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Research paper

pH-sensitive polymeric physical-mixture for possible site-specific delivery of ibuprofen

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Abstract

Delivery of drugs to the large bowel has been extensively investigated during the last decade. The aim of this work was to study polymethacrylic acid-co-methylmethacrylate substituted with fatty acids (lauric, myristic, palmitic and stearic) at 20% substitution degree (PMA–LAUR20, PMA–MIR20, PMA–PALM20 and PMA–STEA20) or 40% substitution degree (PMA–LAUR40, PMA–MIR40, PMA–PALM40 and PMA–STEA40) for preparing a pH-sensitive physical mixture for site–specific delivery of ibuprofen chosen as a model drug. The preparation and characterization of the substituted polymers were described. In vitro release studies were conducted at different pH levels (3 h at pH 2.0, 2 h at pH 5.5, 4 h at pH 7.4 and until 24 h at pH 7.0) and phase-solubility diagrams of ibuprofen with the different substituted polymers were obtained at pH 7.0 to obtain information on the influence of amphiphilic polymers in increasing drug solubility and drug availability in the colon.

Keywords: Ibuprofen; Substituted polymethacrylic acid-co-methylmethacrylate; Physical mixture; Drug solubility; Site-specific delivery

1. Introduction

In recent years, oral site-specific drug delivery systems, such as colon targeting systems, have been the focus of intense research. A wide range of different approaches for targeting the drug to the colon, such as coated tablets, capsules or pellets [1], formulations coated with porous ethylcellulose films [2,3] and prodrugs [4] have been studied. Among the different approaches is the use of pH-sensitive polymers to prevent drug release in the upper gastrointestinal tract [5]. They are insoluble at low pH values, but soluble at high pH values. In particular, acrylic polymers, such as Eudragit S, are, suitable for colonic drug delivery [6]. The aim of this work was to investigate lipophilic polymers obtained from the substitution of polymethacrylic acid-co-methylmethacrylate with fatty acids for the delivery of ibuprofen to the colon. Ibuprofen was chosen as a model drug because it is readily absorbed throughout the gastrointestinal tract [7]. Ibuprofen is indicated for the relief of mild to moderate pain and inflammation in conditions such as dysmenorrhea, migraine, postoperative pain and dental pain, in which an immediate available dose is required. Ibuprofen is also used in chronic disorders like ankylosing spondylitis, osteoarthritis and rheumatoid arthritis for all of which a sustained release is desirable [8]. In this work we describe the preparation and characterization of the substituted polymers and correlate their physical-chemical properties with the in vitro release studies and phase-solubility diagrams of ibuprofen with the different polymers.

2. Materials and methods

2.1. Chemicals and supplies

Polymethacrylic acid-co-methylmethacrylate (PMA) (M_r 20 000 Da, 60% free acid), lauroyl chloride (LAU), myristoyl chloride (MIR), stearoyl chloride (STEA), palmitoyl chloride (PALM) and ibuprofen were from Fluka (Milan, Italy) and all the solvents employed were from Carlo Erba (Milan, Italy).

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2.2. Preparation of the substituted polymers

Polymethacrylic acid-co-methylmethacrylate (1.00 g; 10.79 mmol of monomer) was dissolved in 100 ml of *N*-methylpyrrolidone. The solution was supplemented with triethylamine (TEA, 10.79 mmol), and subsequently with substituents: lauroyl chloride (C12), myristoyl chloride (C14), stearoyl chloride (C16) or palmitoyl chloride (C18) in a molar ratio corresponding to 0.2 (2.16 mmol) or to 0.4 (4.32 mmol) mol substituent per mol monomer. Immediately a precipitate of the TEA salt was observed. The solution was stirred for 24 h at room temperature. The precipitate of TEA salt was removed by filtration and the substituted polymer was separated by precipitation into water. The precipitate obtained was purified by reprecipitating twice from ethanol into water, and then dried under vacuum to constant weight (Fig. 1). The experimental yields for each polymer synthesized were: PMA–LAU20, 0.82 g; PMA–MIR20, 0.85 g; PMA–PALM20, 0.91 g; PMA–STEA20, 0.99 g; PMA–LAU40, 1.64 g; PMA–MIR40, 1.75 g; PMA–PALM40, 1.88 g; PMA–STEA40, 2.01 g.

2.3. Substituted polymer characterization by Fourier transform infrared spectrometry

Infrared (IR) spectra were recorded with a Jasco FT-IR-410 spectrophotometer. The samples were prepared by processing compressed KBr disks.

