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Macromolecular prodrugs. VIII. Synthesis of polymer–gemfibrozil conjugates

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Abstract

Gemfibrozil is covalently linked to two similar polymers: poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)] and poly[α,β-(*N*-3-hydroxypropyl-DL-aspartamide)]. The synthesised polymer–drug conjugates differ in average molecular mass, type of covalent bonding, length of spacer, drug-loading and solubility.

Keywords: Gemfibrozil; Macromolecular prodrug; Polymer-drug conjugate; Poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)]; Poly[α,β-(*N*-3-hydroxypropyl-DL-aspartamide)]; Poly-DL-(2,5-dioxo-1,3-pyrrolidinediyl)

1. Introduction

Gemfibrozil is a fibrate lipid-lowering agent beneficial in the treatment of dyslipidaemias and atherosclerosis. It appears to be most useful in lipoprotein disorders characterised by elevation of very-low-density (VLD) lipoproteins and plasma triglycerides, since it lowers triglycerides and both total and VLD-cholesterol, while high-density lipoprotein (HDL)-cholesterol levels increases (Aberg et al., 1998; Miller and Spence, 1998). Gemfibrozil is also useful in the clearance of postprandial lipoproteins in hypertriglyceridemic patients (Weintraub et al., 1998). However, its short plasma half-life requires relatively frequent dosing. In order to improve its pharmacokinetics and bioavailability, aliphatic and aromatic gemfibrozil esters (Laruelle and Lepant, 1991; Zhong

Abbreviations: BtcCl, *N*-1-benzotriazole carboxylic acid chloride; BtH, benzotriazole; DMF, *N*,*N*-dimethylformamide; Gem, gemfibrozil; Gem-Bt, gemfibrozil benzotriazolide; M_r, average molecular mass; PAHA, poly[α,β-(*N*-2-aminoethyl-DL-aspartamide)]-poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)] copolymer; PHEA, poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)]; PHEA-Gem-A, poly[α,β-(*N*-2-hydroyethyl-DL-aspartamide)]-gemfibrozil amide conjugate; PHEA-Gem-E, poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)]-gemfibrozil ester conjugate; PHPA, poly[α,β-(*N*-3-hydroypropyl-DL-aspartamide)]; PHPA-Gem, poly[α,β-(*N*-3-hydroxypropyl-DL-aspartamide)]-gemfibrozil conjugate; PSI, poly-DL-(2,5-dioxo-1,3-pyrrolidinediyl); PSI-Gem, poly-DL-(2,5-dioxo-1,3-pyrrolidinediyl)-gemfibrozil conjugate; SMA, styrene-maleic anhydride copolymer; TEA, triethylamine.

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and Yin, 1992; Piccoli et al., 1994), benzamides (Sircar and Holmes, 1983), nicotinic acid (Hoefle, 1981) and 3-ethoxy derivatives (Wang et al., 1996) have been synthesised.

A promising approach to improve drug delivery is to link an active agent as a side substituent to a polymeric structure by means of a cleavable bond (Giammona et al., 1994, 1995, 1998; Vasey et al., 1999). Such obtained macromolecular prodrugs (polymer–drug conjugates) may offer many advantages compared to other drug delivery systems: increased drug solubility, prolonged drug release, more convenient drug regiment, increased stability and targetability.

In authors' previous papers, the use of poly[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)] (PHEA) (Zorc et al., 1993a,b; Zorc and Butula, 1994), poly[α,β-(*N*-2-aminoethyl-DL-aspartamide)]-poly-[α,β-(*N*-2-hydroxyethyl-DL-aspartamide)] copolymer (PAHA) (Zorc et al., 1995) and styrene-maleic anhydride copolymer (SMA) (Kalčić et al., 1996) as drug carriers for carboxylic acid, amino acid, hydroxyl and amino drugs was described. In this paper, the attachment of gemfibrozil to PHEA and its newly synthesised analogue poly[α,β-(*N*-3-hydroxypropyl-DL-aspartamide)] (PHPA) through hydrolytically and enzymatically cleavable ester and amide bondings is reported. Such prepared polymer–gemfibrozil conjugates could be potentially useful gemfibrozil prodrugs of increased solubility and prolonged drug release.

