Supplementary Information for

Diffusion doping of analgesics into UHMWPE for prophylactic pain management

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Effect of the doping temperature on the drug uptake

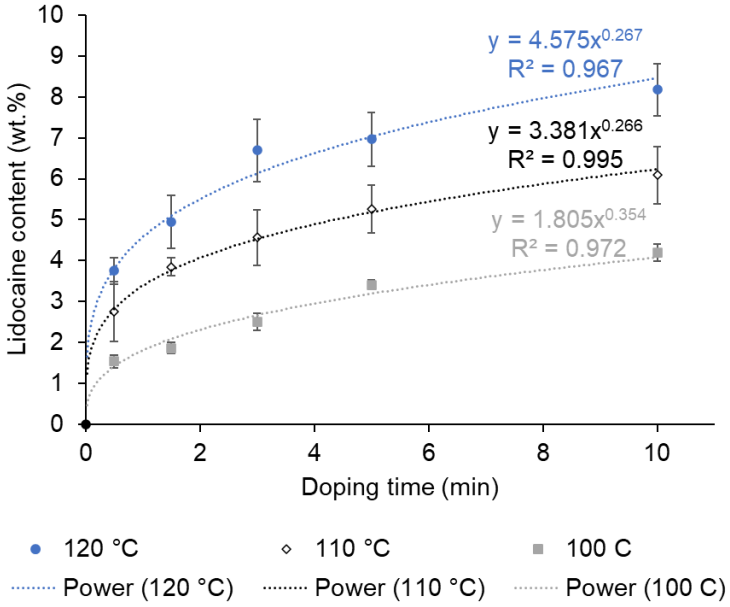

Fig. S1. Diffusion kinetics for lidocaine into non-irradiated UHMWPE thin samples as a function of temperature. Thin UHMWPE samples (thickness: 150 µm, section: 6.35x12.75 mm^2, n=3 for each time point) were doped with lidocaine for increasing duration (0-10 min) at various temperatures (120 °C: blue circles; 110 °C: black empty diamonds; 100 °C: grey squares) and their mass was measured before and after doping to obtain the drug content (wt.%). Experimental points were fitted with a power law (equations reported close to their experimental data series, including R^2 value). The exponents of the power law are smaller than 0.5, supporting Fickian diffusion.

Diffusion kinetics

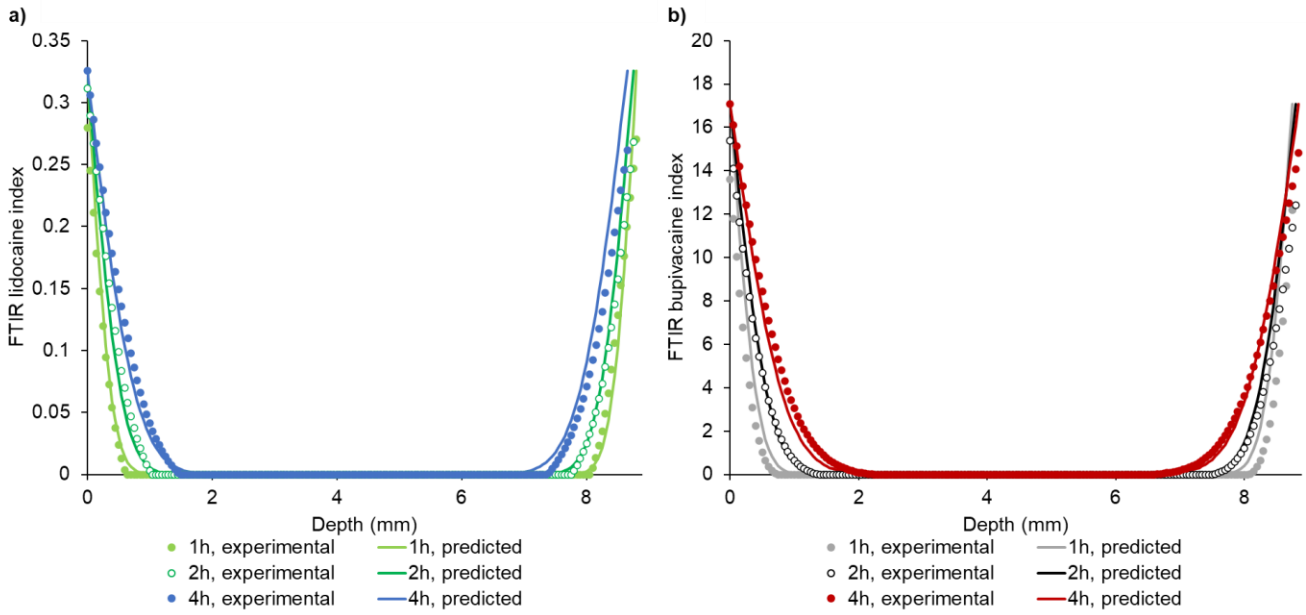

Fig. S2. Spatial distribution of the drug by FTIR depth profiling showing diffusion kinetics for lidocaine (a) and bupivacaine (b) into non-irradiated UHMWPE thick samples for various doping period (from 1h to 4h). Thick UHMWPE samples (thickness: 8.8 mm, approximately, n=3 for each time point) were doped with lidocaine or bupivacaine for increasing duration and the drug distribution along the thickness was monitored by FTIR. Experimental points (empty circles) are plotted against the predicted values (solid lines) obtained by applying the Fick's second law of diffusion, shown in Equation S1.

Equation S1:

$$C(x,t) = C_0 \left[erfc\left(\frac{x}{2\sqrt{Dt}}\right) + erfc\left(\frac{depth-x}{2\sqrt{Dt}}\right)\right] \quad \text{(S1)}$$

where C_0 is the saturation concentration of the material, x is the position along the depth ($depth$), D the diffusion coefficient, t the doping time, and $erfc$ is the complementary error function.

Equation S1 is the solution of Fick's second law of diffusion for the case of diffusion from boundaries located at positions $x = 0$ and $x = depth$, where the concentration is kept at a value of C_0.

The saturation concentration was assumed to be reached at the surface of samples doped after 4h, thus its values was taken from the experimental data for doping after 4h. The diffusion coefficient D was used as a fitting variable and it resulted equal to 1.25 x 10^{-5} and 1.50 x 10^{-5} mm^2/s for lidocaine and bupivacaine, respectively.

