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Polymer Edition

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The *Journal of Biomaterials Science, Polymer Edition*, will publish fundamental research on the mechanism of interaction between biomaterials and living organisms, with attention being focused at the molecular and cellular levels. The journal will publish original research papers, short communications and review articles. The publication of fundamental research is expected to contribute significantly to future progress in the practical applications of biomaterials.

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The existing journals on biomaterials tend to publish papers which emphasize the applications of biomaterials. The *Journal of Biomaterials Science, Polymer Edition*, seeks to redress the balance and to provide an international forum for fundamental biomaterials research.

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Pharmacokinetic results on naproxen prodrugs based on poly(ethyleneglycol)s

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Abstract—Five prodrugs of S(+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen), in which the drug was bound by ester linkages to diethyleneglycol (**I**), triethyleneglycol (**II**), octanediol (**III**), butyl-triethyleneglycol (**IV**), and butyl-tetraethyleneglycol (**V**), respectively, were prepared and tested for their pharmacokinetic properties after oral administration. It was found that bioavailabilities decreased in the order, and in all cases were lower than that of the free drug.

Key words: S(+)-2-(6-methoxy-2-naphthyl)propionic acid; naproxen pharmacokinetics; oligomeric prodrugs; oligomeric poly(ethyleneglycol)s.

INTRODUCTION

By analogy with conventional prodrugs [1], an oligomeric prodrug can be defined as an oligomeric substance that, once administered, gives rise to an active drug, as a consequence of a chemical transformation occurring within the body [2]. Typically, an oligomeric prodrug is composed of two parts: an oligomeric carrier promoiety; and a drug moiety linked by a chemical bond cleavable under physiological conditions. The oligomeric prodrug approach, using poly(ethyleneglycol)s (PEGs), has been followed in the past with excellent results, with the purpose of increasing bioavailability and reducing toxicity of pyromidic acids, 4-isobutylphenyl-2-propionic acid (ibuprofen) [3] and ursodeoxycholic acid [4, 5]. Similar derivatives with other families of drugs also show interesting properties.

In this paper, we thought it interesting to report on a new set of derivatives all containing the same drug moiety, coupled with ester bond with oligomers having different molecular size and a different hydrophilic–lipophilic balance (HLB). As a drug we have selected S(+)-2-(6-methoxy-2-naphthyl)propionic acid (naproxen) which has the advantage of being very easily detectable in the blood stream, and of having, as a free drug, very good pharmacokinetic characteristics and high bioavailability after oral administration. Naproxen does not undergo first pass metabolism in the liver [6]. The aim of this paper was to study the effect of the promoiety on pharmacokinetic properties of oligomeric derivatives in which the drug moiety is highly hydrophobic, and the bond is of the ester type, without interferences by a protection towards liver inactivation.

EXPERIMENTAL

Materials and methods

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spectra were run on a 60 MHz 360A Varian spectrometer, in $CDCl_3$ solutions, using TMS as internal reference. Elemental analyses were performed by Redox Laboratory (Cologno Monzese-Milano). TLC were run on Merck silica gel layers using chloroform/isopropanol 4:1 as eluent.

Diethyleneglycol, triethyleneglycol, tetraethyleneglycol, *n*-butanol, 1,8-octanediol, 1,1′-carbonyldiimidazole and S(+)-2-(6-methoxy-2-naphthyl)-propionic acid (naproxen) were purchased from Fluka and used without further purification.

Naproxen imidazolide—naproxen (14.00 g, 60.80 mmol) was dissolved in alcohol-free chloroform (100 ml). *N*,*N*′-carbonyldiimidazole (19.71 g, 121.6 mmol) was added at once, under inert atmosphere, and the solution was maintained under stirring for 30 min. The reactive solution was used as such in the following reactions.

Diethyleneglycol-naproxen adduct (**I**)—diethyleneglycol (2 g, 18.85 mmol) was dissolved in alcohol-free chloroform (10 ml) and dried over calcium hydride. The chloroform solution was then filtered off and added to the naproxen imidazolide solution previously prepared. The reaction mixture was maintained in anhydrous conditions, at 60°C for 24 h. After this time it was diluted with chloroform, extracted with 0.1 sodium hydroxide aqueous solution (2 × 20 ml), then with water (5 × 20 ml), and dried over desiccator. The solvent was then evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel, chloroform/isopropanol 4:1 as eluent). Yield = 5.150 g (85%). Elemental: experimental C% 67.82, H% 7.07; and calculated C% 67.94, H% 6.92. IR (cm^{-1}): 2820–2960 (ν C—H); 1730 (ν C=O); 1600 (ν C=C); and 1140 (ν C—O). ^{1}H NMR (δ, ppm): 0.8 (3H, *d*, CH_3—C); 3.95–4.33 (13H, *m*, CH_2—O, H—O, CH_3—O, CH_2—O—CO, CH—Ar); and 6.1–6.8 (6H, *m*, aromatic H).

Triethyleneglycol-naproxen (**II**), and octanediol-naproxen adduct (**III**) were prepared with the same procedure as that for diethyleneglycol, by substituting equivalent amounts (on a molar base) of the above diols for diethyleneglycol.

