Journal of Macromolecular Science, Part A
Publication details, including instructions for authors and subscription information:
http://www.informaworld.com/smpp/title~content=t713597274

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Samaresh Ghosh[a]; Santi M. Mandal[b]
[a] Department of Chemistry, Bankura Sammilani College, Kenduadihi, Bankura, WB, India [b] Central Research Facility, Indian Institute of Technology, Kharagpur, India

Online publication date: 04 January 2011

To cite this Article Ghosh, Samaresh and Mandal, Santi M.(2008) 'Novel Ibuprofen-based Polyurethane: A New Approach for Drug Delivery', Journal of Macromolecular Science, Part A, 45: 6, 445 — 448
To link to this Article: DOI: 10.1080/10601320801977707
URL: http://dx.doi.org/10.1080/10601320801977707

Journal of Macromolecular Science ®, Part A: Pure and Applied Chemistry (2008) **45**, 445–448

ISSN: 1060-1325 print / 1520-5738 online
DOI: 10.1080/10601320801977707

Novel Ibuprofen-based Polyurethane: A New Approach for Drug Delivery

SAMARESH GHOSH[1] and SANTI M. MANDAL[2]

[1]*Department of Chemistry, Bankura Sammilani College, Kenduadihi, Bankura, WB, India*
[2]*Central Research Facility, Indian Institute of Technology, Kharagpur, India*

Received and accepted October, 2007

Facile synthesis of novel ibuprofen bearing polyurethane **1** has been achieved for the first time and found to display the release pattern of ibuprofen based on the easy cleavage of ester linkages. Thorough characterizations (FT-IR, UV-Vis, NMR, and elemental analysis) were performed to ascertain the structure of polyurethane **1**.

Keywords: polyurethane; polyethylene glycol; ibuprofen; drug release

1 Introduction

Polymer-based drug delivery technology (1–3) represents one of the emerging and challenging frontier areas of research in modern medication and pharmaceuticals. In this context, polyurethane and polyethyleneglycol (PEG) based drug delivery systems (3–6) have been recognized as a group of useful pharmaceutical excipients owing to their excellent biocompatibility. However, ibuprofen has several pharmacological actions, such as anti-inflammatory, analgesic and antipyretic properties playing an important role in the clinical treatment of rheumatoid arthritis, osteoarthritis and mild to moderate pain. In this regard, the ability to construct polyurethane based ibuprofen drug delivery systems aiming to achieve effective therapies is presently an ultimate challenge in contemporary biomedical and pharmaceutical research. Therefore, this paper reports for the first time the PEG based novel polyurethane bearing non-steroidal ibuprofen drug and investigated the release characteristics of ibuprofen from this polymeric backbone.

2 Experimental

2.1 Synthesis

*2.1.1 Synthesis of **1a***

A 50 ml round bottomed flask equipped with a condenser, was charged with ibuprofen (0.4 g, 2.4 mmol), triethylamine (catalyst). The mixture was then refluxed with 1,4-dioxane for 30 min. The butanediol diglycidylether (0.2 g, 0.98 mmol) was added into the mixture and continued refluxing for further 4.5 h. The reaction mixture was then washed with aqueous 10% $NaHCO_3$ solution and extracted with CH_2Cl_2 and dried by anh. Na_2SO_4 to afford the yellowish gummy-like product. Yield (85–90%).

2.2 Polymerization

For the polymerization reaction (Scheme 2), conducted in bulk, stoichiometric amounts of PEG (MW= 6000) (1.71 g, 0.285 mmol), TDI (0.25 g, 1.446 mmol) and catalytic amount of dibutyl tin dilaurate (DBTL) were initially mixed in dry dichloromethane and stirred under argon atmosphere for 30 min upon which the solution becomes gradually viscous. Then, ibuprofen modified diol **1a** (0.7 g, 1.161 mmol) was added into the reaction mixture after which the solvent was immediately evaporated. The reaction mixture was then further heated at 70°C under inert atmosphere. Next, the reaction mixture was dissolved in DMF and the polymer product was precipitated by adding this mixture to water. The white precipitate was filtered and dried to yield the targeted polyurethane **1** as a yellowish waxy-like product.