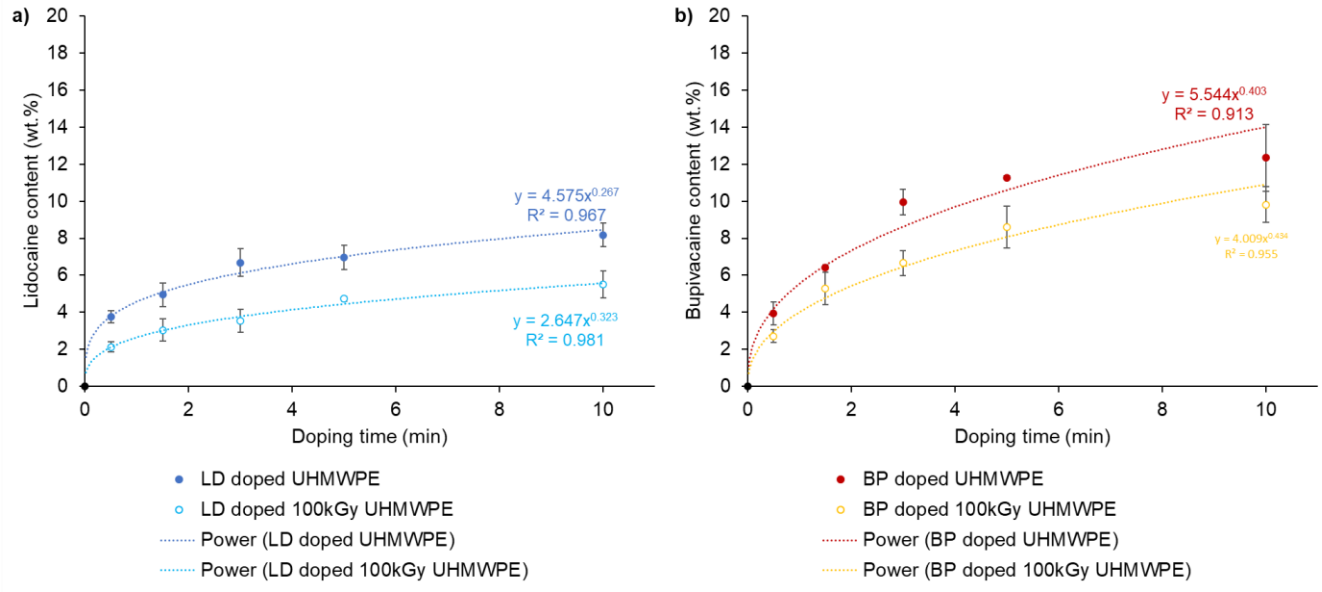

Fig. S3. Diffusion kinetics for lidocaine (a) and bupivacaine (b) into non-irradiated and 100kGy irradiated UHMWPE thin samples. Thin non-irradiated UHMWPE samples (full circles) or 100kGy irradiated UHMWPE samples (empty circles) (thickness: 150 µm, section: 6.35x12.75 mm^2, n=3 for each time point) were doped with lidocaine or bupivacaine for increasing duration (0-10 min) and their mass was measured before and after doping to obtain the drug content (wt.%). Experimental points were fitted with a power law (equations reported close to their experimental data series, including R^2 value). The exponents of the power law are smaller than 0.5, supporting Fickian diffusion.

Quantification of the drug uptake after diffusion doping

Composition analysis by thermogravimetric analysis (TGA)

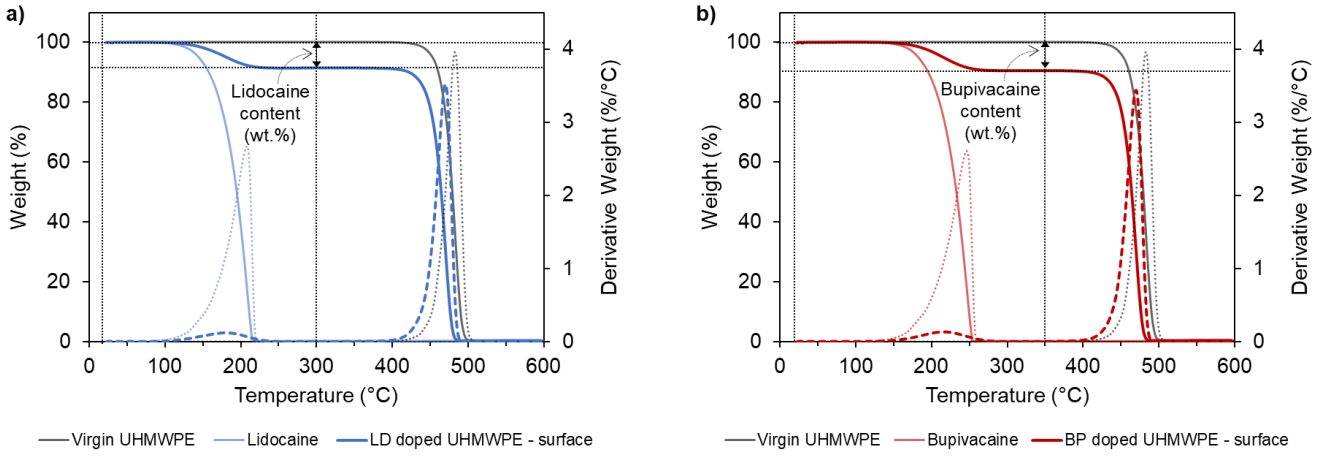

Fig. S4. Method for quantification of doped drug content using thermogravimetric analysis (TGA). Evaluation of drug content for a) lidocaine and for b) bupivacaine in doped UHMWPE. TGA scans for virgin UHMWPE (grey solid line) and for the free-drug (light blue solid line for lidocaine and light red solid line for bupivacaine) are also reported. Derivative weight curves are plotted on the secondary vertical axis (dotted line).

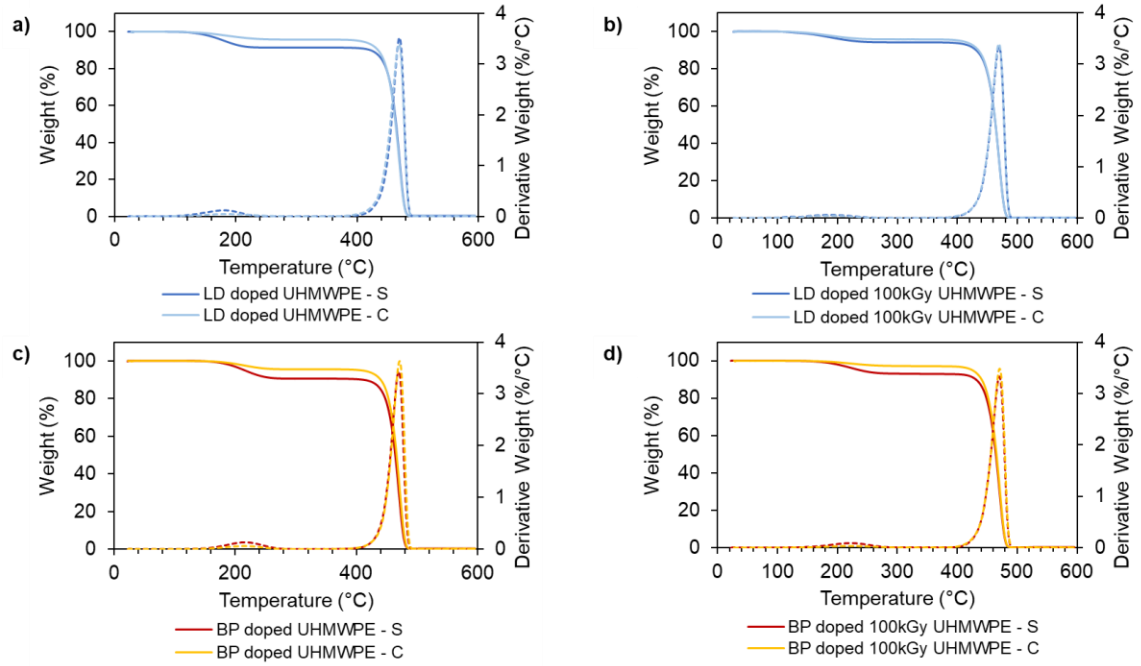

Fig. S5. Composition analysis by TGA. Representative TGA scans of samples from the surface (S) and the core (C) of the 3x5x20mm^3 prismatic strips for a) lidocaine-doped UHMWPE, b) lidocaine-doped 100kGy UHMWPE, c) bupivacaine-doped UHMWPE, d) bupivacaine-doped 100kGy UHMWPE.