2. Materials and methods

2.1. Materials

IR spectra were recorded on a FT-IR Paragon 500 spectrometer (Perkin–Elmer, UK) and UV spectra on a Hewlett Packard 8452A Diode Array spectrophotometer (Hewlett Packard, Germany). ^{1}H and ^{13}C NMR spectra were recorded on a Varian Gemini 300 spectrometer (Varian, USA), operating at 75.5 MHz for the ^{13}C nucleus. Samples were measured from CD_3COCD_3 solutions at 20°C in 5-mm NMR tubes. Chemical shifts (ppm) are referred to TMS. Viscosity measurements were carried out at 25°C using an Ostwald viscosimeter, with a flow time for water from 100–200 s. Polymer solutions were dialysed against several changes of deionised water using 18/22 inch Visking dialysis tubing (Serva, Germany) with a molecular cut-off of 8000–15 000. For thin layer chromatography, silica gel sheets Kieselgel 60 F_{254} (Merck, Germany) were used. Solvent systems were chloroform/methanol (9:1), hexane/acetone (3:1) and *n*-butanol/water/acetic acid (8:1:1). For spot detection iodine vapours were used. Gemfibrozil was obtained from Lek (Slovenia). L-aspartic acid was purchased from Aldrich (USA). The amines were distilled and dried prior to use. All solvents were of analytical grade purity and dry.

2.2. Chemistry

2.2.1. Poly-DL-(2,5-dioxo-1,3-pyrrolidinediyl) (PSI, 1)

PSI was prepared from L-aspartic acid and fractionated in four fractions 1a–d with different average molecular masses (Neri et al., 1973; Jakopović et al., 1996).

2.2.2. Poly[α,β-(N-2-hydroxyethyl-DL-aspartamide)] (PHEA, 2)

PHEA (2a–d) was synthesised following the method described by Neri (Neri et al., 1973). The average molecular masses (M_r) were determined by viscosimetric method (Antoni et al., 1974). M_r were 31 000 (2a), 51 000 (2b), 56 000 (2c) and 61 000 (2d).

2.2.3. Poly[α,β-(N-3-hydroxypropyl-DL-aspartamide)] (PHPA, 3)

To a solution of 31.00 g PSI (1d) in 160 mL *N*,*N*-dimethylformamide (DMF), 59.94 g (0.798 mol) of 3-hydroxypropylamine was slowly added. The reaction mixture was stirred at room temperature for 2.5 h and then acidified with diluted sulfuric acid to pH 4. The solution was diluted with water, dialysed against several changes of deionised water and lyophilised. Yield: 34.78 g (63.3%) of product 3. IR (KBr): ν_{max} 3396, 3086,

2936, 2882, 1654, 1543, 1438, 1378, 1292, 1197, 1061, 1000, 658 cm^{-1}.

2.2.4. Gemfibrozil benzotriazolide (Gem-Bt, 4)

The compound 4 was prepared from gemfibrozil and *N*-1-benzotriazole carboxylic acid chloride (BtcCl) (Lovrek et al., 2000).

2.2.5. Poly[α,β-(N-2-hydroxyethyl-DL-aspartamide)]/-gemfibrozil ester conjugate (PHEA-Gem-E, 5a–d)

(a) A solution of 0.63 g PHEA (2a), 2.11 g (0.006 mol) Gem-Bt (4), and 4.25 g (0.042 mol) triethylamine (TEA) in 23 mL DMF was stirred at room temperature for 3 days. The reaction mixture was evaporated under reduced pressure. The sticky residue was then triturated with cyclohexane, acetone and ether in order to remove benzotriazole, amine and eventually unbound 4, since these compounds were soluble in the used solvents and conjugate 5 was not. The final loose product 5a was filtered off. Yield: 0.59 g (27.9%). IR (KBr): ν_{max} 3336, 3080, 2932, 1725, 1656, 1538, 1389, 1261, 1196, 1153, 1056, 805, 698, 588 cm^{-1}. UV: λ_{max} 276 nm ($A = 0.895$; $\gamma = 135$ μg ml^{-1}, H_2O).

(b) An analogous procedure as for (a) but different molar ratio of reactants were used. Reaction conditions: 2b, 0.50 g; 4, 0.35 g (0.001 mol); TEA, 0.71 g (0.007 mol); DMF, 10 ml; reaction time, 3 days. Yield on product 5b: 0.26 g (35.6%). UV: λ_{max} 276 nm ($A = 0.509$; $\gamma = 700$ μg ml^{-1}, H_2O).