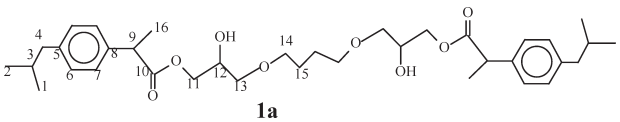
2.3 Characterization

*2.3.1 Compound **1a***

FT-IR (KBr): ν_{max} = 3395 (br, O-H str.), 2945 CH str. asym), 2862 (CH str. sym), 1730 (ester C=O str.), 1582 and 1505 (aryl C=C), 1460, 1383, 1332 (aryl group), 1255. 1205

Address correspondence to: Samaresh Ghosh, Department of Chemistry, Bankura Sammilani College, Kenduadihi, Bankura 722102, WB, India. E-mail: gsamaresh@yahoo.com

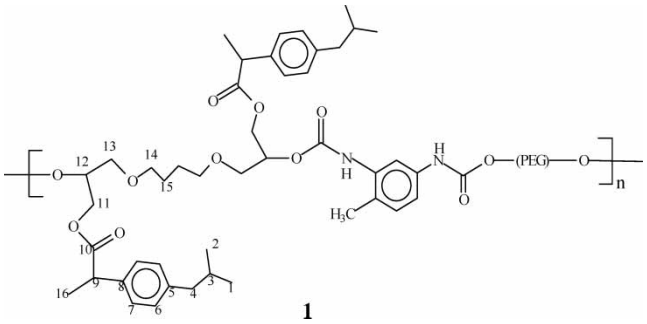
(CO-O-C str.), 1107 (C-O-C and C-O-H), 843, 798 cm^{-1}; ^1H NMR ($CDCl_3$, 500 MHz) δ_H: 7.29 (d, J = 4 Hz), 7.19 (d, J = 4 Hz), 7.08 (d, J = 4 Hz), 7.02 (d, J = 4 Hz), 4.12 (m, 4H, $H_{11,11'}$), 3.9 (bs, 4H, $H_{13,13'}$), 3.77 (m, 2H, $H_{12,12'}$), 3.70–3.28 (bm, 6H, $H_{14,14'}$, $H_{9,9'}$), 2.43 (d, J = 4 Hz, 4H, $H_{4,4'}$), 2.22 (bs, 2H, -CH-O*H*), 1.85 (m, 4H, $H_{15,15'}$), 1.61–1.42 (m, 6H, $H_{16,16'}$), 1.25 (m, 2H, $H_{3,3'}$), 0.89 (d, J = 2 Hz, 12H, $H_{1,1',\ 2,2'}$); Anal. Calcd for **1a**: C, 71.52; H, 8.94; found: C, 71.01; H, 8.41.