Calibration curves to correlate the FTIR index based on the drug absorbance to a weight percentage of the drug uptake

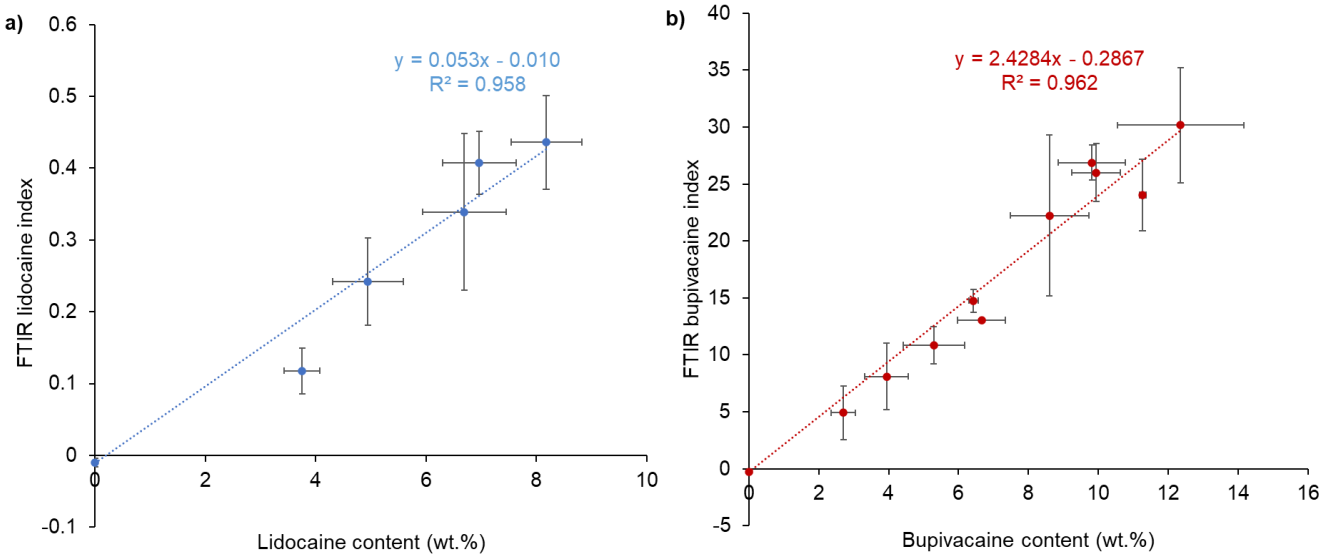

Fig. S6. Linear correlation between the FTIR drug index and the drug weight content for (a) lidocaine and (b) bupivacaine. Thin non-irradiated UHMWPE samples and 100kGy irradiated UHMWPE samples (thickness: 150 µm, section: 6.35x12.75 mm^2, n=3 for each time point) were doped with lidocaine or bupivacaine for increasing duration (0-10 min) and their mass was measured before and after doping to obtain the drug content (wt.%). FTIR was performed (n=3 independent measurements on each of the n=3 samples for each time point) to obtain the FTIR drug index (according to Fig. 2). The equation of the calibration curve and the R^2 value are reported in each plot for lidocaine (a) and bupivacaine (b).

***trans*-Vinylene index by FTIR**

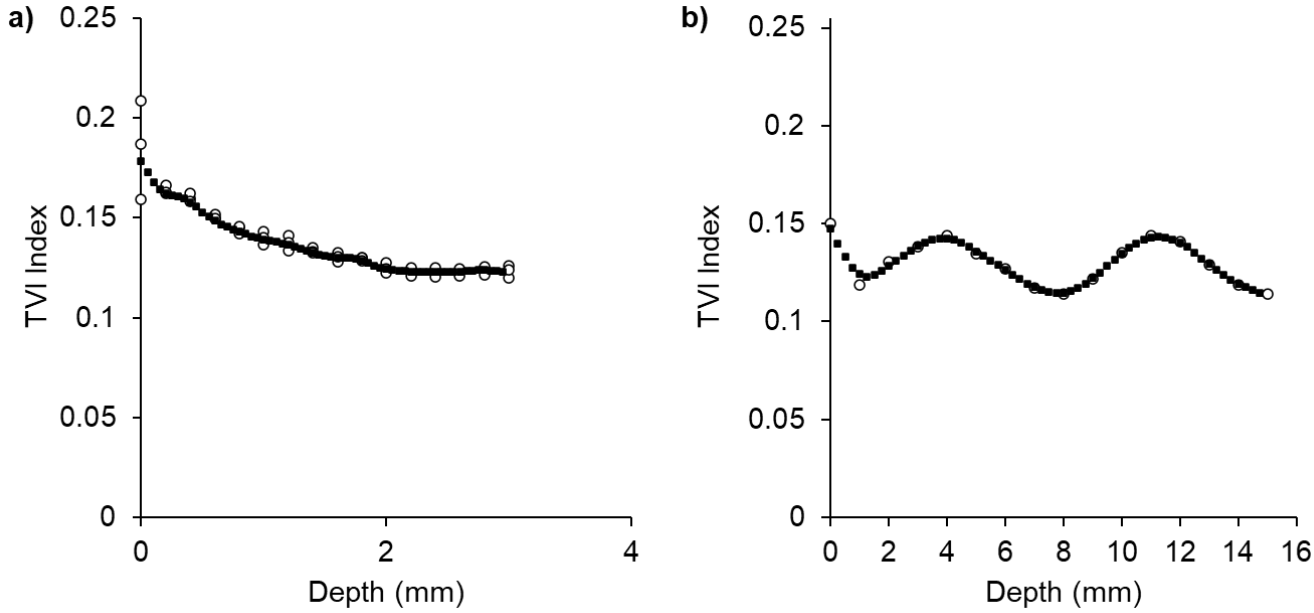

Fig. S7. Depth profiles of *trans*-Vinylene (TVI) index for a) 3mm-thick blocks irradiated from one side at a total nominal dose of 100kGy; b) 15mm-thick blocks irradiated from two sides at a total nominal dose of 100kGy. Black circles represent the interpolation of scans from multiple sections by a spline function.

