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Architecture-controlled release of ibuprofen from polymeric nanoparticles

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Smart polymeric systems are required that are able to release a therapeutic drug with control over timing and location of delivery. Herein we investigated the architecture-controlled and pH-triggered release of ibuprofen from a polymeric nanoparticle system prepared using ring-opening metathesis polymerisation. The co-polymerisation of norbornene-derived ibuprofen (NB-Ibu) and poly(ethylene glycol) (NB-PEG) monomers produced polymers with block and random sequence architectures. Self-assembly into nanoparticle systems and release of ibuprofen only under basic conditions was shown to be controlled by polymer sequence.

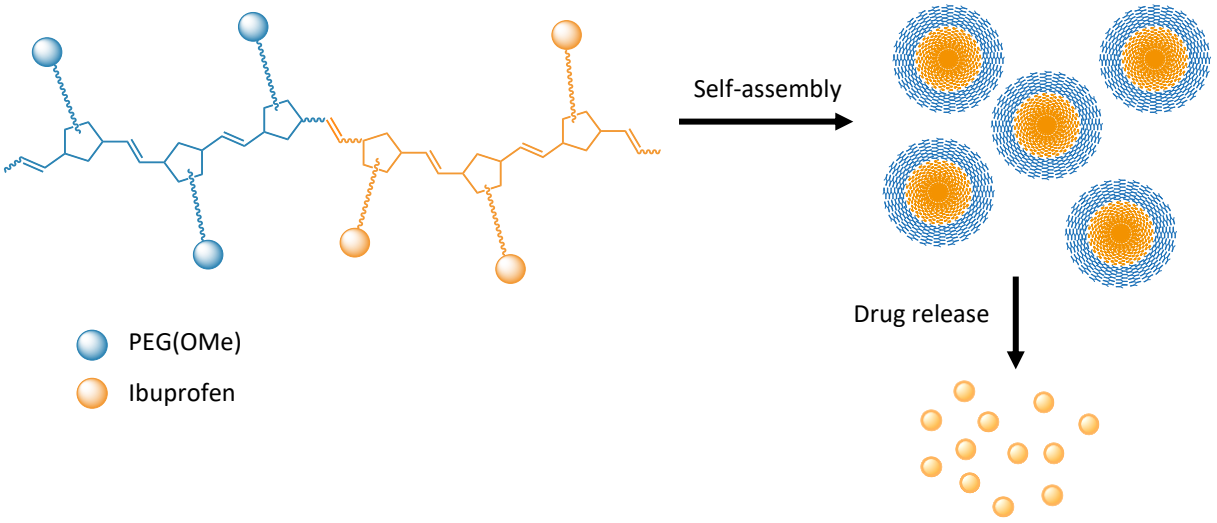


Figure 1: schematic representation of an amphiphilic block copolymer which undergo self-assembly forming spherical aggregates. Under precise condition these polymeric nanoparticles can release the chemotherapeutic drug.