1a

2.3.2 Polyurethane *1*

FT-IR (KBr): ν_{max} = 3440 (br, O-H, N-H str.), 2911 (CH str. asym), 2869 (CH str. sym), 1727 (ester C═O, urethane C═O str.), 1599 (aryl C═C), 1543 (-OCONH, aryl CH), 1466, 1348, 1280 (aryl group), 1235 (CO-O-C str.), 1114 (C-O-C), 957, 847 cm^{-1}; ^1H-NMR (DMSO-d_6, 500 MHz) ($_H$: 8.19 (bs, 1H, NHCO ortho to CH_3 from TDI), 7.95 (bs, 1H, NHCO para to CH_3 from TDI), 7.51 (bm, 1H, ArH^3 from TDI), 7.19 (d, J = 2 Hz, ArH from ibuprofen unit), 7.12-6.98 (bm, ArH^6 from TDI unit, ArH from ibuprofen unit), 6.80 (bm, 1H, ArH^5 from TDI unit), 5.0 (bm, 2H, $H_{12,12'}$), 4.19 (s, 4H, $H_{11,11'}$), 3.95 (m, 4H, $H_{13,13'}$), 3.72 (m, 4H, -NHCO-O-CH_2-CH_2-O- from PEG unit), 3.6 (s, 4H, -NHCO-O-CH_2-CH_2-O- from PEG unit), 3.52–3.20 (bm, other CH_2 from PEG unit, $H_{9,9'}$ of ibuprofen unit), 2.5 (s, 3H CH_3 of TDI unit), 2.4 (m, 2H, $H_{4,4'}$ deshielded), 2.2 (m, 2H, $H_{4,4'}$ shielded), 1.8 (m, 4H, $H_{15,15'}$), 1.61–1.42 (m, 6H, $H_{16,16'}$), 1.2 (m, 2H, $H_{3,3'}$), 0.84 (d, J = 2 Hz, 12H, $H_{1,1',\ 2,2'}$). ^{13}C-NMR (DMSO-d_6, 100 MHz) δ_C: 173.7 (-COO-), 161.8 (-OCONH-), 139.6, 137.8 (unresolved), 130.0 (unresolved), 128.9, 127.0, 95.3, 71.0, 70.2, 69.7, 68.7, 67.0, 65.0, 44.1, 29.5, 29.0, 25.7, 22.0, 18.3. Anal. Found for **1**: C, 56.55; H, 9.20; N, 2.44.



1

2.4 Drug Release Study

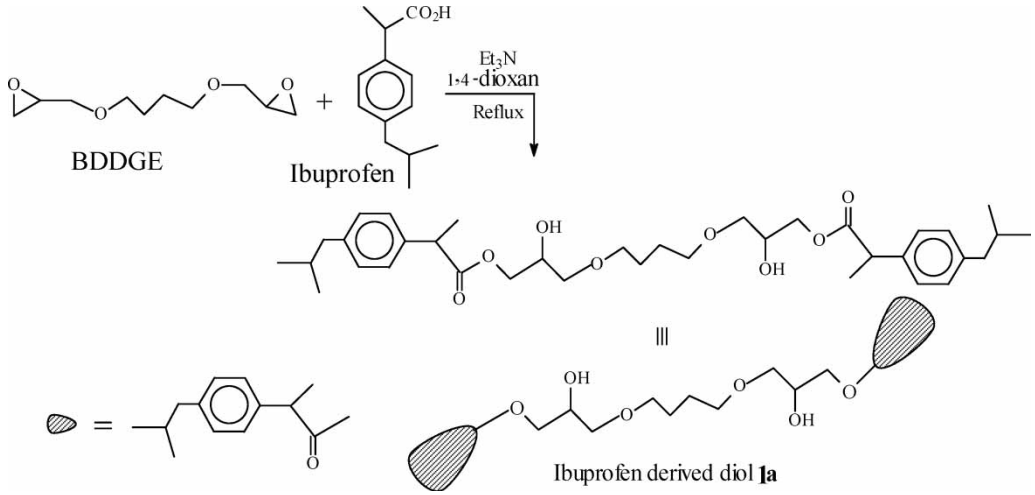
Polymer sample was immersed in PBS solution and incubated at 37 ±0.1°C. At suitable time intervals, the sample was centrifuged at 200 rpm, supernatant was collected and analyzed by UV-Vis and HPLC monitored at 220 nm. HPLC analysis was performed on Reverse Phase C_{18} Column (4.6 × 150 mm, particle size 5 mm, Agilent-1100 Series). A 20 ml of released media was injected. The mobile phase was used in this separation in a gradient from (methanol: acetonitrile) 60:40 to 65:35 for 10 min with 1 ml/min flow rate and monitored at 220 nm. Diode array detector (DAD) coupled with HPLC system was used to check its identity by the overlaying UV-vis spectrum.

