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Synthesis and characterization of complexes between poly(itaconic acid) and poly(ethylene glycol)

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Summary

Interpolymer complexes of poly(itaconic acid) and poly(ethylene glycol) (PIA/PEG) were prepared by two different procedures: simple mixing of preformed PIA and PEG and by polymerization of itaconic acid on poly(ethylene glycol) as a template. Complex formation was attributed to hydrogen bond formation between the carboxyl group of PIA and the ether group of PEG. The two types of complexes were characterized by viscometric measurements, thermogravimetric analysis (TGA), Fourier-transform infrared (FTIR) spectroscopy and adhesive force measurements. The results indicate that complexes prepared by template polymerization have a stronger hydrogen bonding and hence more ordered structure and better mucoadhesive properties.

Introduction

Complexation between synthetic polymers has been extensively investigated. The association in these complexes can occur by ionic or hydrogen bonds, hydrophobic interaction etc. [1].

The formation of interpolymer complexes by the interaction of a proton acceptor and a proton donor polymer in aqueous solution has been studied by many groups. These complexes are of great significance as models of biological systems, such as the formation of two- or three-stranded polynucleotides, supermolecular assemblies in virus shells, and muscle contraction, where hydrogen bonds play an important role.

During the last few decades, considerable effort has been devoted to the study of association of poly(acrylic-) and poly(methacrylic acid) (PAA, PMAA) with nonionic polybases, such as poly(ethylene glycol) (PEG), polyacrylamide (PAM), etc [2-7]. It has been claimed that such complexation involves 'non-interrupted linear sequences of bonds' (or non-interrupted ladder structures) between continuous monomer residues of the hydrogen bonded donor and acceptor polymers [8].

Template or matrix polymerization [9] is defined as a polymerization in which chain propagation occurs along a preformed template, i.e. a polymer, added to the reaction system. The presence of the template may influence the polymerization kinetics (e.g. polymerization rate, activation energy, reaction order with respect to monomer and

initiator), the characteristics of the produced polymer (average molecular weight, molecular weight distribution, microstructure, stereoregularity) and the reactivity ratios in the case of copolymerization. The concept of template polymerization originates from natural processes such as the self-replication of DNA and the biosynthesis of proteins. An understanding of the mechanisms involved in such systems can help in designing polymeric materials with a predetermined structure.
It is assumed that the template induces an ordering effect on the monomer molecules and such complexes have an ordered structure.
In the case of interpolymer complexes (IPC) obtained by simple mixing, the polymer chains are in the form of random coils, therefore, not all the functional groups of one component are able to pair with those of the other component, so complexes with different properties with respect to template polymerization are produced [5].
In recent years, drug delivery systems using mucoadhesive drug carriers have gained increasing importance, since they can adhere to mucosal surfaces of the gastrointestinal tract and increase the therapeutic efficacy [10]. The mucoadhesive polymers have been shown to offer several advantages in a prolonged contact with the mucus of the target area [11]. Typical polymers that have been used as mucoadhesive carriers include poly(acrylic acid), poly(methacrylic acid), carboxymethyl cellulose and some interpolymer complexes of these polymers with nonionic polymers [12-14].
The aim of this work was the preparation and characterization of poly(itaconic acid) /poly(ethylene glycol) (PIA/PEG) complexes by template polymerization (TP) of itaconic acid on poly(ethylene glycol) and by the simple mixing (SM) of two preformed polymers. In both cases, the acid concentration was kept constant, while the molar ratios [IA]/[PEG] and [PIA]/[PEG] in the feed were varied.
The complexes obtained by TP and SM were investigated by thermogravimetric analysis (TGA), Fourier-transform infrared (FTIR) spectroscopy, viscometry and by adhesive force measurements in order to compare their properties as potential mucoadhesive drug carriers.