Introduction

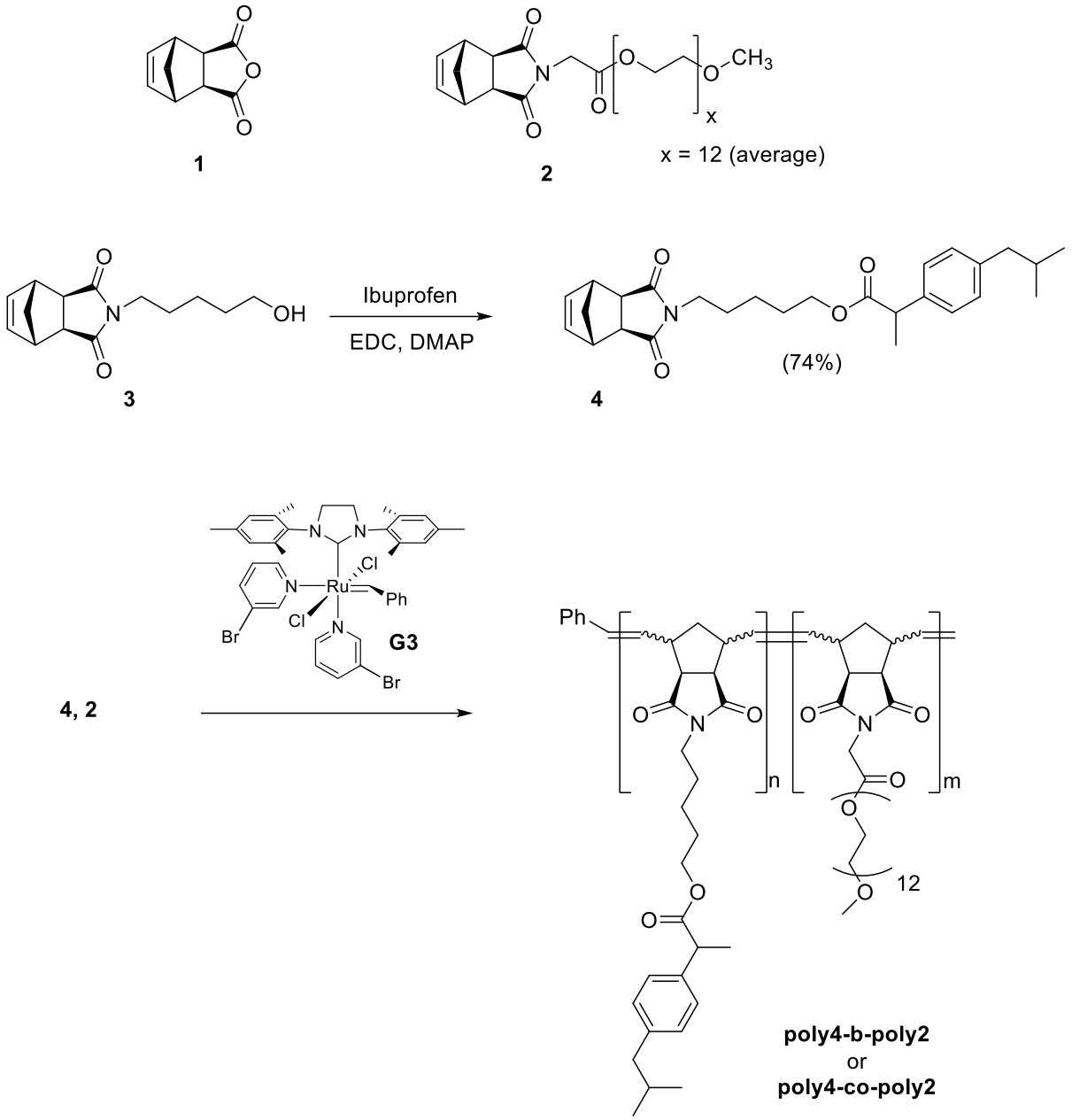
Non-steroidal anti-inflammatory drugs (NSAIDs) possess analgesic, antipyretic and anti-inflammatory properties, and are amongst the most widely prescribed drugs worldwide.[1] Pain relief is the primary clinical use for NSAIDs but the well-known association between inflammation and cancer has resulted in numerous investigations of NSAIDs for cancer prevention and treatment. Studies in various types of cancers, including prostrate[2], breast[3], colorectal[4,5] and ovarian[6] cancers indicate a positive effect linked to NSAID use. NSAIDs typically act by blocking the cyclooxygenase (COX) enzyme which is key in the synthesis of prostaglandins (PGs) which are required for the vasodilation associated with inflammation. There are however also epidemiological studies that contraindicate NSAID use[7] which are associated with increased cancer risks, especially renal[8], although the mechanism of action is unclear[1]. Furthermore, NSAIDs have been associated with unwanted nausea and dyspeptic symptoms including ulcers[1,9] and internal bleeding[10]. These latter complications are related to the oral ingestion of NSAIDs and we therefore wished to investigate a polymer approach for the delivery of these drugs[11] for tumour therapy.