(c) An analogous procedure as for (a) but different molar ratio of reactants were used. Reaction conditions: 2c, 0.33 g; 4, 0.70 g (0.002 mol); TEA, 1.42 g (0.014 mol); DMF, 10 ml; reaction time, 3 days. Yield on product 5c: 0.39 g (48.4%). UV: λ_{max} 276 nm ($A = 0.645$; $\gamma = 333$ μg ml^{-1}, NaH_2PO_4/HCl buffer, pH = 7.45).

(d) An analogous procedure as for (a) but different molar ratio of reactants were used. Reaction conditions: 2d, 0.33 g; 4, 0.70 g (0.002 mol); TEA, 1.42 g (0.014 mol); DMF, 20 ml; reaction time, 3 days. Yield on product 5d: 0.28 g (34.6%). UV: λ_{max} 276 nm ($A = 0.523$; $\gamma = 228$ μg ml^{-1}, NaH_2PO_4/HCl buffer, pH = 7.45).

2.2.6. Poly[α,β-(N-3-hydroxypropyl-DL-aspartamide)]/-gemfibrozil conjugate (PHPA-Gem, 6)

A solution of 1.03 g PHPA (3), 2.11 g (0.006 mol) Gem-Bt (4) and 4.27 g (0.042 mol) TEA in 22 ml DMF was stirred at room temperature for 3 days. The reaction mixture was evaporated under reduced pressure. The sticky residue was then triturated with cyclohexane, acetone and ether in order to remove benzotriazole, amine and eventually unbound 4, since these compounds were soluble in the used solvents and conjugate 6 was not. The final white loose product 6 was filtered off. Yield: 1.10 g (45.3%). IR (KBr): ν_{max} 3430, 2929, 1724, 1646, 1539, 1434, 1388, 1261, 1155, 1129, 1056, 804, 558 cm^{-1}. UV: λ_{max} 276 nm ($A = 0.643$; $\gamma = 490$ μg ml^{-1}, H_2O).

2.2.7. Gemfibrozil 2-aminoethylamide (7)

Solution of 0.60 g (0.0017 mol) Gem-Bt (4) in 40 ml toluene was added dropwise during 50 min to a solution of 10.27 g (0.171 mol) ethylenediamine in 5 ml toluene. The reaction mixture was stirred for 6 h at room temperature and extracted four times with water. The organic layer was dried over sodium sulphate, filtered and evaporated under reduced pressure. Yield: 0.42 g (83.5%) of oily product 7. IR (film): ν_{max} 3358, 2953, 2924, 2870, 2732, 1714, 1663, 1644, 1586, 1530, 1509, 1476, 1456, 1435, 1415, 1391, 1368, 1265, 1157, 1130, 1042, 999, 934, 896, 844, 803, 731, 695, 587 cm^{-1}. ^1H NMR (CD_3COCD_3), δ (ppm): 7.31 (m, 1H, CONH), 7.08 (d, 1H, arom.), 6.81 (s, 1H, arom.), 6.74 (d, 1H, arom.), 4.02 (t, 2H, OCH_2), 3.52 (m, 2H, $NHCH_2$), 3.38 (m, 2H, CH_2NH_2), 2.38 (s, 3H, CH_3-arom.), 2.25 (s, 3H, CH_3-arom.), 1.82 (m, 4H, $OCH_2CH_2CH_2$), 1.30 (s, 6H, $(CH_3)_2C$). ^{13}C NMR (CD_3COCD_3), δ (ppm): 176.90 (C-1), 157.48 (C-8), 136.63 (C-12), 130.43 (C-10), 123.30 (C-9), 120.85 (C-11), 112.95 (C-13), 68.20 (C-7), 50.65 (C-17), 41.63 (C-2), 40.31 (C-16), 37.64 (C-5, 6), 25.22 (C-3, 4), 20.77 (C-14), 15.33 (C-15). Elemental analysis for $C_{17}H_{27}N_2O_2$ (291.54) (%): calcd. C 70.04, H 9.34, N 9.65; found: 70.23, 9.30, 9.61.

2.2.8. Poly-DL-(2,5-dioxo-1,3-pyrrolidinediyl)-gemfibrozil conjugate (PSI-Gem, 8)

To a solution of 0.42 g PSI (1d) in 10 ml DMF, a solution of 0.38 g (0.0013 mol) gemfibrozil 2-aminoethyl amide (7) in 7 ml DMF was added. The reaction mixture was stirred at room temperature for 1 day. The solution of thus formed product 8 was used for the synthesis of conjugate 9. In another experiment the solution of 8 was evaporated under reduced pressure and the crude product 8 was isolated. Yield: 0.56 g (70.2%). It was used for the synthesis of the conjugate 9 as well.