3 Results and Discussion

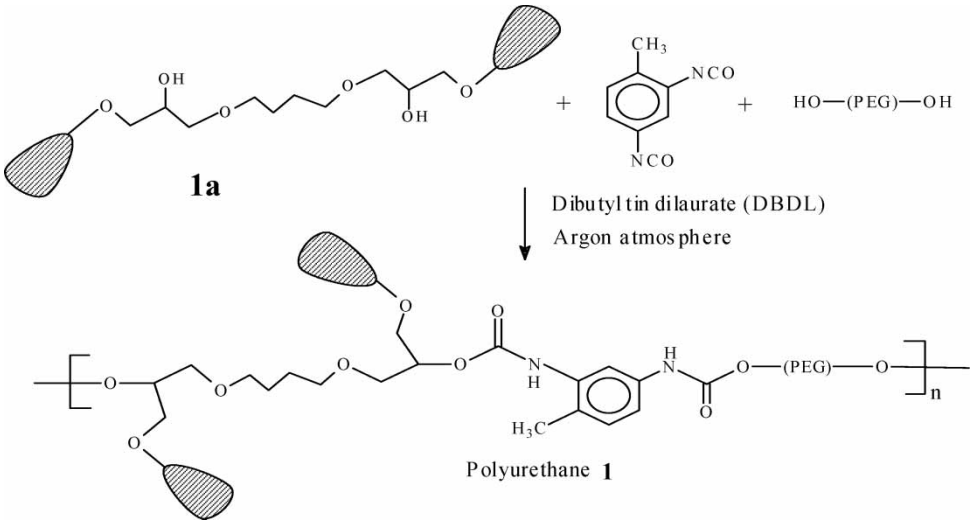
3.1 Synthesis and Characterization

The synthetic scheme for the polyurethane is shown in Schemes 1 and 2. Ibuprofen was first reacted with butane diol diglycidyl ether (BDDGE) forming ester derivative **1a** (Scheme 1) having two hydroxyl groups.

The synthesis of polyurethane **1** was then commenced (Scheme 2) by a simple polymerization reaction of the



Sch. 1. Synthesis ibuprofen derived monomer **1a**.



Sch. 2. Synthesis of polyurethane **1**.

ibuprofen-derived diol **1a**, and 2,4-toluidene diisocyanate (TDI) in presence dibutyltin dilaurate (DBDL) catalyst.

Targeted polyurethane **1** was unequivocally characterized using a range of techniques- FT-IR, NMR (^{1}H, ^{13}C), and elemental analysis. The ratio of ibuprofen-derived diol (**1a**) unit and PEG unit in the polyurethane was determined by ^{1}H-NMR spectroscopy. By the intensity ratio of methyl protons in **1a** unit appearing in 0.84 ppm vs. methylene protons in PEG unit appearing in 3.72, 3.60 and 3.52–3.20 ppm, the ratio of **1a** vs. PEG units in the polyurethane was found to be 02.66.

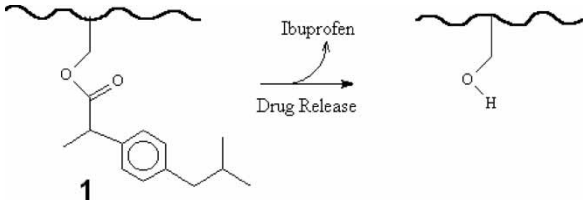
$$\frac{\text{Diol (1a) unit}}{\text{PEG-unit}} = \frac{I_{CH_3}(\delta 0.84)/12}{I_{CH_2}(\text{PEG unit})/400}$$

where,

$$I_{CH_2}(\text{PEG unit}) = I_{CH_2}(\delta 3.72) + I_{CH_2(\delta 3.60)} + I_{CH_2}(\delta 3.52 - 3.20)$$

$$I_{CH_2}(\delta 3.52 - 3.20) = I_{CH_2 + CH_{9',9}} \text{ of ibuprofen unit} - \left[I_{CH_{9',9}} \equiv I_{CH_{3',3}}\right]$$

The introduction of ibuprofen into the polymer backbone is especially attractive in this new approach. The pre-made drug bound diol **1a** was achieved through the epoxy ring opening with ibuprofen. Thus, this route has advantages of attaching ibuprofen via ester linkages that are susceptible to hydrolysis under physiological pH (Scheme 3).