The field of polymer therapeutics spans several decades, developing polymer-drug systems that rely on a degradable or bio-degradable process to release a drug from a polymer[12,13]. There are several advantages in using these polymer prodrug systems, such as an increase in the drug water solubility, an enhancement of drug bioavailability, protection of the drug during its circulation to the site of action and an improvement in pharmacokinetics[14,15]. In cancer therapy the enhanced permeation and retention (EPR) effect is also a common property associated with therapeutic macromolecules[16,17] although this effect has been questioned more recently[18,19]. Having previously made a pure drug polymer platform from salicylic acid[20], we were interested in utilising the ring opening metathesis polymerisation (ROMP) process as a means of approaching a more precisely controlled polymer-drug release system. The exquisite control that ROMP affords in preparing functionally dense polymers and architecturally-defined copolymers,[21,22] and their resulting self-assembly has led to several examples of bio-related and therapeutic ROMP polymers[23–30]. The concept of chemically degradable ROMP polymers, i.e. when the mechanism of drug release is a chemical process such as ester hydrolysis rather than a biological process, is currently gaining more attention[31–33]. Previous work in our laboratories has shown that the copolymerisation of a poly(ethylene glycol) (PEG) moiety in a peptide-derived ROMP polymer leads to self-assembled molecular architectures[34,35] and we were therefore interested in investigating the stability and release of a non-steroidal anti-inflammatory drug (NSAID), namely ibuprofen, integrated into a ROMP-PEG polymer system. Nanoparticles derived from ROMP-PEG polymers have been shown to exhibit good stealth properties in tumour therapy studies[31] and the excellent control afforded by the living nature of ROMP polymerisation allows for the post-released scaffold in parenteral administration to be under 45 kDa, a requirement for renal excretion[36]. Recent progress in polymer-ibuprofen conjugate systems include a PEG-Ibuprofen micellar system for the delivery of paclitaxel and doxorubicin[37,38]although the release of ibuprofen in these studies was implied from improved therapeutic effects rather than directly observed. Hydroxycellulose-ibuprofen conjugates have shown promising anti-inflammatory properties in paw-edema assays,[39] and polymethacrylate-ibuprofen conjugates have also been investigated,[40–42] including a pH sensitive oral formulation,[43] as have ibuprofen-polymer conjugates prepared via ADMET-polymer functionalisation[44]. The ROMP process possesses the advantages of other polymer systems in its capacity for formation of nanoparticles with multiple pendant moieties, and is an alternative to free-radical polymerisations which are not compatible with pendant groups which can act as free radical scavengers e.g. some dyes. This investigation is focussed on the preparation of ROMP-based ibuprofen conjugates and their assembly into nanoparticles that can release the drug. Taking the lead from proteins and nucleic acids, the effects of polymer sequence are of rapidly increasing interest in synthetic polymer systems[45,46]. Since ROMP enables control of polymer architecture, it provides opportunities to use this aspect of polymers to provide tuning of self-assembly and resultant degradation.

Results and Discussion

Monomer synthesis

The monomers required for this investigation are not commercially available. Condensation reactions with the *exo*-carbic anhydride derivative **1** were chosen as these lead to symmetrical norbornene derivatives which minimise head to tail effects. The norbornene PEG-derivative **2** was prepared in a similar route to our previously reported methodology[34], whereas the ibuprofen derivative **4** was prepared from *N*-(hydroxypentanyl)-*cis*-5-norbornene-*exo*-2,3-dicarboximide **3**[47], (Scheme 1, refer to ESI for experimental details). The corresponding *endo*-carbic anhydride derivatives of the above were also prepared as these are more readily available and useful to optimise reaction conditions for synthesis of ibuprofen conjugates, but were not polymerised as it is known that they do not polymerise as well as the *exo*-norbornene derivatives[48].