2.4. Substituted polymer characterization by ^{1}H-nuclear magnetic resonance (^{1}H-NMR)

^{1}H-NMR spectra were obtained using a Gemini 300 instrument and recording the spectrum in $(CD_3)_2SO$.

2.5. Physical mixtures preparation

In a mortar mill 0.5 g of the substituted polymers were mixed with 0.5 g of ibuprofen until homogeneity and the mixture subsequently sieved to collect the fraction corresponding to 100 ± 10 μm for use in the present study.

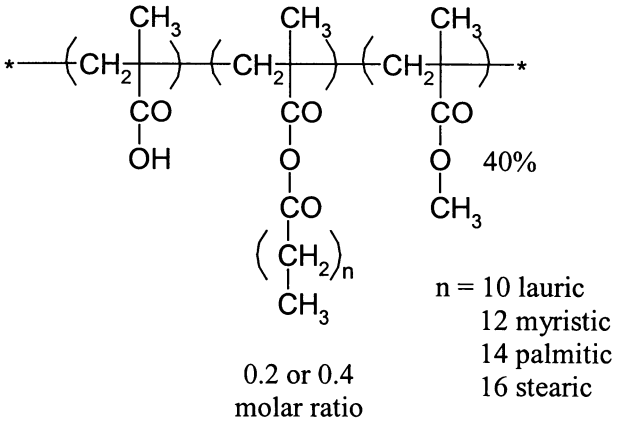

Fig. 1. Chemical structure of the substituted polymethacrylic acid-co-methylmethacrylate.

2.6. Water uptake of the drug–polymer mixtures

In order to quantify the swelling of the drug–polymer mixtures in acidic and alkaline environments, disks weighing approximately 20 mg were prepared by a punch press working at 7 ton/cm^2. The disks were immersed in 10 cm^3 volume pH 2.0 (0.01 N HCl) or pH 7.0 aqueous phosphate-buffers (50 mM sodium phosphate buffer) at 37 °C and weighed after predetermined time intervals. The water uptake was determined as the ratio between the weight of the hydrated disks (W_h) at each time and the initial weight (W_0) of the dry disks.

2.7. Drug–polymer interaction studies

To evaluate the interactions between the drug and the polymers in solution, excess drug (50 mg) was added to 10 ml aqueous pH 2.0 (0.01 N HCl) and pH 7.0 phosphate buffers (50 mM sodium phosphate buffer) containing the different substituted polymers at concentrations ranging from a minimum of 0.5 mM to a maximum of 1.0 mM. The suspensions were magnetically stirred at 37 °C for 1 week then filtrated (0.22 μm Millipore) to analyze the drug solution spectrophotometrically ($\lambda = 256$ nm).

2.8. In vitro release studies

To detect the amount of free drug available from the drug–polymer mixtures, the solid mixtures (100 mg) were placed in a donor cell containing 3 ml of pH 2.0 (0.01 N HCl) separated by a dialysis membrane (M_r cutoff = 14 000) from a receiving compartment containing 10 ml of the same aqueous phosphate-buffer, which was replaced after time intervals suitable to guarantee sink conditions throughout the runs. In order to simulate gastrointestinal conditions [9], the donor and receiving compartment pH was maintained at pH 2.0 (0.01 N HCl) for 3 h, at pH 5.5 (50 mM sodium phosphate buffer) for 2 h, at pH 7.4 (50 mM sodium phosphate buffer) for 4 h and pH 7.0 (50 mM sodium phosphate buffer) up to 24 h. The system was thermostated at 37 °C and the drug spectrophotometrically detected in the receiving phase.

2.9. Statistical analysis

All the data are the means of results from three experiments ± SD. Statistical data analysis was performed using the one-way analysis of variance, with $P < 0.05$ as minimum level of significance.

3. Results and discussion

3.1. Fourier transform infrared spectrometry

The FT-IR spectra show the absorption assigned to the carboxylic acid carbonyl at 1690 cm^{-1}, the ester carbonyl at 1735 cm^{-1} and the two characteristic peaks relative to anhydride absorption at 1760 cm^{-1} and 1820 cm^{-1}.