Experimental

Itaconic acid (99+ %), poly(ethylene glycol) (MW = 20 000) and potassium persulphate (KPS 99.99% purity) were provided by Aldrich Chemie.
Itaconic acid was polymerized according to a published procedure [15]. Limiting viscosity numbers (LVN) were measured in methanol at 25^{o}C using an Ubbelohde viscometer. The PIA molar mass was calculated from the LVN to be 100.000, using the Kuhn Mark Houwink equation [15].

$$[\eta] = 1.51 \times 10^{-3} \cdot M_w^{0.82} \qquad \textbf{(1)}$$

Preparation of complexes by template polymerization (TP)

The IA template polymerizations were performed at 40^{o}C in degassed 0.1 M HCl solution using KPS (0.05 M) as initiator and PEG as the template polymer. The IA concentration (0.0144 M) was constant for all samples, while the IA/PEG mole ratio was varied between 0.5 and 1.125 (Table 1).
The complexes were precipitated with ethanol, separated from the solution, washed twice with ethanol and dried under vacuum at room temperature to constant mass.

Preparation of complexes by mixing two polymer solutions (SM)

The SM complexes were prepared by mixing separately obtained dilute methanolic solutions (1 %) of PEG and PIA. The PIA/PEG molar ratio was varied between 0.5 and 1.125, while the PIA concentration (0.0144 M) was constant for all samples (Table 1).

Table 1. The molar ratio of the initial feeds for simple mixing and template polymerization

Sample	TP (IA/PEG)	SM (PIA/PEG)
1	1/0.500	1/0.500
2	1/0.625	1/0.625
3	1/1.000	1/1.000
4	1/1.125	1/1.125
5	1/1.250	1/1.250

Viscosity measurements

Viscosity measurements in diluted solutions for all samples were carried out in 0.1 M HCl and 0.1 M KOH at 25±0.1^{o}C, using Ubbelohde viscometer.

Fourier-transform infrared spectroscopy

FTIR spectra were measured with a BOMEM Michelfan MB-102 FTIR spectrophotometer, with a resolution of a 4 cm^{-1}, as KBr pellets.

Thermogravimetric analysis

The thermogravimetric analysis was performed with dry finely grinded samples using a Perkin-Elmer TGS-2 system, in the temperature range of 50-650^{o}C at a heating rate of 10^{o}C/min under a dynamic nitrogen atmosphere (flow rate of 26 cm^3/min).

Measurement of adhesive force

An adhesionmaster 525 MC (ERICHSEN GMBH&CO KG, Germany) was used to measure the adhesive force of the PEG/PIA interpolymer complexes to a polypropylene plate. A polypropylene plate was used instead of intestinal mucosa since there is a relatively good correlation between the adhesive force of the PAA/PEG polymer complexes to pig intestinal mucosa and that of the complexes to polypropylene plate [16]. The specimens, discs with an area of 3.14 cm^2, were wetted with a phosphate buffer solution of pH 6.8 at room temperature for 60 s before testing, and then placed between two plastic plates. The plates were then subjected to a pressure of 20.0 N/cm^2 for 60 s before the measurements. The peak force required to detach the disc from the polypropylene plates was measured.

Results and discussion

The interpolymer complexation between PEG and PIA, which is attributed to the hydrogen bonding, could be described by the following equation:

$PIA + PEG \leftrightarrow IPC\text{-}H_n$

where IPC-H_n is a hydrogen bonded interpolymer complex and n the number of carboxylic hydrogens related to the degree of polymerisation of the PIA and also involved in hydrogen bonding interactions with the PEG ether oxygens.

Table 2. The yield of PIA/PEG polymer complexes prepared by SM and TP

Sample	TP (PIA/PEG)	SM (PIA/PEG)
1	52.3	77.3
2	75.0	87.0
3	87.5	90.9
4	83.6	84.9
5	55.8	75.6

Interpolymer complexation in solution is always accompanied by a contraction or collapse of the component polymer coils, which result in a decrease in the viscosity, turbidity or even precipitation of the polymer phase. The hydrogen-bonded interpolymer complexes are stable at low pH values. The variation of reduced viscosity (η_{red}) values with composition can be used as a basis for an estimation of complex formation. The variation of the reduced viscosity with the molar ratio PIA/PEG (r) for the SM complexes in 0.1 M HCl and 0.1 M NaOH, at 25^{o}C is presented in Figure 1. The η_{red} values and molecular weights of the PEG and PIA are presented in Table 3.