2.2.9. Poly[α,β-(N-2-hydroxyethyl-DL-aspartamide)]-gemfibrozil amide conjugate (PHEA-Gem-A, 9)

To a solution of 0.46 g compound 8 in 14 ml DMF 0.75 g (0.012 mol) 2-hydroxyethylamine was added. The solution was stirred at room temperature for 2.5 h and evaporated under reduced pressure. The residue was triturated several times with acetone and ether in order to remove excess of 2-hydroxyethylamine. The insoluble product 9 was filtred off. Yield: 0.48 g (64.3%). IR (KBr): ν_{max} 3424, 2926, 2854, 1665, 1637, 1574, 1542, 1416, 1385, 1335, 1304, 1262, 1128, 1058, 668, 596, 542 cm^{-1}. UV: λ_{max} 276 nm ($A = 0.648$; $\gamma = 840$ μg ml^{-1}, KH_2PO_4/NaOH buffer, pH = 7.45).

3. Results and discussion

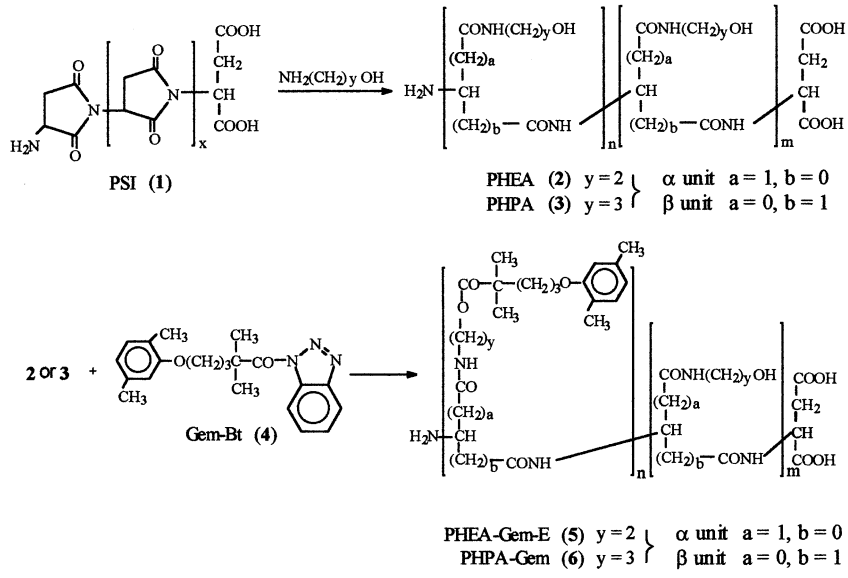
PSI was prepared by thermal polycondensation of L-aspartic acid in the presence of phosphoric acid under reduced pressure at 160 and 180°C, respectively (Neri et al., 1973). Fractional precipitation of PSI was carried out by pouring its DMF solution into ethanol as described earlier (Jakopović et al., 1996). Fractions 1a-d were used in further reactions. Aminolysis of PSI with 2-hydroxyethylamine gave PHEA (2a–d). Average molecular masses were 31 000 (2a), 51 000 (2b), 56 000 (2c) and 61 000 (2d) and they were determined by the viscosimetric method (Antoni et al., 1974). In order to prolong the distance between main chain and hydroxyl side groups aminolysis of PSI (1d) was carried out with 3-hydroxypropylamine as well. In this way a new hydroxy-functionalised polyaspartamide polymer PHPA (3) was prepared. It could be considered that its M_r was very close to 61 000, M_r of PHEA (2d), since both polymers were derived from the same PSI fraction (1d) and PSI was aminolysed under the analogous conditions. Average molecular masses of PSI and PHEA, determined according to the Mark-Houwink equation for PSI $[\eta] = 1.32 \times 10^{-2} \times M_r^{0.76}$ (Vlasak et al., 1979) and for PHEA $[\eta] = 2.32 \times 10^{-3} \times M_r^{0.87}$ (Neri et al., 1973), respectively, revealed that both polymers had practically the same polymerisation degree. Compounds 1–3 proved to be useful in preparation of polymer-drug conjugates 5–9 due to their reactive imide (1) or hydroxyl functionalities (2 and 3) (Schemes 1 and 2). The gemfibrozil-bearing molecules were gemfibrozil–benzotriazolide (4) and gemfibrozil 2-aminoethylamide (7). The synthesis of the conjugates 5 and 6 was essentially esterification of polyhydroxyl polymers 2 and 3 by the azole activated gemfibrozil 4. The conjugate 9 was prepared by partial aminolysis of PSI by aminoamide 7 (synthesis of PSI-Gem, 8), followed by aminolysis of the remaining succinimide units by means of 2-hydroxyethylamine. One could follow the extent of the last reaction step by IR spectroscopy: characteristic absorption of imide group at 1775 and 1716 cm^{-1} disappeared and hydroxyl group absorption at 3430 cm^{-1} appeared. Purification of the conjugates 5, 6 and 9 from the unbound gemfibrozil derivative 4 or 7, benzotriazole by-product or excess of amine was successfully performed by triturating of the crude conjugates with solvents which selectively dissolved impurities, but not the conjugates (TLC control).