Scheme 1: Synthesis of norbornene-derived PEG-Ibuprofen copolymers

Synthesis of polymers

The monomers **2** and **4** were polymerised individually using the commercially available Grubbs G3 initiator[49] in THF at room temperature and were terminated with ethyl vinyl ether. The individual homopolymers were readily formed and after isolation they were characterised by proton NMR and GPC (data presented in Table 1). The polydispersity of the PEG polymer **poly2** was slightly higher than for **poly4** and is most likely a reflection of the PEG chain length of the monomer which is itself an average distribution.

To obtain the block co-polymer **poly4-b-poly2**, the *exo*-norbornenyl ibuprofen monomer **4** was firstly polymerised using G3 initiator and dry DCM as solvent; after 10 minutes *exo*-norbornenyl PEGOMe monomer **2** was added to the reaction mixture (Table 1). Statistical copolymer **poly4-co-poly2** was synthesised by adding both monomers at the same time, into the G3 initiator solution. In each case the polymerisation was terminated by adding ethyl vinyl ether and the pure polymer was obtained by

precipitation with diethyl ether (Scheme 1; GPC traces of homopolymers and copolymers are shown in Figure S30 in the ESI). Batch variability was low (Table 1).

*Table 1: polymerisation characteristics of block and statistical copolymer derived from **2** and 4.*

Polymer	Yield (%)	n:m:G3 (th)[a]	n:m[b]	% NB-Ibu[c]	% NB-PEG[c]	M_n (th)	M_n GPC	M_w GPC	Đ[d] (M_w/M_n)
Poly2*	92	20:1	/	/	100	15 000	11 000	14 200	1.36
Poly4*	98	20:1	/	100	/	8 800	11 100	13 600	1.27
Poly4-b-poly2	78	20:20:1	26:14	64	36	21 900	19 300	24 900	1.29
Poly4-co-poly2	76	20:20:1	25:15	63	37	22 000	19 300	26 200	1.36
Poly4-b-poly2	65	20:20:1	20:20	50	50	23 600	19 600	28 300	1.44
Poly4-co-poly2	76	20:20:1	24:16	60	40	22 700	23 900	30 700	1.56

*poly**2** and poly**4** were both obtained with >99% of monomer conversion in 5 min. [a] Theoretical feed ratio. [b] Observed feed ratio calculated by quantitative ^{1}H NMR analysis. [c] Determined by quantitative ^{1}H NMR analysis. [d] Polydispersity determined by GPC in THF and reported relative to polystyrene standards.

Self-assembly of block and statistical copolymer

Taking into account that polymer self-assembly by nanoprecipitation is solvent-dependent[50], self-assembly of the copolymers was obtained by dissolving the polymer (20 mg) in 1 mL of three different solvents (acetone; THF; acetonitrile), to which deionised water (10 mL) was added dropwise, over a 20 minutes period to the stirred solution to give a polymer with a final concentration of 2 mg/mL. The aggregate solution was subsequently transferred into a dialysis membrane, sealed and dialysed against distilled water for 24 hours (water changed three times over this period) to remove residual organic solvent. The self-assembly was then analysed by dynamic light scattering (DLS, Fig. 2, Fig. S31) and transmission electron microscopy (TEM). DLS data were recorded using a polyphospholipid refractive index of 1.45. TEM samples were analysed on Formvar coated copper grids, to which a negative stain of uranyl acetate was added, allowing for better contrast for nanostructures comprised of low molecular weight atoms (C, H, N) under the electron beam.

Figure 2 shows the DLS particle distribution for the block copolymer **poly4-b-poly2 [64:36]** (PDI = 0.2) and statistical copolymer **poly4-co-poly2 [63:37]** (PDI = 0.4) were self-assembled in acetone, whereas of the block copolymer **poly4-b-poly2 [50:50]** (PDI = 0.5) and statistical copolymer **poly4-co-poly2 [60:40]** (PDI = 0.7) were self-assembled in acetonitrile. Significantly, the statistical copolymers present, as expected, a different distribution of the particle size compared to the block copolymers which were much larger. For example, the largest peak (67% by intensity) seen for **poly4-co-poly2 [63:37]** is for particles at 13 nm. Because of the random distribution of the PEG and ibuprofen side chains tethered to the norbornene backbone, we interpret this as the polymer collapsing in on itself, forming single chain nanoparticles[51]. A small amount of these nanoparticles (32%) form random aggregates of a bigger size (230 nm) that