Table 3. The η_{red} values of PEG and PIA

Polymer	η_{red} in 0.1 M HCl (cm^3/g)	η_{red} in 0.1 M NaOH (cm^3/g)
PEG	42.80	42.80
PIA	17.78	25.36

The η_{red} values are at a minimum when r=1. For r<1, PEG is present in excess and the η_{red} values are higher**.** When there is an excess of PIA (r > 1), the η_{red} values practicaly do not change with changing r. Similar trends are observed in the case of TP for the dependence of η_{red} - r (Figure 2). If these dependences for SM and TP are compared, it can be seen that viscosity values are higher in the case of the SM complexes which is due to 'non-cooperative' binding, in contrast to the TP complexes where 'cooperative' binding occurs.

The complexes are stable in acidic media and there is no electrostatic repulsion between the chains. Even when there is an excess of PIA (1 < r < 2.5) complexation

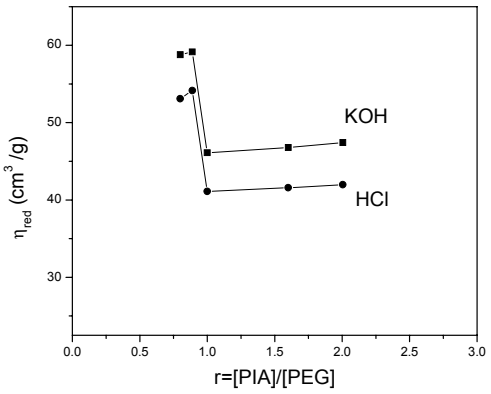

Figure 1. η_{red} vs. r for SM complexes in HCl and KOH.

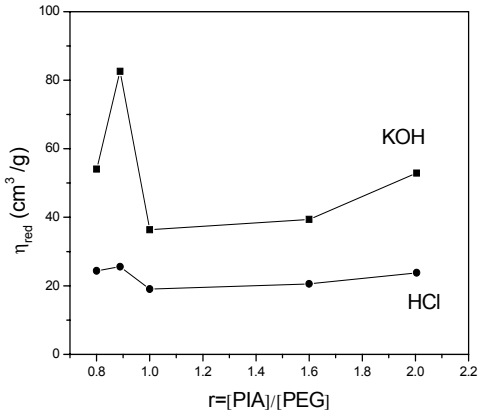

Figure 2. η_{red} vs. r for TP complexes in HCl and KOH.

can occur via the PIA carboxylic groups. The electrostatic repulsions are surpressed in KOH by the shielding effect of the mobile cations, which diffuse into the polyion and produce electrostatic screening of the charged segments.

The differences between viscosity values measured in KOH and in HCl are higher for TP than for SM complexes, when lies between 1 and 2, confirming that both hydrogen bonding and additional hydrophobic interactions contribute to the more compact structure of the TP complexes.

In order to investigate the effect of pH on the viscosity of SM and TP interpolymer complexes, the reduced viscosity of SM and TP complexes with a stoichiometric ratio of the components in the feed (r=1) was measured at various pH values, from 2 to 12 (Figure 3 and 4). There was a sharp increase in the viscosity with increasing pH for both the SM and for TP complexes, which can be explained by the conformational transition of the macromolecular chain from a more or less compact globule to an

extended coil, when ionization of the COOH groups takes place and the hydrogen bonds are broken at a definite pH values. The inflection point occurs at different pH values for the two types of complexes, due to differences in their structure, which is far more ordered in the case of TP complexes due to the mechanism of template polymerization. Kokufuta [17] studied the dissociation properties of various poly(dicarboxylic acids), and found that for poly(itaconic acid) two parameters, electrophoretic mobility and viscosity are not only directly related, but that the net change for both of them is the most abrupt in the pH range between 3-5. That finding is connected with the fact that itaconic acid dissociation constants are in that pH range (pK_{a1} = 3.85, pK_{a2} = 5.44).

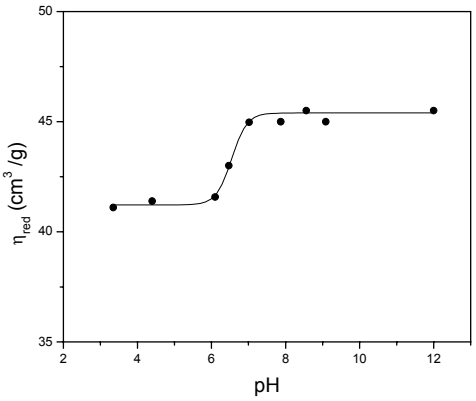

Figure 3. The η_{red} vs pH dependance for SM-3.