Benzotriazolide 4 was prepared from gemfibrozil and *N*-1-benzotriazole carboxylic acid chloride (BtcCl) according the method developed by the authors (Lovrek et al., 2000). The compound 4 was the starting compound in the synthesis of 7 and the nucleophilic component was ethylenediamine (Scheme 3). In this reaction the excess of

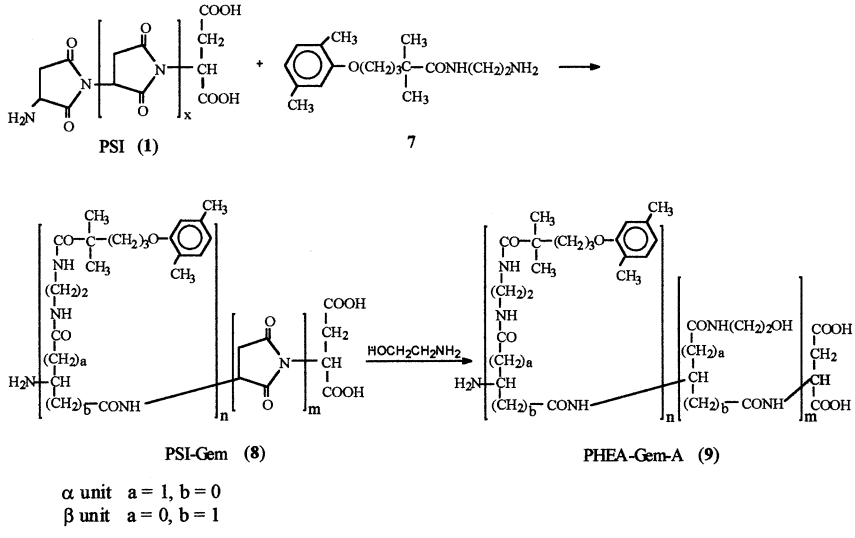
the amine was crucial to avoid the formation of bis-gemfibrozil ethylenediamide. The structure of 7 was characterised in full by IR, ^{1}H and ^{13}C NMR spectra (Fig. 1).

In polymer-drug conjugates 5 and 6 gemfibrozil was linked by an ester bond and in conjugates 8 and 9, by an amide bond. The compounds 5 and 6 differ in the length of spacer between polymer carriers and drug and the compounds denoted with the same number and different letter, differ either in molecular masses or in the drug loading or both.

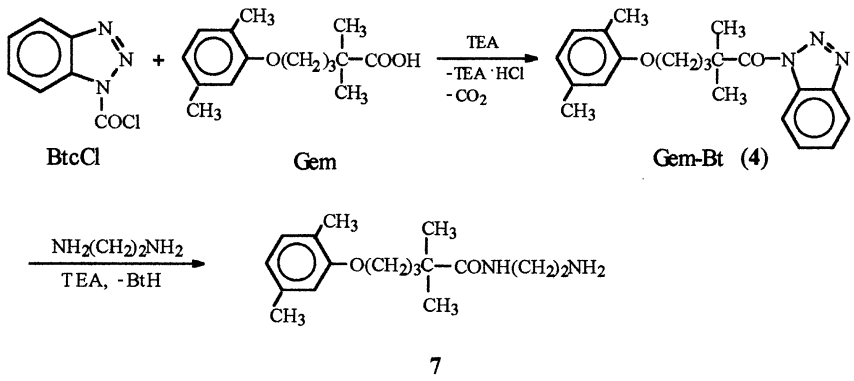
The conjugates 5, 6 and 9 were hydrosoluble gemfibrozil derivatives and 8 was the only conju-



Scheme 1.