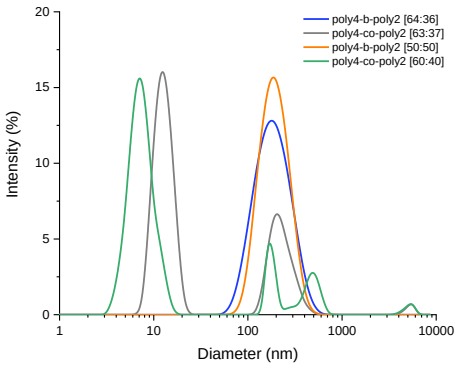


*Figure 2: DLS particle size distributions of **poly4-b-poly2 [64:36]** and **poly4-co-poly2 [63:37]** from acetone **and poly4-b-poly2 [50:50]** and **poly4-co-poly2 [60:40]** from acetonitrile.*

precipitate in solution. TEM analysis of poly4-co-poly2 [63:37] confirmed an absence of ordered self-assembly. The block copolymer poly4-b-poly2 [64:36] instead behaves as a non-ionic amphiphilic polymer and in water formed particles in the size range of 50 - 600 nm as shown in Figure 2 with an average diameter of 196 nm.

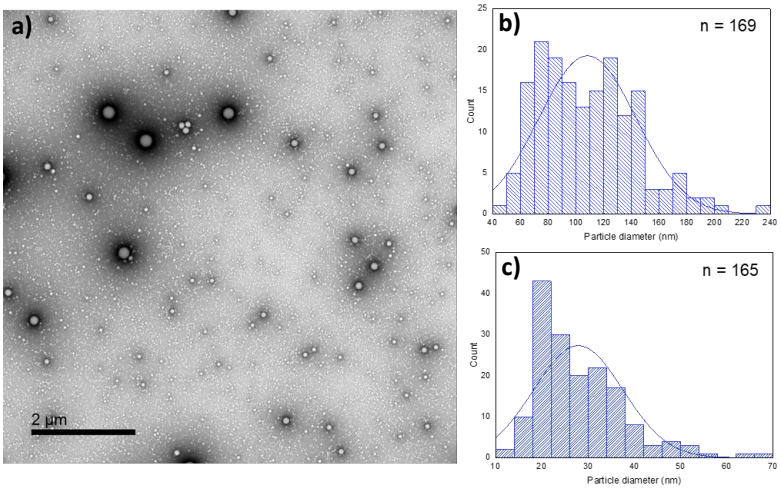


*Figure 3: a) TEM image of block copolymer poly**4-b-poly2** [64:36] ; b) distribution of the larger particles of image (a) with average size (108 ± 35)nm; d) distribution of the smaller particles of image (a) with average size (28 ± 9)nm.*

Figure 3a shows the TEM image obtained for the block copolymer poly4-b-poly2 [64:36]. The image reveals the presence of two different morphologies which we interpret as vesicles and micelles. Figure 3b and 3c indicate that the copolymer poly4-b-poly2 [64:36] has a large distribution of particle size which ranges from 40 nm to 240 nm. Examining the histograms in more detail, it is possible to identify, for each plot, two different particle distributions. For example, in Figure 3b, there are two distributions centred at 70 nm and 120 nm respectively. These results do not entirely correspond to the DLS measurements, which provide a bigger average diameter, as is common due to the solvation sphere measured by DLS, and the compacting effect of the vacuum in TEM. Furthermore, Figures 3c indicates that the formation of spherical micelles is dominant, and they possess an average diameter of 30 nm.

