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# NONSPECIFIC INTERACTIONS IN POLYMER–POLYMER REACTIONS—3. COMPLEX FORMATION BETWEEN POLYCARBOXYLIC ACIDS AND 2-ACETOXYBENZOATE DERIVATIVES OF POLY(ETHYLENE GLYCOL)S

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**Abstract**—Complex formation for poly(methacrylic acid) and poly(acrylic acid) with 2-acetoxybenzoate derivatives of poly(ethylene glycol)s was studied in dilute aqueous solution by potentiometric titration and viscometry. The hydrophobic 2-acetoxybenzoate end-groups were found to stabilize the polycomplexes. The polycomplexes of poly(methacrylic acid) are stable at pH below 6. Introducing biologically active hydrophobic compounds in poly(ethylene glycol)s offers possibilities of developing new drugs on the basis of polycomplexes.

## INTRODUCTION

It has been shown [1, 2] that introducing various hydrophobic groups in the chains of poly(ethylene glycol)s (PEG) increases the stability of their polycomplexes with poly(acrylic acid) (PAA) and poly(methacrylic acid) (PMAA) in aqueous solutions. The stabilizing effect of hydrophobic groups in interpolymer reactions in aqueous media is probably due to reduced free energy of the system as a result of "immersing" of these "anchor" groups into the hydrophobic domains of the polycomplex particles.

Physiologically active compounds with therapeutic action can play the role of hydrophobic "anchor" groups. On complex formation with polyacids, the drug attached to the polymer carrier (PEG) is introduced into the polycomplex and can be used in this form for therapeutical purposes.

Aspirin (2-acetoxybenzoate) is among the best known and most widely used analgesics and antipyretics and its application as an antithrombogenic drug is no less important. Regular oral application of aspirin may cause irritant and ulcerogenic action along the gastrointestinal tract. There are studies reporting ways of binding aspirin to polymers, e.g. soluble starch, poly(vinyl alcohol), PEG by means of easily hydrolysable bonds. Some of these polymers proved to show activity similar to that of aspirin while being less toxic [3].

It was the purpose of the present paper to study the complex formation of PMAA and PAA with mono- and disubstituted PEG containing 2-acetoxybenzoate groups (PEG*) in aqueous solutions.

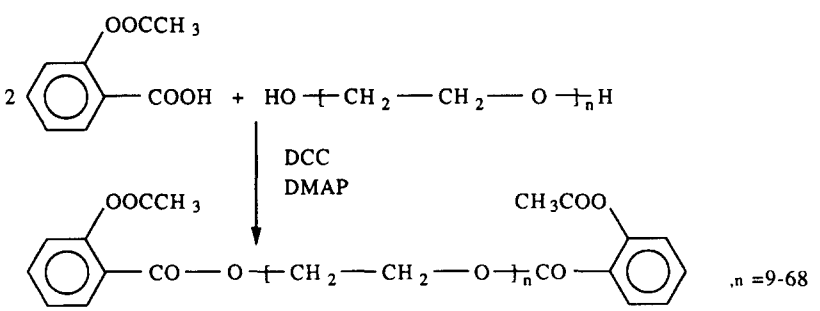
## EXPERIMENTAL PROCEDURES

PMAA was prepared by radical polymerization of methacrylic acid in benzene at 60° under $N_2$ with initiator AIBN. The molecular weight of PMAA was $1.8 \times 10^5$ as determined viscometrically at 30° in 0.002 M HCl using the relation $[\eta] = 6.6 \times 10^{-4} M^{0.5}$ [4].

PAA was similarly prepared by polymerizing acrylic acid with AIBN in toluene at 50° under $N_2$. Its molecular weight was calculated to be $3.5 \times 10^5$ according to the relation $[\eta] = 1.05 \times 10^{-3} M^{0.54}$ [5].