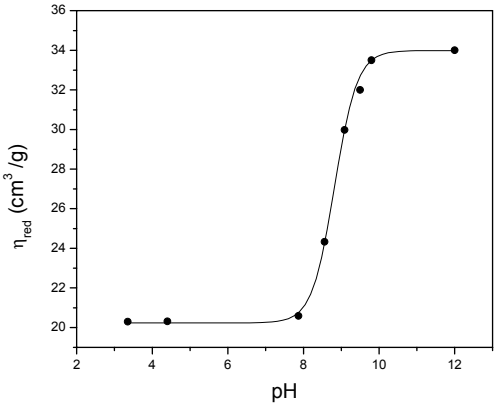

Figure 4. The η_{red} vs pH dependence for TP-3.

In the case of the SM complexes, the transition occurs in the pH range 6-7, very close to the pK_{a2} value, so ionization of the carboxylic groups occurs, inducing a highly expanded state of macromolecular coils caused by the electrostatic repulsions between

the COO^- groups. For TP complexes, the transition from globular to random coil is transferred to a higher pH range (8-9.7) so the ionization of poly(itaconic acid) is shifted to higher values, due to the highly regular structure of the TP complexes, which have a 'ladder' structure. The flexibility of the PEG chain contributes to the strength of the complex.
The yields of the polymer complexes obtained by simple mixing and template polymeriation is shown in Table 2.

FTIR study of the complexes

The FTIR spectra of SM and TP interpolymer complexes are presented in Figure 5. It is well known that the FTIR spectrum of PIA is characterized by the presence of a band at 1715 cm^{-1}, which is typical for the carbonyl stretching of COOH-groups. The bands at 1200 and 950 cm^{-1} in the PEG spectrum are related to vibrations of the ether groups [18]. The same bands are observed in the spectra of complexes, but the bands appear at shifted positions confirming the complex formation.
However, some broadening and splitting of the band at 1209 cm^{-1} (two new bands at 1202 and 1117 cm^{-1}), as well as a shifting of the band typical for the COOH groups to higher wave number values (at 1722 for SM and at 1732 cm^{-1} for TP) is visible in the complexes [19]. These effects are is related to the hydrogen bonding between COOH-groups of PIA with the ether oxygens of PEG, more pronounced in the case of the TP complexes, indicating stronger hydrogen bonding. The spectral results are in good agreement with the data of Cowie et al. [20]. A broader, more intensive band above 3400 cm^{-1} also confirms stronger hydrogen bonding in TP than in SM complexes.

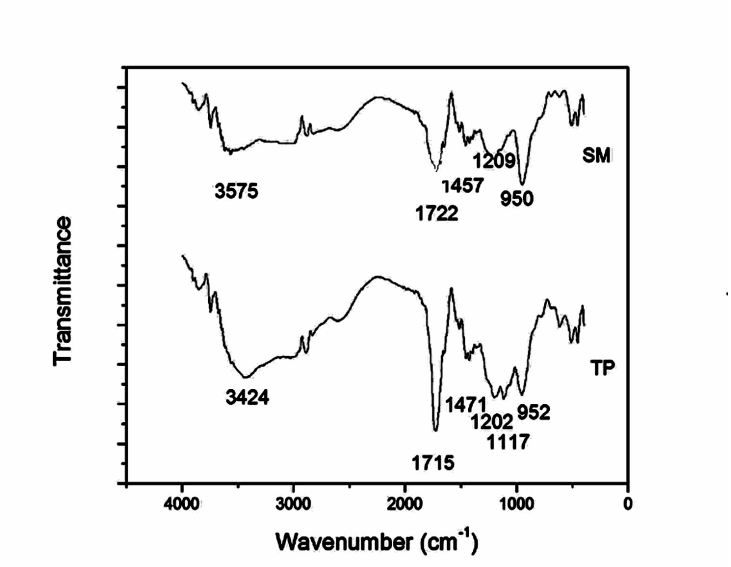

Figure 5. The FTIR spectra of SM and TP interpolymer complexes.