Differential scanning calorimetry (DSC)

The melting enthalpy for the melting of the drug phase, $\Delta H_{m,drug,}$ was calculated in the 60-80 °C temperature interval for the case of lidocaine, and in the 96-104 °C temperature interval for the case of bupivacaine.

The melting enthalpy for UHMWPE, $\Delta H_{m,UHMWPE,}$ was calculated by subtracting the melting enthalpy of the drug to the melting enthalpy calculated for the area under the peak in the 20-160 °C temperature interval.

The crystallinity content of UHMWPE, $\chi_{c,UHMWPE,}$ was calculated according to Equation 1:

$$\chi_{c,UHMWPE} = \frac{\Delta H_{m,UHMWPE}}{\Delta H^{100}_{m,UHMWPE}} \times \frac{1}{w_{UHMWPE}} \quad (1)$$

where $\Delta H^{100}_{m,UHMWPE}$ is the specific melting enthalpy for 100% crystalline UHMWPE (291 J/g) and w_{UHMWPE} is the weight fraction of UHMWPE, obtained from the results of thermogravimetric analysis (TGA), reported in the main text.

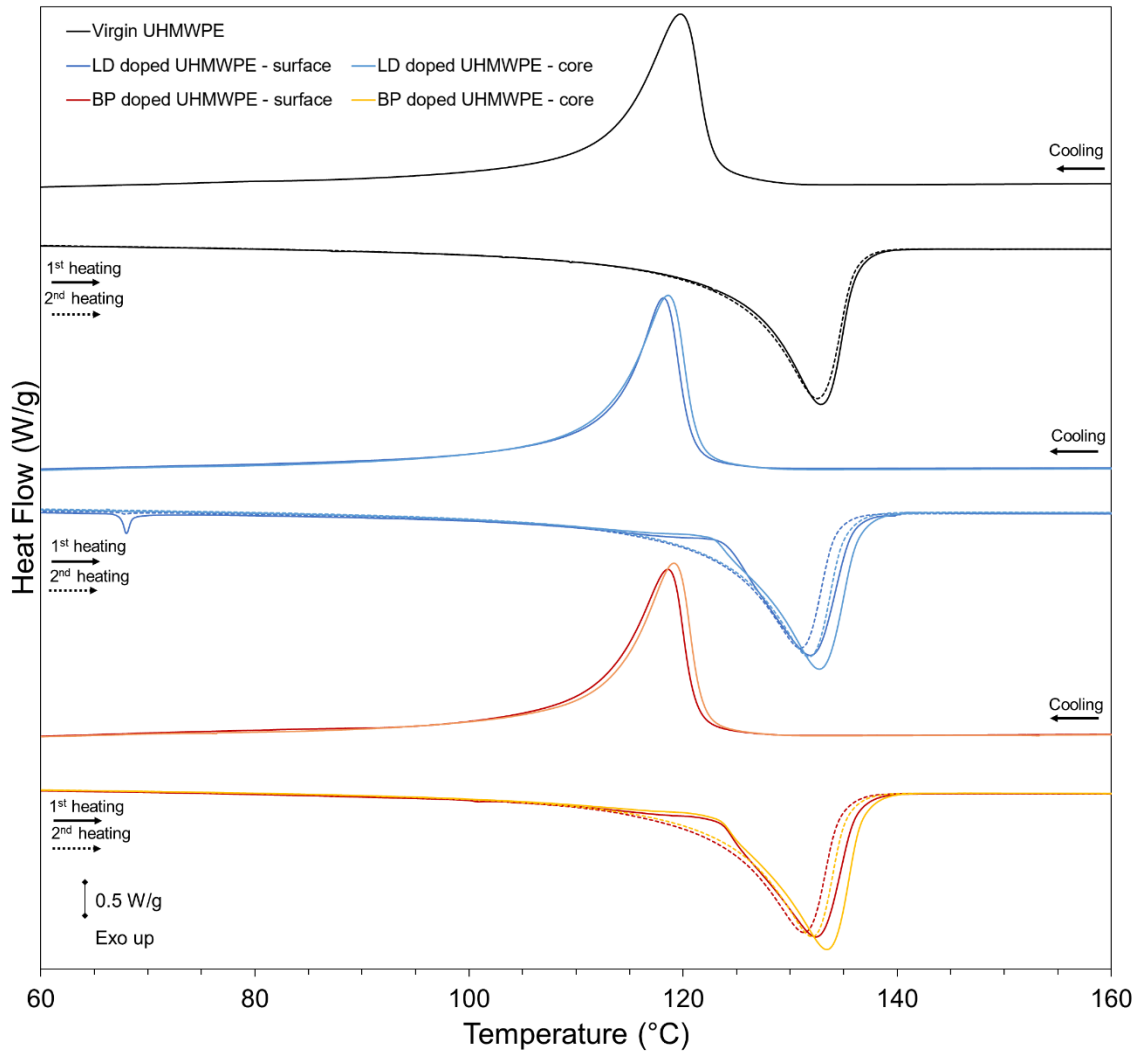

Fig. S8. DSC scans for non-irradiated materials; dashed lines represent the 2nd heating scan.

		$T_{m,peak,drug}$ (°C)	$T_{m,peak,UHMWPE}$ (°C)	$\Delta H_{m,drug}$ (J/g)	$\Delta H_{m,UHMWPE}$ (J/g)	$\chi_{c,UHMWPE}$ (%)
Non-irradiated materials	Virgin UHMWPE	n.a. [a]	134 ± 1	n.a. [a]	168.6 ± 4.7	58.0 ± 1.6
	LD doped UHMWPE - surface	68 ± 0	132 ± 0	2.0 ± 0.1	160.1 ± 2.3	60.2 ± 0.9
	LD doped UHMWPE - core	n.e. [b]	135 ± 2	n.e. [b]	167.8 ± 7.9	60.4 ± 2.9
	BP doped UHMWPE - surface	101 ± 0	133 ± 1	0.2 ± 0.1	159.6 ± 10.8	60.9 ± 4.1
	BP doped UHMWPE - core	n.e. [b]	134 ± 1	n.e. [b]	165.4 ± 6.0	59.5 ± 2.2

Table S1. Thermal properties of non-irradiated materials (1st heating scan). [a]Not applicable; [b]Not evaluable.