PEG* were prepared by reacting PEGs of molecular weights from 400 to 3000 with aspirin in methylene chloride in the presence of dicyclohexyl carbodiimide and dimethylaminopyridine following a known procedure [6]. The monoaspirin derivative ($CH_3O$–PEG*) was prepared similarly from the methyl ether of PEG with mol. wt of 2000. The products thus obtained were characterized by GPC, i.r. spectroscopy and NMR.

GPC analysis of the starting PEG and the resulting PEG* was carried out on Ultrastyrogel columns of pore sizes 100, 100, 500 and 1000 Å, flow rate 1 ml/min (standards—PEGs of narrow molecular weight distribution) at 45° in THF with refractive index and u.v. detection (WATERS).

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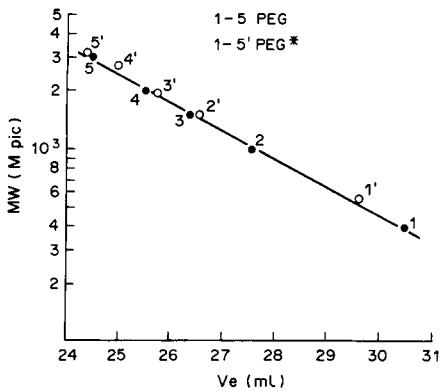
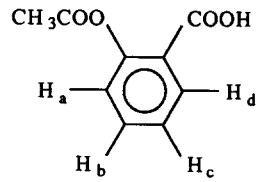



Fig. 1. Dependence of the molecular weight of PEG(PEG*) on Ve.

The GPC traces of PEG* showed that the narrow molecular weight distribution is preserved in the range $\bar{M}_w/\bar{M}_n = 1.05$–$1.1$. Indication of the binding of aspirin to PEG was provided by the increased molecular weights (Fig. 1) and the appearance of u.v. absorption. The values of the area ratio of the chromatographic peaks recorded with the u.v. and the RI detectors, $S_{u.v.}/S_{RI}$ decreased regularly with increasing amount of ethereal groups, (—$CH_2$—$CH_2$—O—) in PEG* (Fig. 2).

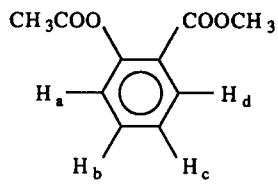
In the i.r. spectra of the PEG*, an absorption band was observed at 1740 $cm^{-1}$ for ester carbonyl group. Its intensity decreased at higher PEG molecular weight. No band for OH groups at 3300–3500 $cm^{-1}$ was recorded. The following signals were present in the $^1$H-NMR spectra of PEG* and model compounds:

*—for 2-acetoxybenzoic acid (aspirin)*



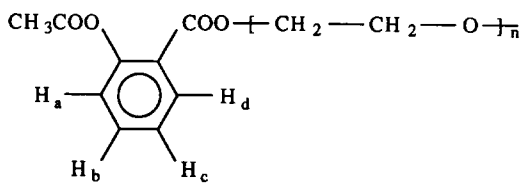

$CH_3COO$—Ar-(2.35 ppm, singlet); $ArH_a$-(7.14 ppm, doublet); $ArH_b$-(7.36 ppm, triplet); $ArH_c$-(7.63 ppm, triplet); $ArH_d$-(8.12 ppm, doublet).

*—for the methyl ester of 2-acetoxybenzoic acid*




Ar—$COOCH_3$-(3.87 ppm, singlet); $CH_3COO$—Ar-(2.36 ppm, singlet); $ArH_a$-(7.11 ppm, doublet); $ArH_b$-(7.56 ppm, triplet); $ArH_c$-(7.32 ppm, triplet); $ArH_d$-(8.02 ppm, doublet).

*—for PEG* of the general formula*




where $n = 9$–$68$ $CH_3COO$—Ar-(2.36 ppm, singlet); —$OCH_2CH_2$-(3.64 ppm, singlet); $ArH_a$-(6.90 ppm, doublet); $ArH_b$-(6.88 ppm, triplet); $ArH_c$-(7.45 ppm, triplet); $ArH_d$-(7.87 ppm, doublet).