3.2. ^{1}H-NMR

Proton assignments for substituted polymethacrylic acid-co-methylmethacrylate in $(CD_3)_2SO$ (relative to dimethyl sulfoxide δ 2.50): δ 3.99 ppm = CH_3 (residual methyl of methylmethacrylate), δ 0.93 ppm = CH_3 (lauroyl), δ 1.10 ppm = CH_2 (lauroyl), δ 1.80 ppm = CH_2 (lauroyl deshielded by carbonyl), δ 0.96 ppm = CH_3 (miristoyl), δ 1.10 ppm = CH_2 (miristoyl), δ 1.82 ppm = CH_2 (miristoyl deshielded by carbonyl), δ 0.92 ppm = CH_3 (palmitoyl), δ 1.20 ppm = CH_2 (palmitoyl), δ 1.45 ppm = CH_2 (palmitoyl deshielded by carbonyl), δ 0.82 ppm = CH_3 (stearoyl), δ 1.10 ppm = CH_2 (stearoyl), δ 1.70 ppm = CH_2 (stearoyl deshielded by carbonyl). The level of substitution, calculated from the ^{1}H-NMR spectrum, was determined as 13.2% for PMA–LAUR20, 12.2% for PMA–MIR20, 12.6% for PMA–PALM20, 12.4% PMA–STEA20, 31.1% for PMA–LAUR40, 32.8% for PMA–MIR40, 32.0% for PMA–PALM40 and 32.9% PMA–STEA40. These data were obtained by comparing the signal of lauroyl (δ 0.93 ppm), miristoyl (δ 0.96 ppm), palmitoyl (δ 0.92 ppm) and stearoyl (δ 0.82 ppm) protons to that of methyl protons (δ 3.99 ppm) present at 40% in the polymethacrylic acid-co-methylmethacrylate.

3.3. Water uptake of the drug–polymer mixtures

The disks obtained from the drug–polymer mixtures strongly swelled at alkaline pH (7.0) (Fig. 2) losing their shape, whereas they did not dissolve or swell at acidic pH (2.0) according to the acidity of the acrylic polymers. At alkaline pH the water uptake was more evident in the presence of polymers with a low substitution degree (20%) as a consequence of a lower lipophilicity and higher number of free carboxylic groups with respect to polymers with a high substitution degree (40%). Moreover, lower chain fatty acids substituted polymers provided higher water uptake than higher chain fatty acids substituted polymers due to a decreasing lipophilicity.

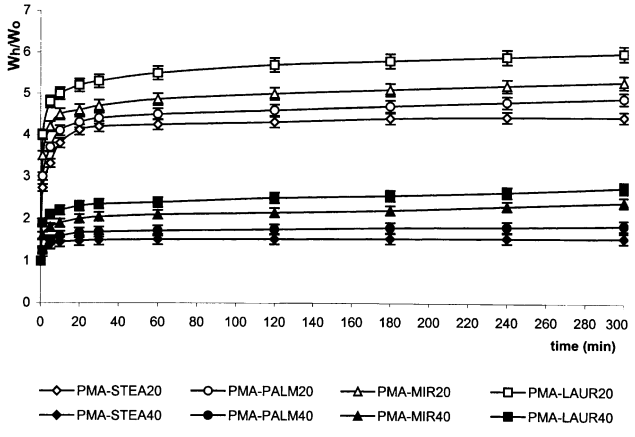

Fig. 2. Water uptake (weight of the hydrated disks/weight of the dry disks) at alkaline pH (7.0). Each datum represents the average of three determinations ± standard deviation.

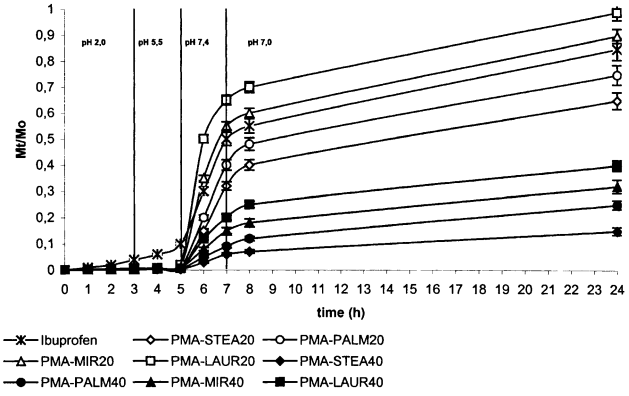

Fig. 3. Fractional release of ibuprofen from the mixture with the substituted polymers at different pHs. Each datum represents the average of three determinations ± standard deviation. (The level of statistical significance was ≤ 0.05 for all the values reported).