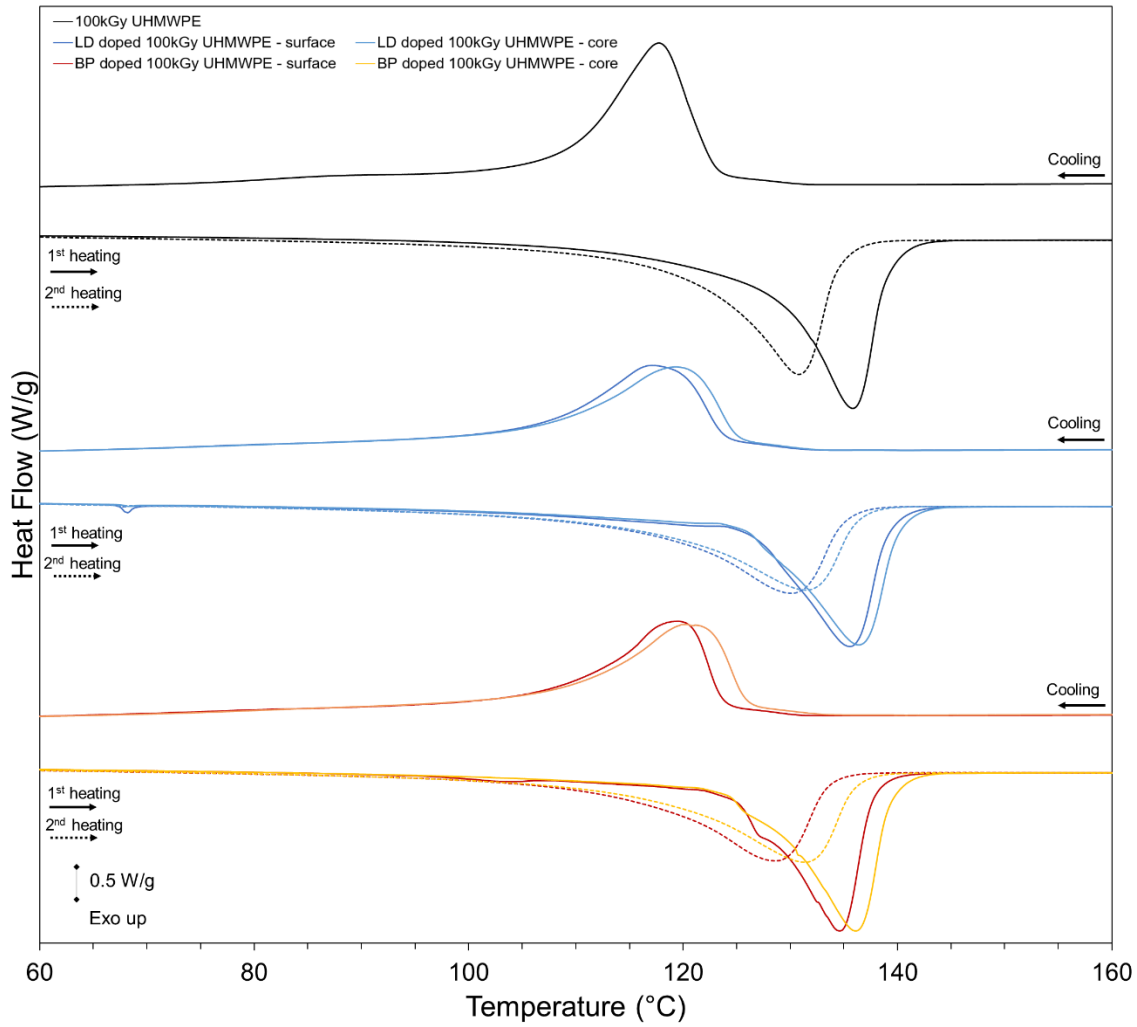

Fig. S9. DSC scans for irradiated materials; dashed lines represent the 2nd heating scan.

		$T_{m,peak,drug}$ (°C)	$T_{m,peak,UHMWPE}$ (°C)	$\Delta H_{m,drug}$ (J/g)	$\Delta H_{m,UHMWPE}$ (J/g)	$\chi_{c,UHMWPE}$ (%)
Irradiated materials	100kGy UHMWPE	n.a. [a]	137 ± 1	n.a. [a]	177.6 ± 7.4	61.0 ± 2.5
	LD doped 100kGy UHMWPE - surface	68	135 ± 0	1.5 ± 0.4	166.3 ± 2.4	60.3 ± 0.9
	LD doped 100kGy UHMWPE - core	n.e. [a]	136 ± 0	n.e. [a]	170.7 ± 1.1	61.2 ± 0.4
	BP doped 100kGy UHMWPE - surface	103	135 ± 1	0.6 ± 0.5	168.1 ± 1.2	64.0 ± 0.5
	BP doped 100kGy UHMWPE - core	n.e. [a]	136 ± 0	n.e. [a]	171.3 ± 4.4	60.7 ± 1.5

Table S2. Thermal properties of non-irradiated materials (1st heating scan). [a]Not applicable; [b]Not evaluable.

^{1}H NMR

Lidocaine stock solution

List of peaks:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.12, 7.02, 3.09, 2.59, 2.58, 2.56, 2.55, 2.09, 1.04, 1.03, 1.01.

List of multiplets:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.12 (s, 1H), 7.02 (s, 3H), 3.09 (s, 2H), 2.57 (q, J = 7.1 Hz, 4H), 2.09 (s, 5H), 1.03 (t, J = 7.1 Hz, 5H).