Potentiometric studies were performed on a Radelkis-OP 208/I pH-meter from Hungary equipped with OP 0808 P glass electrode. Viscometric measurements were made at $25 \pm 0.1$ with an Ubbelohde viscometer.

With the aid of iodophotometry [7], the prepared PEG*s were shown not to form micelles in aqueous solution in the studied concentration range, i.e. the complexation process involved the polyacids and the PEG* macromolecules.

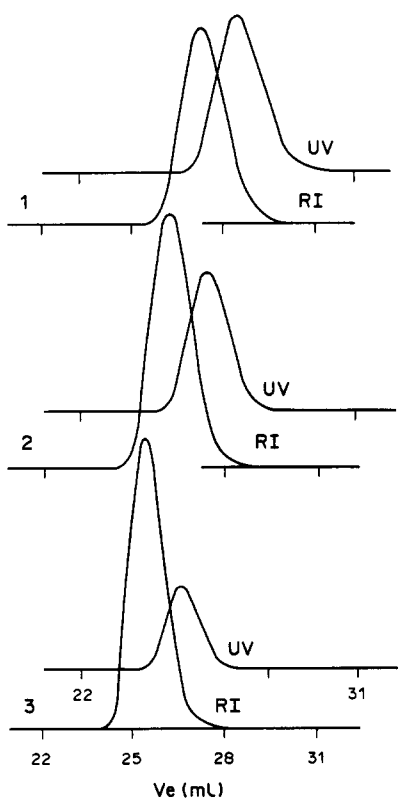



Fig. 2. Chromatograms (GPC) of: (1) PEG*-1000; (2) PEG*-1500 and (3) PEG*-2000. Differential refractometer (RI) and u.v. detectors. Eluent, THF.

## RESULTS AND DISCUSSION

Complex formation between polycarboxylic acids and PEG in aqueous solutions results from hydrogen bonds formed between the PEG oxygen atoms and the hydrogens in the undissociated carboxyl groups of the polyacids [8–10]. For this reason, the acid–base equilibrium of the system is shifted and the pH of the solution increases.

The complex formation is accompanied by a sharp drop in the solution viscosity since the complex particles form compact globules. This effect indicates that the complexation process between polyacids and PEG can be studied by the methods of potentiometry and viscometry.

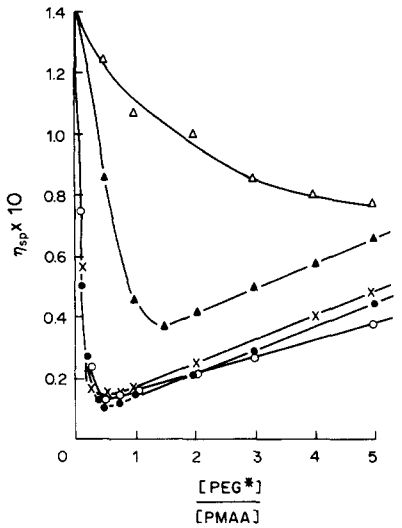



Fig. 3. Dependence of $\eta_{sp}$ of PMAA and PEG* (PEG) aqueous solution mixtures on [PEG* (PEG)]/[PMAA] ratio at fixed concentration of PMAA (0.1 g/dl, 25°): ○, PEG*-1500; ●, PEG*-2000; ×, $CH_3O$–PEG*-2000; △, PEG-1500; ▲, PEG-2000.

