Supplementary Information

Synergistic Antibacterial Drug Elution from UHMWPE for Load-Bearing Implants

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List of prepared materials

Table S1. List of the prepared compositions. BP HCl: bupivacaine hydrochloride; BP base: bupivacaine free base; VC: vancomycin hydrochloride; GS: gentamicin sulfate.

	Name of the formulation	**BP HCl (wt.%)**	**BP base (wt.%)**	**VC (wt.%)**	**GS (wt.%)**	**Total drug loading (wt.%)**
Single drug loaded UHMWPE	0.5%GS	0	0	0	0.5	0.5
	1%VC	0	0	1	0	1
	5%GS	0	0	0	5	5
	5%VC	0	0	5	0	5
	5%BP HCl	5	0	0	0	5
	5%BP base	0	5	0	0	5
	7%GS	0	0	0	7	7
	7%VC	0	0	7	0	7
	7%BP HCl	7	0	0	0	7
	10%BP base	0	10	0	0	10
Dual drug loaded UHMWPE	0.5%GS+4.5%BP HCl	4.5	0	0	0.5	5
	0.5%GS+4.5%BP base	0	4.5	0	0.5	5
	0.5%GS+6.5%BP HCl	6.5	0	0	0.5	7
	0.5%GS+9.5%BP base	0	9.5	0	0.5	10
	1%VC+4%BP HCl	4	0	1	0	5
	1%VC+6%BP HCl	6	0	1	0	7
	BP doped 1%VC	0	<10	1	0	<10

Fourier Transform Infrared Spectroscopy (FTIR) peak absorbances for evaluating spatial distribution of incorporated bupivacaine.

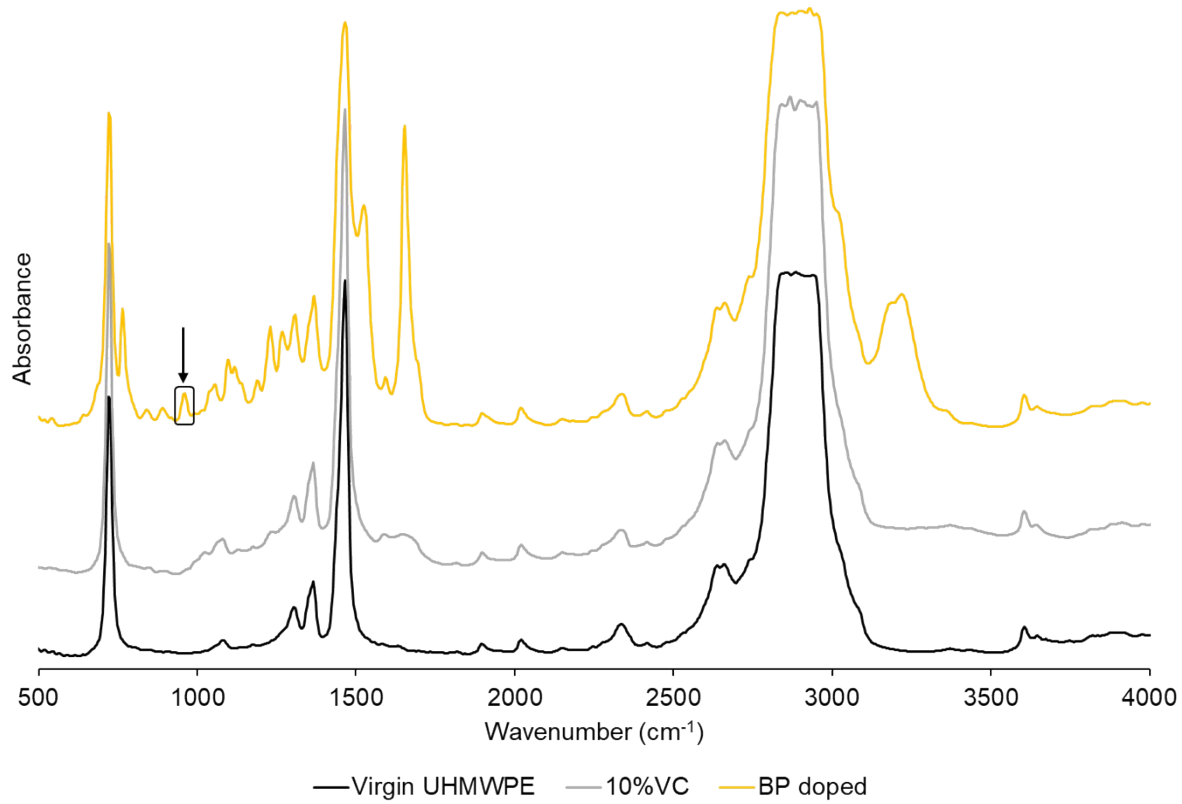

Fig. S1. Representative FTIR spectra for virgin UHMWPE (black), 10% vancomycin loaded UHMWPE (10%VC, grey) and bupivacaine doped UHMWPE (BP doped, yellow). The black arrow indicates the peak selected for the FTIR bupivacaine index.