3.4. Drug–polymer interaction studies

The phase-solubility diagrams of ibuprofen in the presence of the different polymers analyzed revealed no increases in drug solubility at pH 2.0, due to the low solubility of the polymers at this pH, and significant increases at pH 7.0. The slopes of the linear trends of the phase-solubility diagrams at pH 7.0 (Table 1) were considered representative of the drug–polymer interaction. The slopes were slightly decreased on lengthening the chain of the substituent on the polymer and were strongly decreased by raising the substitution degree.

Table 1
Slopes (± SD; $n = 3$) of the linear trends of the phase-solubility diagrams of ibuprofen in the presence of substituted polymethacrylic acid-co-methylmethacrylate at 37 °C in aqueous buffers (pH 2.0 and pH 7.0)

Polymer type	Slope	
	pH 2.0	pH 7.0
PMA–STEA20	–	0.036 ± 0.002
PMA–STEA40	–	0.005 ± 0.001
PMA–PALM20	–	0.048 ± 0.003
PMA–PALM40	–	0.008 ± 0.001
PMA–MIR20	–	0.078 ± 0.002
PMA–MIR40	–	0.015 ± 0.002
PMA–LAUR20	–	0.091 ± 0.003
PMA–LAUR40	–	0.022 ± 0.003

Table 2
Percent fractional release of ibuprofen alone and of ibuprofen from the mixture with the substituted polymers at different time release: 3 h (pH 2.0), 5 h (pH 5.5), 7 h (pH 7.4) and 24 h (pH 7.0)

	% Mt/Mo			
	3 h (pH 2.0)	5 h (pH 5.5)	7 h (pH 7.4)	24 h (pH 7.0)
Ibuprofen	4.02 ± 0.20	10.03 ± 0.50	49.98 ± 2.49	85.00 ± 4.25
PMA–STEA20	0.30 ± 0.01	0.65 ± 0.03	32.07 ± 1.60	65.05 ± 3.25
PMA–STEA40	0.15 ± 0.01	0.31 ± 0.01	5.96 ± 0.30	15.02 ± 0.75
PMA–PALM20	0.34 ± 0.02	1.22 ± 0.06	40.11 ± 2.00	74.97 ± 3.75
PMA–PALM40	0.22 ± 0.01	0.55 ± 0.03	9.09 ± 0.45	24.91 ± 1.24
PMA–MIR20	0.50 ± 0.02	1.59 ± 0.08	54.91 ± 2.74	90.14 ± 4.50
PMA–MIR40	0.31 ± 0.01	0.99 ± 0.05	15.02 ± 0.75	31.99 ± 1.60
PMA–LAUR20	0.66 ± 0.03	2.01 ± 0.10	50.12 ± 2.50	98.93 ± 4.94
PMA–LAUR40	0.25 ± 0.01	0.06 ± 0.00	19.93 ± 0.99	40.01 ± 2.00

Each datum represents the average of three determinations ± standard deviation. The level of statistical significance was ≤ 0.05 for all the values reported.

3.5. In vitro release studies

Drug availability, expressed as fractional release over time (Fig. 3), or percent fractional release (Table 2) was lower from the drug–polymer mixtures than the pure drug at each pH analyzed. This may be attributed to the presence of the carboxylic groups and lipophilic groups in the polymer hindering the dissolution of the drug–polymer mixture at acidic pHs and to the gel ability of the ionized polymers hindering the diffusion of the drug toward the external environment at alkaline pHs. In particular, low substituted polymers (20%) provided low release at acidic pHs and significant release at alkaline pHs, whereas high substituted polymers (40%) provided very low release at acidic pHs and low release at alkaline pHs. Among the different polymers used in this work PMA–LAU20 and PMA–MIR20 (shortest chain fatty acid and lowest substitution degree) provided the best release: after a very low release at acidic pHs the fractional release at pH 7.0 was higher than the pure drug. This behavior indicated the ability of these physical mixtures to slow down the release in the gastrointestinal tract, providing a high availability of the drug in the colon.

4. Conclusions

The preparation of physical mixtures with ibuprofen and polymethacrylic acid-co-methylmethacrylate substituted with fatty acids (lauric, myristic, palmitic and stearic) provided a pH-sensitive system for site-specific delivery. In vitro release profiles and phase-solubility diagrams revealed that between the different polymers studied PMA–LAU20 and PMA–MIR20 slowed down the release in the gastrointestinal tract and provided a high availability of the drug in the colon.

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