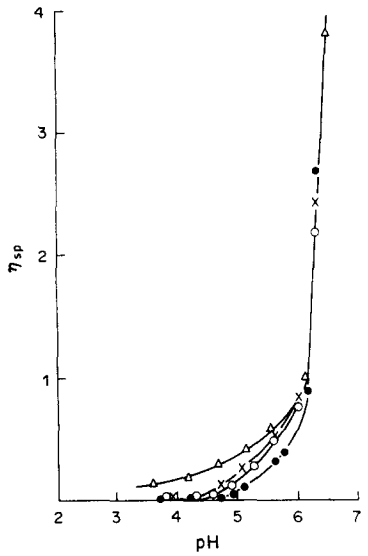



Fig. 5. Specific viscosities $\eta_{sp}$ of solutions of pure PMAA and polycomplexes (PMAA·PEG*) at various pH: ○, PEG*-1500; ●, PEG*-2000; ×, $CH_3O$–PEG*-2000; △, PMAA.

The changes in the specific viscosities of aqueous solutions of mixtures of PEG*-2000, PEG*-1500 and $CH_3O$–PEG*-2000 with PMAA, with the weight ratio between the components at fixed PMAA concentration (0.1 g/dl) are illustrated on Fig. 3. The specific viscosities of solutions of the PMAA and PEG* mixtures sharply drop with increasing PEG*/PMAA ratio due to association of the PMAA macromolecules with PEG* and formation of the compact polycomplex particles. For comparison, the same specific viscosity plots for aqueous solutions of the mixtures of PMAA with unmodified PEGs of molecular weight 1500 and 2000 are shown. As seen, introducing 2-acetoxybenzoate groups into the chains of PEG essentially increases the stability of the polycomplex with PMAA. Besides, introducing a single 2-acetoxybenzoate group as in $CH_3O$–PEG* suffices for the formation of a stable polycomplex with PMAA.

The stoichiometry of (PMAA·PEG*) polycomplexes is close to equimolar, calculated per base mole units, since the minimal value of $\eta_{sp}$ is registered at the weight ratio PEG*/PMAA = 0.5, as for the polycomplexes of PMAA with PEG of higher molecular weights [8].

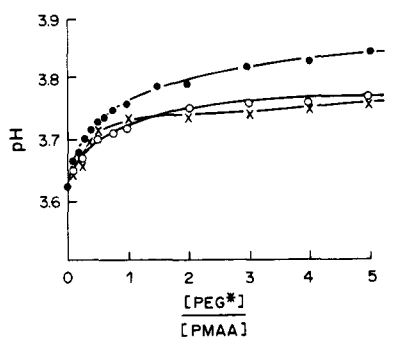



Fig. 4. Dependence of pH of PMAA and PEG* (PEG) aqueous solution mixtures on [PEG*(PEG)]/[PMAA] ratio at fixed concentration of PMAA (0.1 g/dl, 25°): ○, PEG*-1500; ●, PEG*-2000; ×, $CH_3O$–PEG*-2000.

Figure 4 shows the dependence of the pH of solutions of PEG* and PMAA mixtures on the weight ratio PEG*/PMAA. It is seen that, on increasing the concentration of PEG*, pH of the solution increases so, as previously noted, giving evidence of complex formation.

Figure 5 shows the dependence of $\eta_{sp}$ of solutions of (PMAA·PEG*) polycomplexes and pure PMAA on pH. In all cases the weight ratio PEG*/PMAA is 0.5 corresponding to the stoichiometry of the polycomplex. pH of the solutions was changed by addition of 0.1 M NaOH in amounts negligible compared with the total volume of the initial solution.

As seen from the figure, on raising the pH the specific viscosity of polycomplex solutions increases and at pH above 6 becomes comparable to the specific viscosity of solutions of pure PMAA. It is logical to assume that, at this particular pH, there is complete dissociation of the polycomplex to its components so that $\eta_{sp}$ of mixed PEG* and PMAA solutions coincides with $\eta_{sp}$ of the solution of pure PMAA (the relatively low molecular PEG* has negligible influence on $\eta_{sp}$ of the solutions compared with PMAA). Decomposition of the polycomplexes at higher pH is caused by increased dissociation of PMAA resulting in breaking of the hydrogen bonds between the components. The pH at which decomposition of the polycomplexes occurs can be used as a measure of their stability. As can be expected, the polycomplex (PMAA·PEG*-2000) is more stable than (PMAA·PEG*-1500) because of the higher molecular weight of the PEG component.