The comparison between the FTIR spectra of virgin UHMWPE, vancomycin loaded UHMWPE and bupivacaine doped UHMWPE led to the identification of the FTIR bupivacaine index, defined as the ratio of the area under the drug peak (*i.e.*, 960 cm^{-1}, integration limit: 930-980 cm^{-1}) and the polyethylene skeletal absorbance (*i.e.*, 1895 cm^{-1}, integration limit: 1850-1985 cm^{-1}).

Table S2. Bupivacaine intake after diffusion doping. Drug mass and normalized drug mass by surface area for 1%VC samples with different nominal geometries after diffusion doping of bupivacaine free base.

Sample type	Nominal geometry	Doped bupivacaine mass (mg)	m_{bupi}/SA (mg/cm^2)
Elution strips	3x5x20 mm^3	27.0 ± 5.1	7.3 ± 1.3
Tensile sections	3.2x25x65 mm^3	282.4 ± 19.5	7.5 ± 0.5
Izod coupons	6.35x12.70x63.50 mm^3	189.9 ± 6.4	5.8 ± 0.3

Pharmacokinetic modeling: fitting for the Korsmeyer–Peppas model

Table S3. Korsmeyer–Peppas fitting of the cumulative drug mass release profiles. Release rate constant, K, release exponent, n, and R^2 value. *values fitted excluding timepoints with concentration under the limit of detection (2 and 3 days)

Composition	Drug	K	n	R^2
0.5%GS+4.5%BP HCl	**GS**	0.094	0.317	0.981
	BP HCl	0.816	0.201	0.992
1%VC+4%BP HCl	**VC**	0.100	0.208	0.961
	BP HCl	0.784	0.219	0.978
BP doped 1%VC	**VC**	0.013	0.102	0.871
	BP base	0.402	0.388	0.987
0.5%GS+9.5%BP base	**GS***	0.011	0.160	0.924
	BP base	0.208	0.395	0.993

Pharmacokinetic modeling: parameters for the profiles of the intraarticular concentration of the analgesic

Table S4. Pharmacokinetic parameters of the intraarticular analgesic concentration profiles. Comparison of the peak concentration (C_{max}), the peak time (t_{max}) and the area under the curve (AUC) between 0 and 7 days, and between 0 and 14 days for the UHMWPE drug eluting devices and the bolus intraarticular injection of bupivacaine (50 mg).

Composition	**C_{max} (mg/ml)**	**t_{max} (h)**	**$AUC_{0\text{-}7days}$ (mg h/ml)**	**$AUC_{0\text{-}14days}$ (mg h/ml)**
50 mg bupivacaine intraarticular injection	25.0	-	6.5	6.5
BP HCl from 1%VC+4%BP HCl	2.7	0.18	5.5	6.5
BP HCl from 0.5%GS+4.5%BP HCl	3.0	0.18	5.5	6.4
BP base from BP doped 1%VC	0.7	0.18	4.0	5.3
BP base from 0.5%GS+9.5%BP base	0.4	0.18	2.4	2.8

