hinton broth at 35 °C under shaking. The bacteria viability was determined by a luminescence assay (BacTiter-Glo™, Promega)[4]; the remaining solution was centrifuged, and the bacteria were resuspended in fresh broth.

RESULTS SECTION: The antibacterial activity of gentamicin loaded UHMWPE was highly dependent on the drug loading (**Figure 1**): while elution from 5% gentamicin-blended UHMWPE could eradicate bacteria, elution from 0.5% gentamicin-blended UHMWPE was only inhibitory until day 3. The addition of bupivacaine hydrochloride significantly improved the antibacterial properties by achieving full eradication in 2 days, while bupivacaine free base could provide growth inhibition up to 3 days under the test conditions. Tensile mechanical properties were dependent on the drug loading and selection: a total drug loading of 5% led to an ultimate tensile strength (UTS) greater than 30 MPa and a elongation at break (EAB) greater than 300 % (**Table 1**).

DISCUSSION: A complimentary and additive antibacterial activity was found for the 0.5% gentamicin + 4.5% bupivacaine HCl loaded UHMWPE compared to 5% gentamicin loaded UHMWPE. Differences in the drug elution kinetics and solubility could explain the improved antibacterial performances of the salt form of bupivacaine compared to its free base form. Loading UHMWPE with additives decreased the tensile properties, especially for the case of bupivacaine HCl, while loading the free base resulted in a lower decrease. The overall mechanical properties of this composition could also be improved by adopting a composite layering approach. Based on our previous work, we expect the impact strength to be a linear function of the drug thickness layer to the total thickness ratio (Izod impact strength for virgin UHMWPE: 147 ± 3 kJ/m^2)[2].

SIGNIFICANCE/CLINICAL RELEVANCE: This study demonstrates the possibility of leveraging dual drug loaded UHMWPE for an optimized antibacterial effect based on the use of additive drug combinations of antibiotics and analgesics. The elution of the analgesic can also help addressing post-surgical pain after joint replacement. The development of novel antibiotic/analgesic loaded UHMWPE is a promising avenue for the optimization of therapeutic implant materials.

REFERENCES: 1. E. Oral, O.K. Muratoglu, Polyethylene for Total Joint Replacement Implants, in: M. Mishra (Ed.) Encyclopedia of Biomedical Polymers and Polymeric Biomaterials, Taylor & Francis, New York, 2015; 2. S. Grindy et al., Acta biomaterialia 93, 63-73, 2019; 3. V.J. Suhardi et al., Nature Biomedical Engineering, 1: 0080, 2017; 4. A. Sekar et al., J. Vis. Exp. (193), e64641, 2023.

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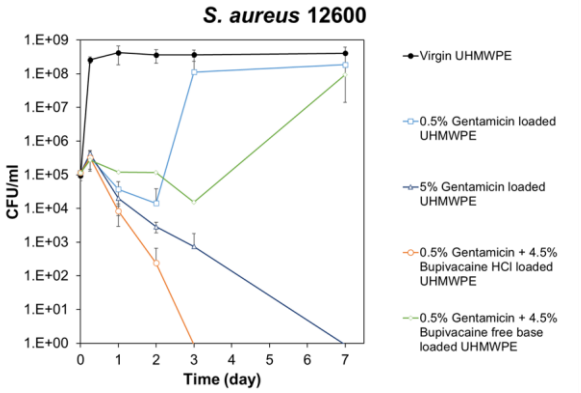

Figure 1 *Antibacterial activity of selected UHMWPE based blends against S. aureus 12600.*

Composition	UTS (MPa)	EAB (%)
Virgin UHMWPE	50.8 ± 2.5	448 ± 34
0.5% Gentamicin loaded UHMWPE	42.9 ± 2.3	373 ± 11
5% Gentamicin loaded UHMWPE	37.7 ± 0.9	356 ± 17
7% Gentamicin loaded UHMWPE	30.6 ± 1.2	340 ± 19
0.5% Gentamicin + 4.5% Bupivacaine HCl loaded UHMWPE	32.9 ± 0.5	333 ± 10
0.5% Gentamicin + 6.5% Bupivacaine HCl loaded UHMWPE	24.6 ± 0.6	272 ± 9
0.5% Gentamicin + 4.5% Bupivacaine free base loaded UHMWPE	38.6 ± 3.2	360 ± 12

Table 1 *Tensile properties of UHMWPE based blends.*