The dissociation curves of the polycomplexes (PMAA·PEG*-1500) and (PMAA·$CH_3O$–PEG*-2000) are practically identical indicating equal stability. The lower PEG molecular weight in PEG*-1500

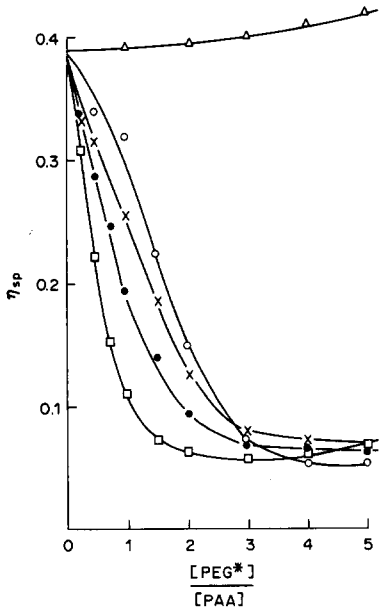



Fig. 6. Dependence of $\eta_{sp}$ of PAA and PEG*(PEG) aqueous solution mixtures on [PEG*(PEG)]/[PAA] ratio at fixed concentration of PAA (0.1 g/dl, 25°): ○, PEG*-1500; ●, PEG*-2000; □, PEG*-3000; ×, $CH_3O$–PEG*-2000; △, PEG-3000.

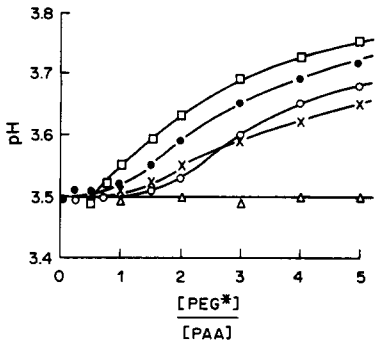



Fig. 7. Dependence of pH of PAA and PEG*(PEG) aqueous solution mixtures on [PEG*(PEG)]/[PAA] ratio at fixed concentration of PAA (0.1 g/dl, 25°): ○, PEG*-1500; ●, PEG*-2000; □, PEG*-3000; ×, $CH_3O$–PEG*-2000; △, PEG-3000.

than in $CH_3O$–PEG*-2000 is balanced by the additional stabilizing effect of the second hydrophobic 2-acetoxybenzoate "anchor" group.

The polycomplexes (PMAA·PEG*) decompose at pH ≈ 6 and are stable at lower pH. This fact confirms their possible application in oral therapy. A drug based on the polycomplex containing PEG* with 2-acetoxybenzoate groups should be stable in the acidic medium of the stomach and decompose to its components at the alkali pH in the intestines. On decomposition of the polycomplex, the biologically active component, PEG* is released which in turn on hydrolysis produces aspirin. In this way the drug is directly delivered in the intestines.

PAA likewise forms polycomplexes with the prepared PEG* although the critical PEG molecular weight below which complexation with PAA does not occur is 6000 [8].

The dependences of $\eta_{sp}$ and pH of aqueous solutions of PEG*/PAA mixtures are shown on Figs 6 and 7. Complex formation occurs even when only a single 2-acetoxybenzoate group has been attached to the chain of PEG–2000. For comparison, the corresponding curves are shown for the system PAA–PEG-3000. It is seen that PEG-3000 does not form a polycomplex.

The experimental data do not provide a precise estimate of the stoichiometry of the observed polycomplexes. It is quite possible that they have variable composition depending on the concentration of components and pH of the medium.

The results show that biologically active hydrophobic compounds can be incorporated in polycomplexes as "anchor" groups. This effect offers possibilities for the development of novel drugs based on water soluble polymer carriers.

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