Tensile mechanical properties

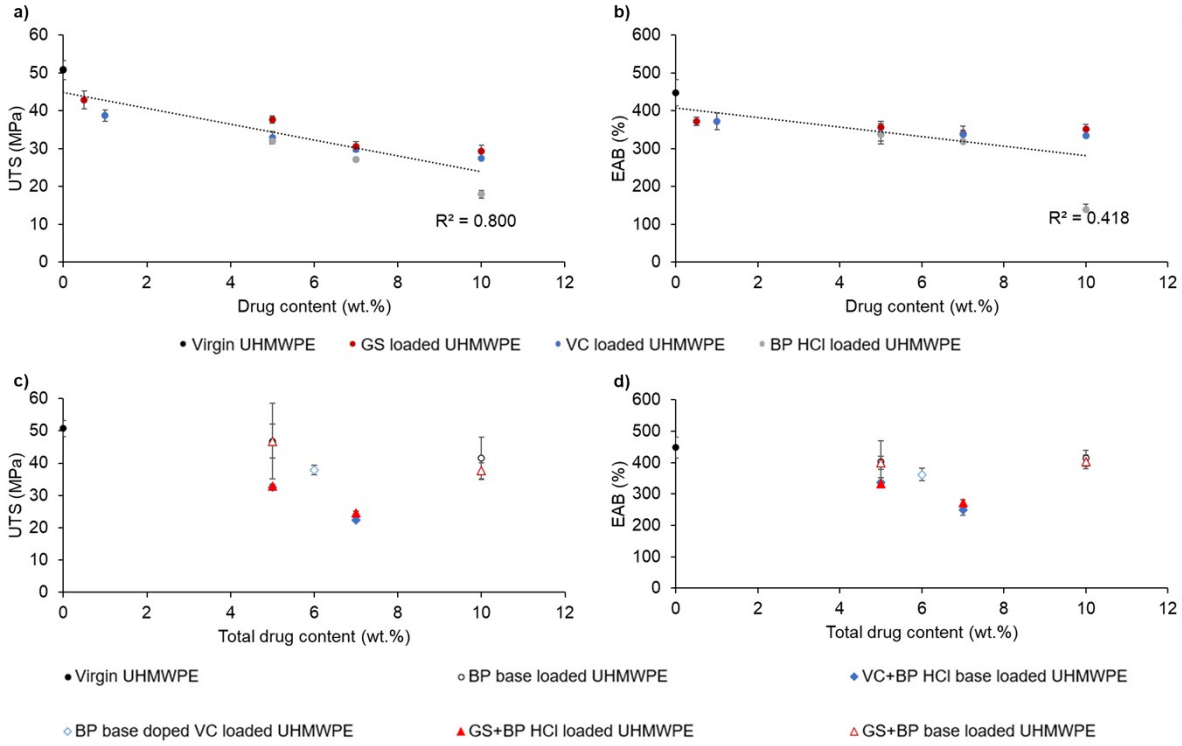

Fig. S2. Tensile mechanical properties as a function of the drug content for drug loaded UHMWPE. a) The ultimate tensile strength (UTS) as a function of the drug content in UHMWPE loaded with antibiotics, or with BP HCl, and b) the elongation at break (EAB) as a function of the drug content in UHMWPE loaded with antibiotics, or with BP HCl. R^2 values of the linear correlation are reported on the plots. c) UTS for dual drug loaded UHMWPE and BP base supplemented UHMWPE and d) EAB for dual drug loaded UHMWPE and BP base supplemented UHMWPE.

Additional fracture morphology

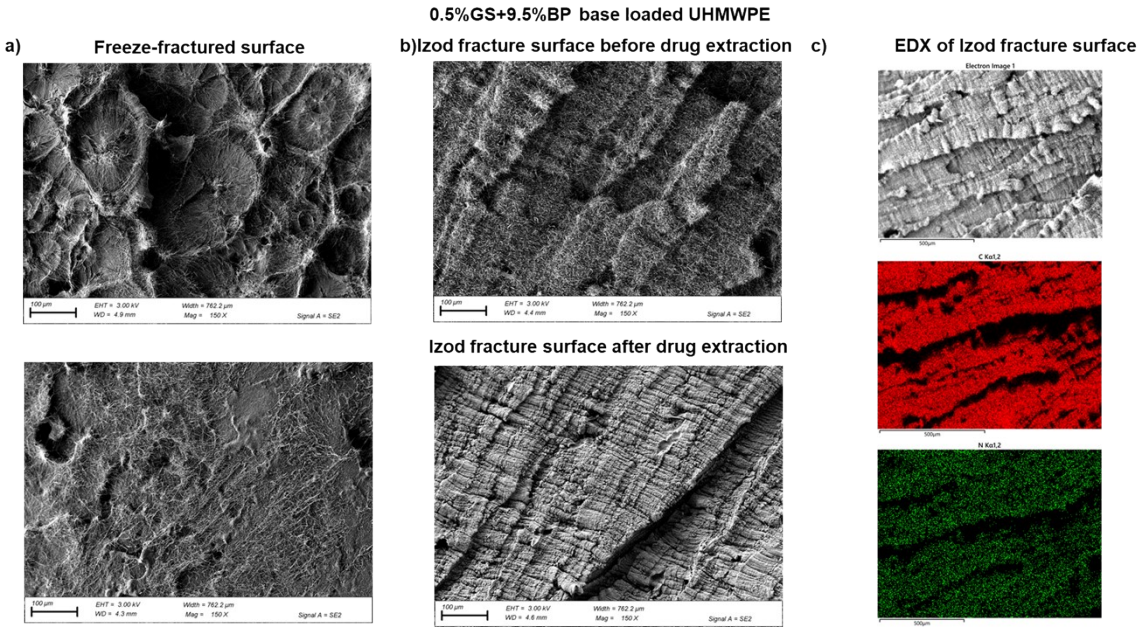

Fig. S3. Morphology by SEM of fracture surfaces for 0.5%GS+9.5%BP base loaded UHMWPE. a) Freeze-fractured surface (scale bar: 100µm), b) Izod fracture surface after drug extraction (scale bar: 100µm), c) EDX of Izod fracture surface (scale bar: 500µm): electron image (top row), Kα1,2 signals for Carbon (middle row), Kα1,2 signals for Nitrogen (bottom row).