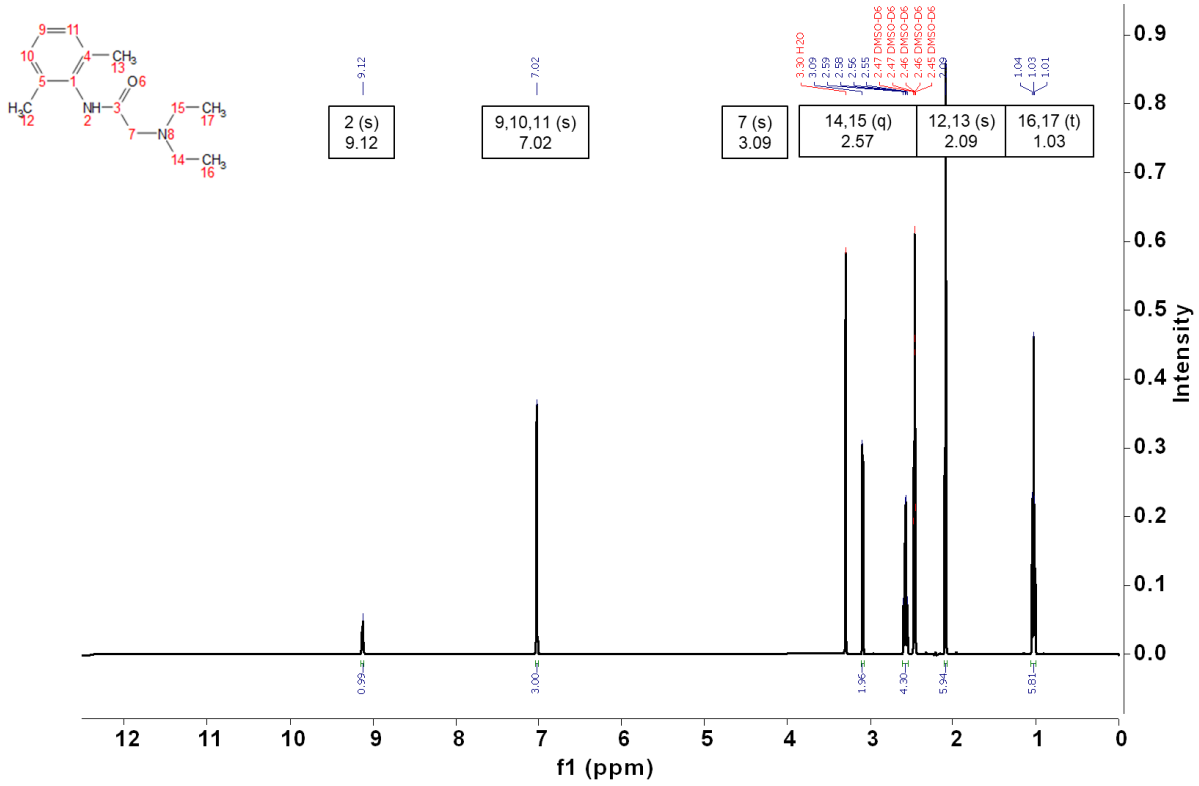

Fig. S10. ^{1}H NMR spectrum for stock solution of lidocaine with multiplets assignment. Solvent peaks are highlighted in red (DMSO-D_6: 2.47-2.45 ppm; residual H_20: 3.30 ppm).

Lidocaine eluent

List of peaks:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.13, 7.02, 3.09, 2.59, 2.58, 2.56, 2.55, 2.09, 1.04, 1.03, 1.01.

List of multiplets:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.13 (s, 0H), 7.02 (s, 2H), 3.09 (s, 1H), 2.57 (q, J = 7.1 Hz, 2H), 2.09 (s, 3H), 1.03 (t, J = 7.1 Hz, 3H).

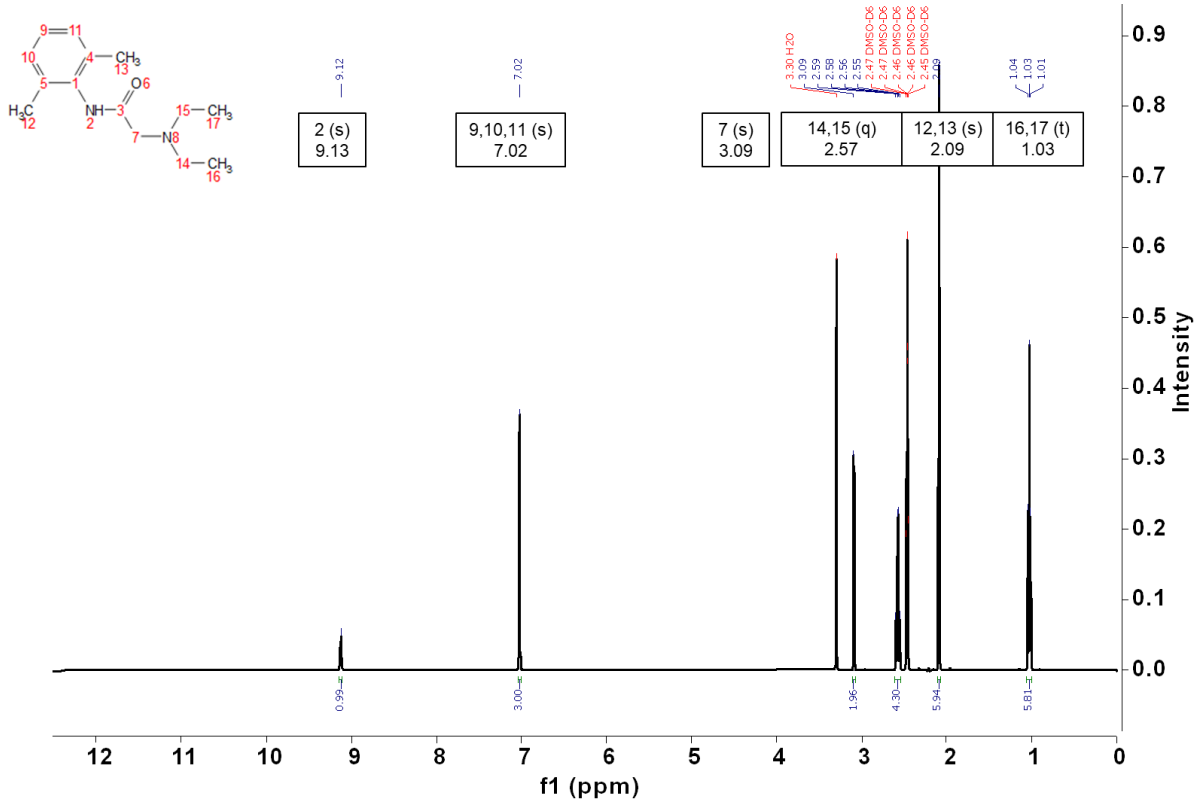

Fig. S11. ^{1}H NMR spectrum for lidocaine eluted from UHMWPE with multiplets assignment. Solvent peaks are highlighted in red (DMSO-D_6: 2.47-2.45 ppm; residual H_20: 3.30 ppm).

Bupivacaine stock solution

List of peaks:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.05, 7.04, 7.03, 7.02, 7.01, 7.01, 7.00, 6.99, 3.07, 3.07, 3.06, 3.05, 3.04, 3.03, 2.82, 2.81, 2.80, 2.79, 2.62, 2.61, 2.60, 2.60, 2.59, 2.58, 2.57, 2.56, 2.21, 2.20, 2.19, 2.18, 2.18, 2.17, 2.17, 2.16, 2.15, 2.08, 1.98, 1.97, 1.96, 1.95, 1.94, 1.93, 1.80, 1.80, 1.79, 1.77, 1.70, 1.69, 1.68, 1.67, 1.66, 1.66, 1.64, 1.64, 1.62, 1.61, 1.58, 1.57, 1.56, 1.55, 1.54, 1.52, 1.50, 1.49, 1.48, 1.47, 1.46, 1.46, 1.44, 1.44, 1.43, 1.42, 1.42, 1.41, 1.41, 1.40, 1.27, 1.26, 1.25, 1.23, 1.22, 1.22, 1.21, 1.20, 1.19, 1.17, 1.16, 0.85, 0.84, 0.82.

List of multiplets:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.05 (s, 1H), 7.07 – 6.94 (m, 3H), 3.05 (dt, *J* = 11.5, 4.0 Hz, 1H), 2.80 (dd, *J* = 9.8, 3.3 Hz, 1H), 2.59 (ddd, *J* = 12.3, 10.3, 6.0 Hz, 1H), 2.17 (ddd, *J* = 12.2, 9.9, 4.8 Hz, 1H), 2.08 (s, 6H), 1.96 (td, *J* = 11.3, 3.0 Hz, 1H), 1.83 – 1.75 (m, 1H), 1.73 – 1.60 (m, 2H), 1.56 (dd, *J* = 10.8, 6.8 Hz, 1H), 1.53 – 1.37 (m, 3H), 1.30 – 1.15 (m, 3H), 0.84 (t, *J* = 7.4 Hz, 3H).