TG analysis of the complexes

The thermal degradation was studied in order to evaluate the thermal stability of the complexes. Figure 6 represents the relationship of the residual weight fraction vs. temperature for the pure homopolymers and the PIA/PEG (1:1) complexes obtained by simple mixing and template polymerization**.** The TG scan of pure PIA shows four degradation steps in the temperature range from 50-650^{o}C, with a residue of 24 wt %. In the temperature region from 120-270^{o}C, two processes are detected; the first one is assigned to the elimination of water adsorbed to the hydrophilic polymer, and the second to anhydride ring formation in the PIA chain. In the second temperature region, from 270-450^{o}C, two degradation stages are noticed, connected probably with some decarboxylation and carbonization processes [19, 21].

However, PEG shows just one thermal degradation stage, in the temperature range from 250 to 450^{o}C, leading to almost 100% mass loss.

The thermal degradation of PIA/PEG (1:1) polymer complexes takes place in three stages, similar to those for PIA. In the first stage, from 80 to 230^{o}C, the weight loss is about 24%. In the temperature interval from 230 to 500^{o}C two main degradation steps are present, with the weight loss of about 55% and 45% for TP and SM complexes, respectively. The residue at 650^{o}C is higher for SM (~22%) than for TP complexes (~17%). It is obvious that the presence of PEG in the complexes contributes to their higher thermal stability, in the temperature range between 240 and 430^{o}C, but they degrade faster than PEG homopolymer over the same temperature range. The complexes obtained by template polymerization have a higher thermal stability than those obtained by simple mixing.

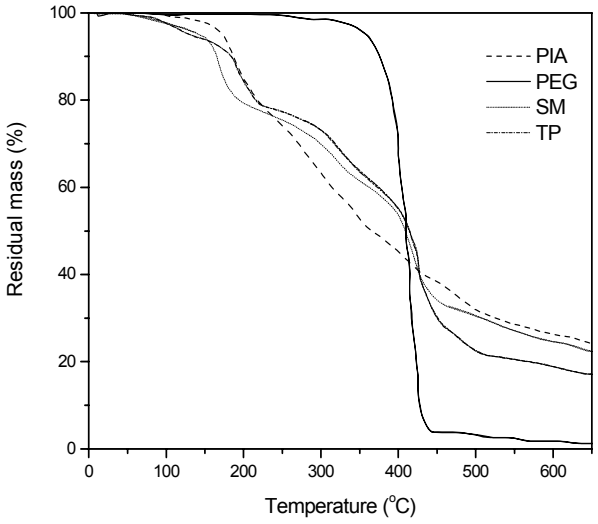

Figure 6. The TG curves of PIA, PEG and SM and TP complexes.

Adhesive force of the complexes

The adhesive force values for the PIA/PEG interpolymer complexes and for the commercial Carbopol 971 P adhesive are presented in Table 4. The adhesive force was measured by determining the force required to break the contact between a polypropylene plate and the applied polymer. For the 1:1 SM and TP complexes, the adhesive force of was greater than in the case of Carbopol 971 P. The highest adhesive force value was measured for the complex obtained by template polymerization, which is in good accordance with our earlier conclusions that hydrogen bonding is stronger in the TP complexes.

Table 4. Comparison of the adhesive forces of the PEG/PIA interpolymer complexes versus Carbopol 971 P to plastic (polypropylene) plate

Sample	Adhesive force (N/cm^2) (mean ± S.D.[a])
TP-2	34.63 ± 0.12
TP-3	39.43 ± 0.07
TP-4	36.13 ± 0.21
SM-2	27.83 ± 0.48
SM-3	30.33 ± 0.21
SM-4	29.30 ± 0.17
Carbopol 971 P	28.37 ± 0.06

[a] Standard deviation.

It is obvious that these complexes, especially those obtained by TP polymerization show good mucoadhesive properties.

CONCLUSION

The results of viscosity measurements, FTIR spectroscopy and thermal analysis confirm that in the case of PIA/PEG complexation, stronger hydrogen bonding takes place during template polymerization due to the highly regular structure of the TP complexes, which have a 'ladder' structure. The flexibility of the PEG chains contributes to the strength of the complex. All complexes showed satisfactory mucoadhesive properties, so these materials have potential as drug carriers.

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