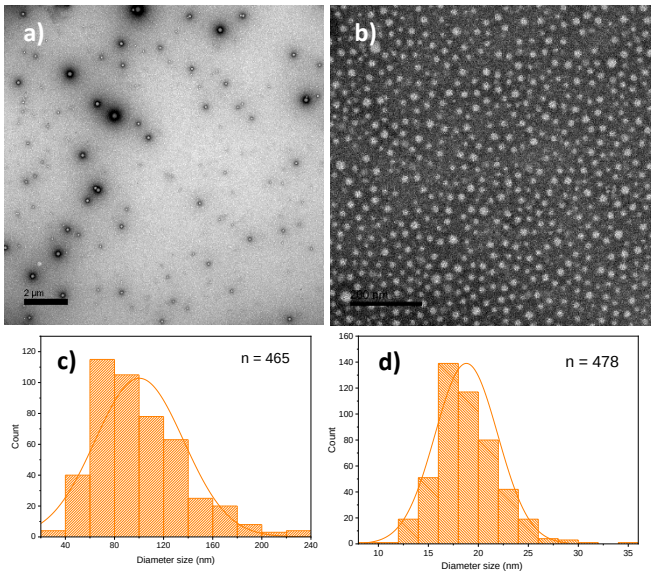


*Figure 4: a) TEM of larger nanoparticles of **poly4-b-poly2 [50:50]** scale 2000 nm; b) TEM of smallest nanoparticles of **poly4-b-poly2 [50:50]** scale 200 nm; c) and d) size distribution for **poly4-b-poly2 [50:50]** in acetonitrile TEMs for a) (100 ± 36)nm and b) (19 ± 3)nm respectively*

This result is in agreement with the estimation made using Chem3D, which afforded a repeating unit length of 0.617 nm that multiplied by the degree of polymerisation (DP = 40) gave a predicted approximate particle radius of 25 nm. Table 2 shows the diameters obtained by TEM for the self-assembly systems investigated.

Of all the samples analysed, poly4-b-poly2 [50:50] (PDI = 0.5) self-assembled from acetonitrile showed the most regular distribution of vesicles in the TEM centred around 80 nm. The DLS analysis was not in full agreement but again may be due to the effect of the TEM preparation process contrasting with DLS where greater aggregation can occur. TEM analysis of the poly4-co-poly2 samples in all cases showed irregular supramolecular morphologies (see Figures S36-38, ESI). The poly4-b-poly2

[50:50] and poly4-co-poly2 [60:40] (PDI = 0.7) systems prepared from acetonitrile therefore afforded us two comparable polymer sequences that would allow us to investigate any differences in the release of ibuprofen against differences in polymer sequence architecture.

*Table 2: table comparing the diameter of all the self-assemblies obtained. Different organic solvents were used to dissolved block copolymers **poly4-b-poly2 [64:36]** and **[50:50]** affording nanoparticles with comparable size.*

Polymer	Solvent	d (nm)$_{micelles}$[a,b]	d (nm)$_{vesicles}$[a,c]
Poly4-b-poly2 [64:36]	$CO(CH_3)_2$	28 ± 9	108 ± 35
Poly4-b-poly2 [50:50]	$CO(CH_3)_2$	20 ± 3	118 ± 38
Poly4-b-poly2 [50:50]	THF	20 ± 2	110 ± 29
Poly4-b-poly2 [50:50]	CH_3CN	19 ± 3	100 ± 36

[a] Determined by TEM. [b] Average size of smaller nanoparticles. [c] Average size of larger nanoparticles. (see Figure S31-S33, ESI)

In vitro release studies

Poly4-b-poly2 [50:50] and poly4-co-poly2 [60:40], both self-assembled from acetonitrile to give a final concentration of 1 mg/mL in 2M aqueous NaOH (pH 14.3), phosphate buffered saline (PBS, pH 7.4), foetal bovine serum (FBS, pH 7.3), pig liver esterase 30 units/mL in water (PLE, pH 7), and unbuffered water (pH 7) were added to different sets of tubes. The samples were incubated at 40 degrees in a thermocycler. Each sample was removed at predefined time points (2 hr, 4 hr, 8 hr, 24 hr, 48 hr, 96 hr), frozen to quench the reaction and analysed afterwards by HPLC (Fig. S41). A gradient processing method was used, starting from 28% methanol in water with 0.1% of formic acid. Samples (10 µL) were run at 35 °C at a flow rate of 4 mL/min. Absorbance was monitored at λ = 225 nm. The instrument was calibrated using standard solutions of ibuprofen in methanol (50, 100, 150, 200, 250 ppm, Fig. S42).