Scheme 2.



Scheme 3.

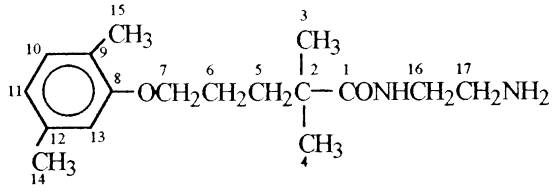


Fig. 1. Chemical structure and atom enumeration of gemfibrozil 2-aminoethylamide (7).

gate insoluble in water because of the lack of polyhydroxyl functionalities. Solubility of the conjugates 5a–d was related to the drug loading. As could be expected, solubility decreased with the increase of the bound drug. To assure hydrosolubility maximum half of the available hydroxyl groups in PHEA were substituted by gemfibrozil residue.

The drug loading in polymer–gemfibrozil conjugates was estimated by UV-spectroscopy using the molar absorption coefficient for gemfibrozil $\varepsilon_{276} = 1866$ dm^3 mol^{-1} cm^{-1} (in 96% EtOH, $c = 4.99 \times 10^{-4}$ mol l^{-1}). The percentage of gemfibrozil in PHEA-Gem-E (5a–d) was in the range from 10.9 to 53.4%, in PHPA-Gem (6), 19.7% and finally in PSI-Gem (8) and PHEA-Gem-A (9) 12.1% (Table 1). The drug loading depended on the molar ratio of the reactants 4 or 7 and

Table 1
Preparation and characterisation of polymer–gemfibrozil conjugates 5–9[a]

Conjugates	Reactants		Yield (%)	Drug loading (%)	A (276 nm)
PHEA-Gem-E (5a)	PHEA (2a)	Gem-Bt (4)	27.9	53.4	0.895[b]
PHEA-Gem-E (5b)	PHEA (2b)	Gem-Bt (4)	35.6	10.9	0.509[c]
PHEA-Gem-E (5c)	PHEA (2c)	Gem-Bt (4)	48.4	29.1	0.645[d]
PHEA-Gem-E (5d)	PHEA (2d)	Gem-Bt (4)	34.6	34.4	0.523[e]
PHPA-Gem (6)	PHPA (3)	Gem-Bt (4)	45.3	19.7	0.643[f]
PSI-Gem (8)	PSI (1)	Amide 7	70.2	12.1[g]	–
PHEA-Gem-A (9)	PSI-Gem (8)	$HOCH_2CH_2NH_2$	64.3	12.1	0.648[h]

[a] γ (μg ml^{-1}, solvent).
[b] 135, H_2O.
[c] 700, H_2O.
[d] 333, NaH_2PO_4/HCl buffer, pH = 7.45.
[e] 8228, NaH_2PO_4/HCl buffer, pH = 7.45.
[f] 490, H_2O.
[g] Drug loading was determined indirectly, after converting conjugate 8 to 9.
[h] 840, KH_2PO_4/NaOH buffer, pH = 7.45.

monomer units of the corresponding polymer 1, 2 or 3, but was not strictly stoichoimetric. The values of experimentally determined drug loading were always less than the expected ones.

The proof that gemfibrozil was covalently bound in the synthesised polymer-drug conjugates could be found in IR- and UV-spectra. The IR-spectra of 5 and 6 showed an ester carbonyl band at 1725 cm^{-1}. All prepared conjugates absorbed UV-light in the same absorption ranges as gemfibrozil, whereas PHEA and PHPA themselves had no UV-absorption at these wavelengths. The absence of nonconjugated drug was confirmed by TLC using hexane/acetone (3:1) solvent system in which polymer derivatives remained at start and gemfibrozil, its benzotriazolide 4 or aminoamide 7 had R_f value 0.38, 0.68 and 0, respectively. The absence of compound 7 was checked by *n*-butanol/water/acetic acid (8:1:1) solvent system ($R_f = 0.5$).

Preliminary hydrolysis studies showed that gemfibrozil could be released from the prepared polymer–drug conjugates, but detail kinetic studies still remain to be done. The prepared polymer–gemfibrozil conjugates could be considered as an example of 'drug reservoir' that might sustain a drug to be available in the body for longer time periods after chemical or enzymatic hydrolysis.

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