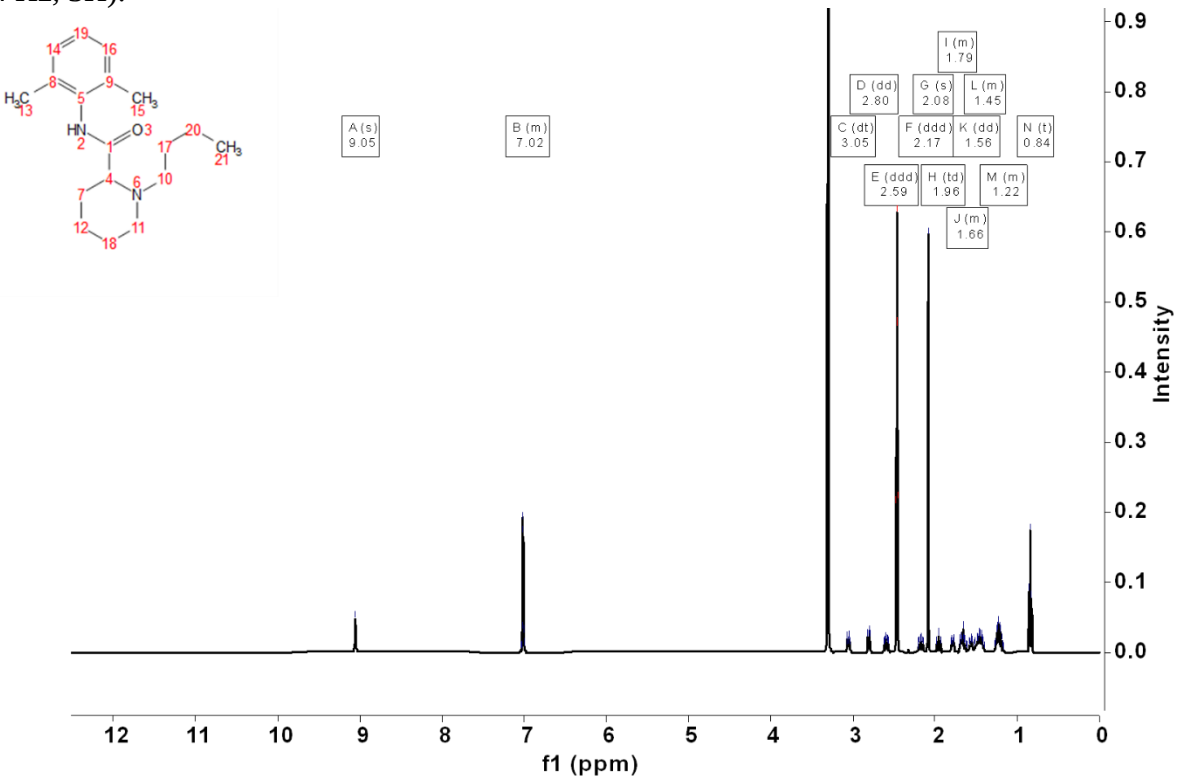

Fig. S12. ^{1}H NMR spectrum for stock solution of bupivacaine with multiplets assignment. Solvent peaks are at 2.47-2.45 ppm (DMSO-D_6), at 3.30 ppm (residual H_20).

Bupivacaine eluent

List of peaks:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.05, 7.04, 7.03, 7.02, 7.01, 7.00, 6.99, 3.07, 3.07, 3.06, 3.05, 3.04, 3.03, 2.82, 2.81, 2.80, 2.79, 2.62, 2.61, 2.60, 2.60, 2.59, 2.58, 2.57, 2.56, 2.21, 2.20, 2.19, 2.18, 2.18, 2.17, 2.17, 2.16, 2.15, 2.08, 1.98, 1.97, 1.96, 1.95, 1.94, 1.93, 1.81, 1.80, 1.80, 1.79, 1.77, 1.70, 1.69, 1.68, 1.67, 1.66, 1.66, 1.64, 1.64, 1.62, 1.61, 1.58, 1.56, 1.55, 1.54, 1.52, 1.50, 1.49, 1.48, 1.47, 1.46, 1.46, 1.44, 1.44, 1.43, 1.42, 1.42, 1.41, 1.41, 1.40, 1.39, 1.28, 1.27, 1.26, 1.25, 1.25, 1.23, 1.22, 1.22, 1.20, 1.19, 1.17, 1.16, 0.85, 0.84, 0.82.

List of multiplets:

^{1}H NMR (500 MHz, DMSO-D_6) δ 9.05 (s, 1H), 7.06 – 6.97 (m, 3H), 3.05 (dt, *J* = 11.5, 4.1 Hz, 1H), 2.80 (dd, *J* = 9.7, 3.3 Hz, 1H), 2.59 (ddd, *J* = 12.3, 10.3, 6.0 Hz, 1H), 2.17 (ddd, *J* = 12.3, 9.9, 4.9 Hz, 1H), 2.08 (s, 6H), 1.96 (td, *J* = 11.2, 2.9 Hz, 1H), 1.83 – 1.74 (m, 1H), 1.73 – 1.60 (m, 2H), 1.56 (dd, *J* = 10.4, 6.4 Hz, 1H), 1.53 – 1.39 (m, 3H), 1.31 – 1.15 (m, 3H), 0.84 (t, *J* = 7.3 Hz, 3H).