Sch. 3. Release sketch of ibuprofen from polyurethane **1**.

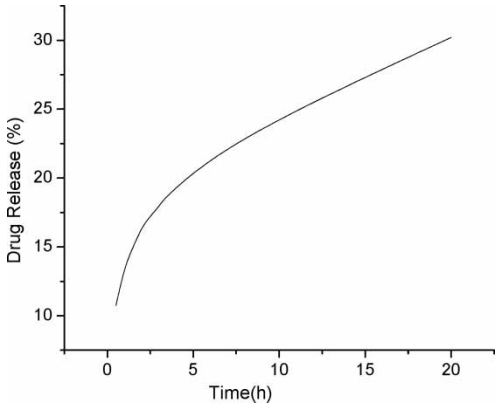


Fig. 1. Release profile for ibuprofen from **1** at the PBS solution at 37°C.

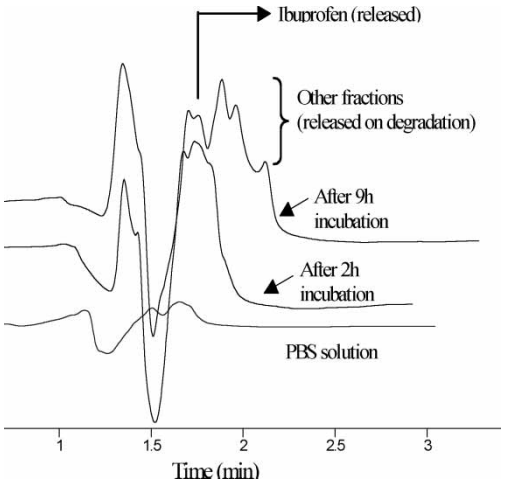


Fig. 2 HPLC profiles of supernatant PBS solution incubated at 37°C.

The drug release was studied in phosphate buffer saline (PBS) solution (pH 7.4) at 37°C by monitoring on a UV-Vis spectrophotometer at 220 nm. Figure 1 shows the qualitative release (%) of ibuprofen with time demonstrating the significant dissociation of ester linkages responsible for the release of ibuprofen from polymer main chain. Also urethane linkages are susceptible for the hydrolysis under the condition specified and its degraded product can interfere with UV absorption at 220 nm. Therefore, it is very important to cross check drug release kinetics by another analytical instrument such as HLPC.

The HPLC result (Figure 2) further supports the release of ibuprofen ($t_R = 1.8$ min, also confirmed by overlay of UV-spectrum with the standard ibuprofen solution) through labile ester bond cleavage under specified conditions. Ibuprofen release was detected by monitoring the absorbance at 220 nm, and a single peak was observed upto 3 h incubation. Interestingly, with increasing the incubation time (after 3 h), in the given condition, HPLC pattern changes (appearance of multiple peaks), suggesting the release of other aromatic unit, most likely occurring through the breakage of more stable urethane linkages. Thus HPLC result further indicates the degradability of the polymer back-bone that is also extremely important.

As an alternative measure to confirm the dissociation of the ester/urethane linkages during drug release, FT-IR spectral study was carried out. The gradual decrease in intensity of the peak at 1727 cm^{-1} assignable to the ester/urethane groups indicates breakage of these groups in the PBS medium.

4 Conclusions

A new approach to the preparation of novel polyurethane bearing ibuprofen drug has been developed. This new macromolecular design technique involves the introduction of ibuprofen into the polymeric backbone through ester linkages displaying the release profile of ibuprofen. It thus shows the promise for the development of degradable polymer based drug delivery devices for efficient release of ibuprofen in physiological media. Further studies are under progress to explore the development of other novel polymeric materials bearing a series of pharmaceutically active drugs and their tunable drug release events.

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