The products were characterized as follows: (**II**) Elemental: experimental: C% 66.02, H% 7.89; and calculated C% 66.31, H% 7.18. IR (cm^{-1}): 2820–2960 (ν C—H); 1730 (ν C=O); 1600 (ν C=C); 1500 (ν C=C); and 1140 (ν C—O). ^{1}H NMR (δ, ppm): 0.8 (3H, *d*, CH_3—C); 3.95–4.33 (17H, *m*, CH_2—O, CH_2—O—CO, CH_2—O, CH—Ar, H—O); and 6.1–6.8 (6H, *m*, aromatic H). (**III**) Elemental: experimental C% 71.07, H% 7.69; and calculated C% 71.54; H% 7.28. IR (cm^{-1}): 2820–2960 (ν C—H); 1730 (ν C=O); 1600 (ν C=C); and 1140 (ν C—O). ^{1}H NMR (δ, ppm): 0.8 (3H, *d*, CH_3—C); 0.89–1.30 (12H, *m*, CH_2—C); 3.95–4.33 (9H, *m*, CH_3—O, CH_2—O—CO, CH—Ar, C—CH_2—O, H—O); and 6.1–6.8 (6H, *m*, aromatic H).

Butyl-triethyleneglycol adduct: butanol (2 g, 27 mmol was dissolved in alcohol-free chloroform (50 ml). *N*,*N*′-carbonyldiimidazole (8.858 g, 54.6 mmol) was added at once, under inert atmosphere, and the solution was maintained under stirring for 30 min. Anhydrous triethyleneglycol (4.057 g, 27.0 mmol), was added to the reaction mixture, and it was maintained overnight under stirring at 60°C. After this time it was diluted with chloroform, extracted several times with water, and dried over desiccator. The solvent was then evaporated under reduced pressure. Yield = 6.808 g (100%). IR (cm^{-1}): 2860 (ν C—H); 1742 (ν C=O); and 1140

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Butyl-triethyleneglycol-naproxen adduct: (**IV**): butyl-triethyleneglycol (5.00 g, 19.82 mmol) was dissolved in alcohol free chloroform (20 ml) and dried over calcium hydride. The chloroform solution was then filtered off and added to the naproxen imidazolide solution prepared as previously described. The reaction mixture was maintained in anhydrous conditions, at 60°C for 24 h. After this time it was diluted with chloroform, extracted several times with water, and dried over a desiccator. The solvent was then evaporated under reduced pressure. The crude product obtained was purified by column chromatography (silica gel, chloroform/isopropanol 4:1 as eluent). Yield = 7.466 g (90%). Elemental: experimental C% 67.82, H% 7.07; and calculated C% 67.94, H% 6.92. IR (cm^{-1}): 2960 (ν C—H); 1740 (ν C=O); 1600 (ν C=C); 1500 (ν C=C); and 1140 (ν C—O). ^{1}H NMR (δ, ppm): 0.80–0.85 (6H, *m*, CH_3—C); 1.0–1.4 (4H, *m*, CH_2—C); 3.95–4.33 (18H, *m*, CH_3—O, CH_2—O—CO, CH—Ar, CH_2—O); and 6.1–6.8 (6H, *m*, aromatic H).

Butyl-tetraethyleneglycol-naproxen adduct (**V**) was prepared with the same procedure as triethyleneglycol one, by substituting equivalent amounts (on a molar base) of tetraethyleneglycol for triethyleneglycol. The product was characterized as follows: IR (cm^{-1}): 2860–2960 (ν C—H); 1730 (ν C=O); 1600 (ν C=C); 1500 (ν C=C); and 1140 (ν C—O). ^{1}H NMR (δ, ppm): 0.80–0.85 (6H, *m*, CH_3—C); 1.0–1.4 (4H, *m*, CH_2—C); 3.95–4.33 (22H, *m*, CH_3—O, CH_2—O—CO, CH—Ar, CH_2—O); and 6.1–6.8 (6H, *m*, aromatic H).

Pharmacokinetic studies

Male CD Sprague Dawley rats (Charles River, Italy), 333 ∓ 90 g (S.D.) body weight were used. A silicone catheter (1.19 mm outer diameter, Silastic, Dow Corning) was inserted in the right jugular vein under light ether anaesthesia 24 h before drug treatment [7]. Overall, 21 rats were utilized for the analysis. Naproxen hydrochloride was used as a reference standard for pharmacokinetic comparisons. It was administered by gavage to nine rats (20 mg kg^{-1}1 body weight).

Naproxen derivatives were given by gavage to twelve rats, at a dose of 20 mg kg^{-1} body weight of naproxen equivalent. All compounds for oral administration were suspended in corn oil. The presence of underivatized naproxen in corn oil suspensions of derivatives was checked by HPLC. Blood samples of 0.8 ml were collected at serial times, up to 30 h, after oral (gavage) administration, and immediately centrifuged. Plasma samples (about 0.4 ml) were stored at −20°C until extraction.

To the 0.3 ml of rat plasma, 10 μg of 6-methoxy-2-naphthylacetic acid (6-MNA) (50 μl of 200 μg/ml solution), as internal standard, and 20 μl of HCl 0.1 M were added. After addition of 5 ml of diethylether the tubes were shaken horizontally for 15 min and centrifuged for 5 min at 600 *g*. The organic phase was transferred and evaporated at room temperature under a stream of nitrogen. The residue was redissolved in 200 μl of acetonitrile and 20 μl as injected into an HPLC [8]. The mobile phase was acetonitrile-phosphate buffer ($H_2PO_4^-$/HPO_4^{2-}) 20 mM 60:40 vol/vol (pH 6.20), delivered at 1 ml min^{-1} (Beckman 112 solvent delivery module). The column effluent was monitored at 280 nm (Beckman 160 UV Absorbance Detector)

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