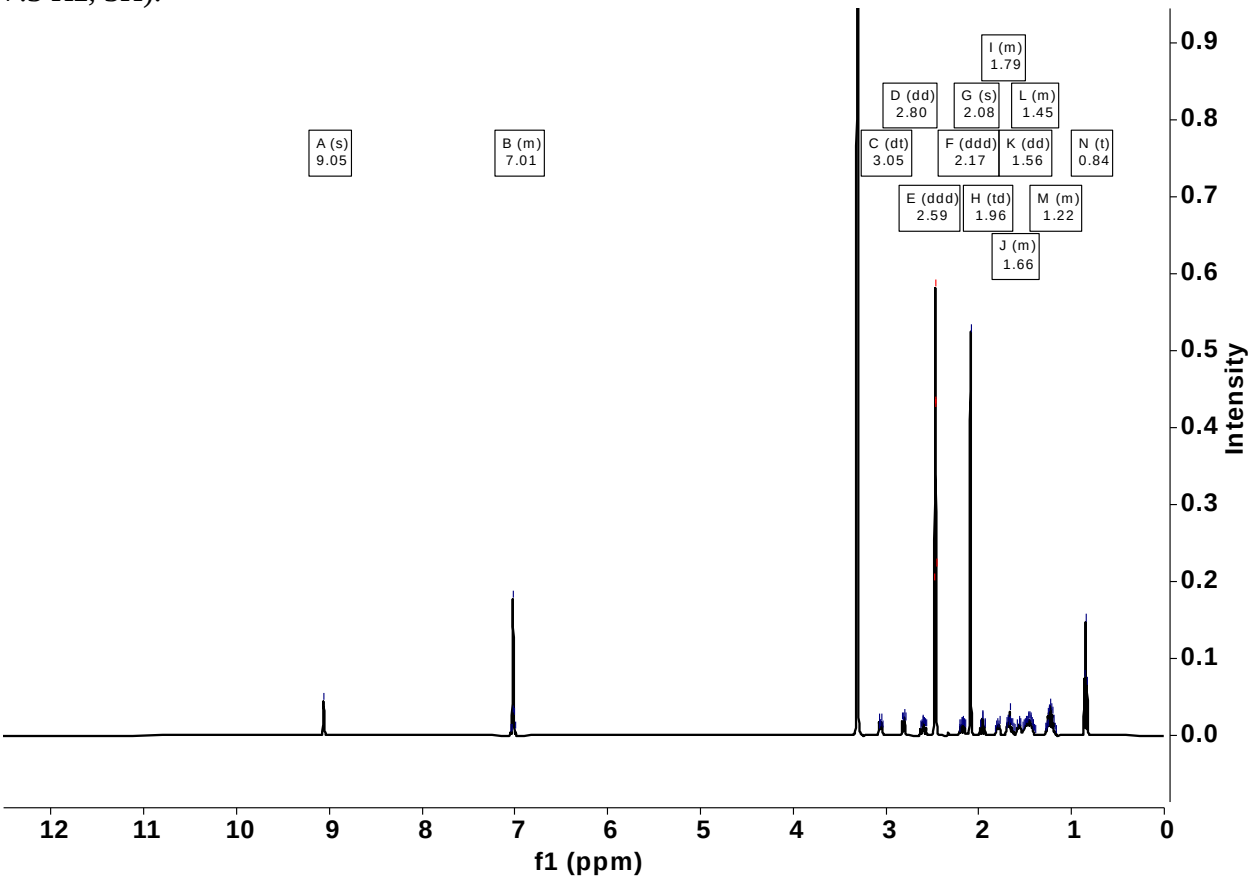

Fig. S13. ^{1}H NMR spectrum for bupivacaine eluted from UHMWPE with multiplets assignment. Solvent peaks are at 2.47-2.45 ppm (DMSO-D_6), at 3.30 ppm (residual H_20).

Effect of the elution medium on the drug release

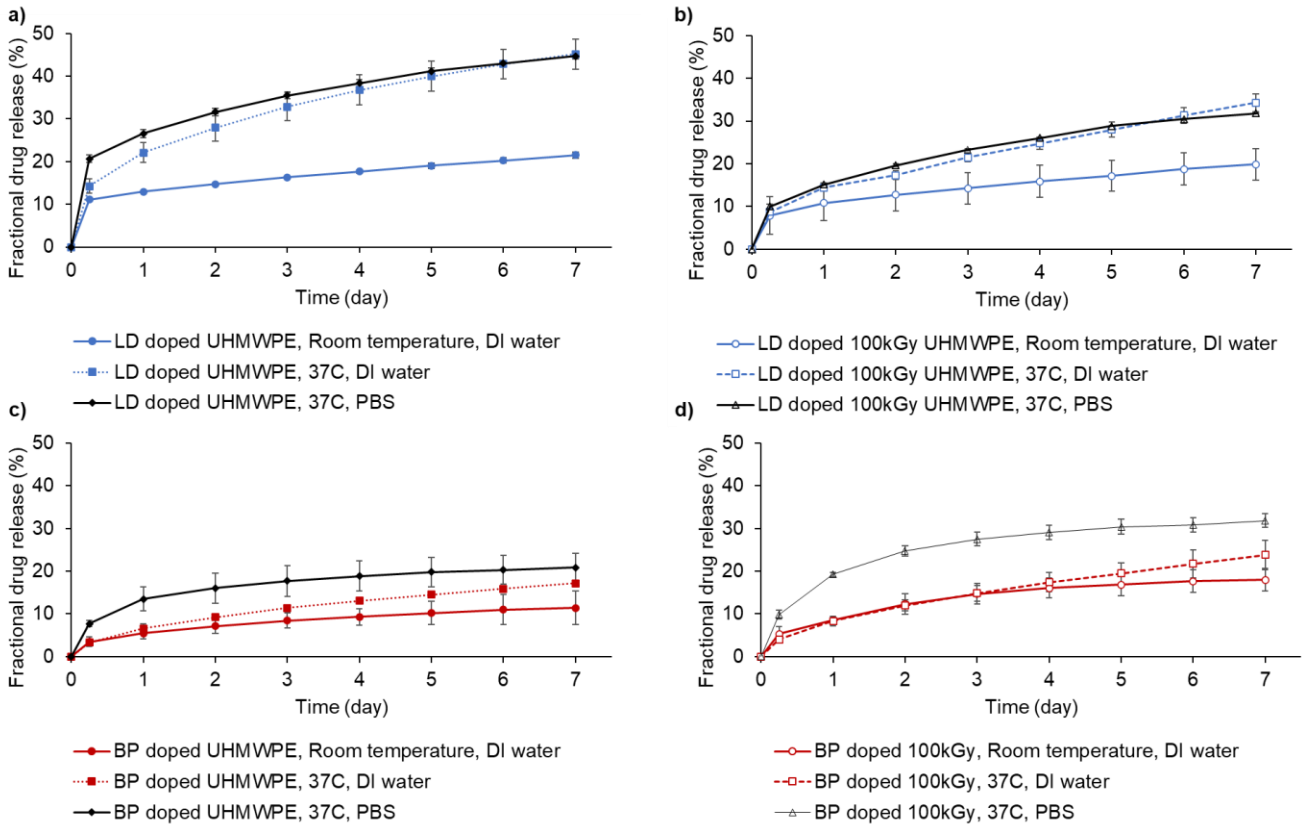

Fig. S14. Drug elution from lidocaine and bupivacaine-doped UHMWPE in different media. Fractional drug release (%) is shown for lidocaine doped UHMWPE (a), lidocaine doped 100kGy irradiated UHMWPE (b), bupivacaine doped UHMWPE (c) and bupivacaine doped 100kGy irradiated UHMWPE (d). Circular markers indicate elution in de-ionized (DI) water at room temperature, square markers indicate elution in de-ionized water at 37 °C, and triangular markers indicate elution in Phosphate Buffered saline (PBS) at 37 °C.

Pharmacokinetic modeling: fitting for the Korsmeyer-Peppas model

Table S3. Korsmeyer-Peppas fitting of the cumulative drug mass release profiles for the drug release study performed at 37 °C in de-ionized water. Release rate constant, K, release exponent, n, and R^2 value.

	K	**n**	**R^2**
Lidocaine-doped UHMWPE	7.61	0.35	0.998
Lidocaine-doped 100kGy UHMWPE	1.64	0.40	0.984
Bupivacaine-doped UHMWPE	1.60	0.50	0.999
Bupivacaine-doped 100kGy UHMWPE	1.52	0.53	0.999