Figures 5 illustrates the release of ibuprofen using NaOH in water. After 10 hr the majority (>90%) of the ibuprofen had been released and very little release appears to occur after 24 hr. By a prior calibration of the instrument, it is also possible to quantify the concentration of the released drug which after 96 hr is in agreement with the theoretically expected value for quantitative hydrolysis which was 170 ppm for poly4-b-poly2 [50:50] and 210 ppm for poly4-co-poly2 [60:40]. The faster release of the statistical copolymer is consistent with higher accessibility of hydroxide ions to the ester linkages in a single chain polymer compared to biphasic micellar structure adopted by the block copolymer. Changing the solvent used for precipitation of the micelles did not alter the degradation kinetics significantly (Fig. S40).

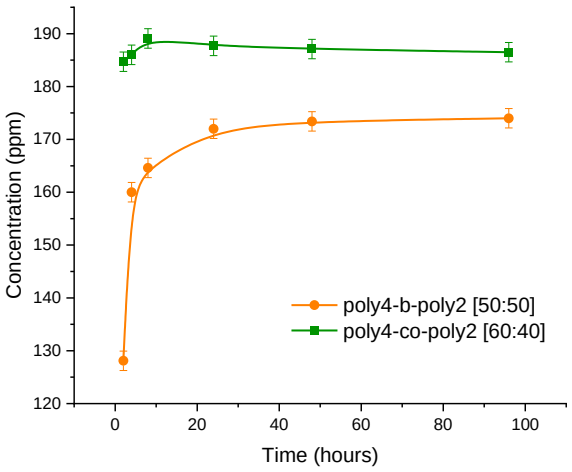


Figure 5: concentration of ibuprofen released (ppm) vs reaction time (hours) in 2M NaOH solution in water. The concentrations were determined by calibration using standards of ibuprofen in methanol at 50, 100, 150, 200 and 250 ppm.

In the media which mimic physiological conditions more closely (PBS, FBS and PLE), the hydrolysis of ibuprofen from both of the copolymers **poly4-b-poly2 [50:50]** and **poly4-co-poly2 [60:40]** was much slower, with none of these media causing release ibuprofen (measurable by HPLC) at a temperature of 40 °C over a period of 96 hr. This suggests that the shielding of the polymer-drug ester linkage within the hydrophobic core of the micelle retards chemical hydrolysis as well as impeding access of enzymes[52]. The resistance to enzymatic degradation from the **poly4-co-poly2 [60:40]** contrasts with the basic chemical hydrolysis result, consistent with formation of single-chain nanoparticles by chain collapse, which provides a steric barrier to enzymes but not ions.

Conclusion

In summary we have shown that the block copolymerisation of norbornene monomers functionalised with poly(ethylene glycol) and ibuprofen leads to the synthesis of a polymer which in an aqueous environment self-assembles to a nanoparticle system which is stable to physiological conditions but in a strong alkaline environment will release ibuprofen over a period of up to four days. This is in contrast to a non-regular system which will instead hydrolyse quantitatively within 10h although it is stable to enzymatic conditions. Further work will explore different linkages between the polymer backbone and the drug with the aim of inducing controlled release in the presence of specific physiological environments, and its effects in cells. In particular we will explore if the system can be tuned to allow for the slow enzymatic release of ibuprofen by esterase enzymes as has been shown in other polymer nanoparticle systems.[53]

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Notes

The authors declare no competing financial interests. All authors have given approval to the final version of the manuscript.

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Data availability

The processed data required to reproduce these findings are available in the Electronic Supplementary Information.

The raw data required to reproduce these findings cannot be shared at this time due to technical limitations but will be available for publication.

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