Colloid Polym Sci (2005) 283: 1033–1040
DOI 10.1007/s00396-004-1268-z

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Solubility of naphthalene in aqueous solutions of poly(ethylene glycol)–poly(propylene glycol)–poly(ethylene glycol) triblock copolymers and (2-hydroxypropyl)cyclodextrins

Received: 9 February 2004
Accepted: 2 December 2004
Published online: 12 March 2005
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Abstract The solubility of naphthalene was investigated in aqueous solutions of triblock copolymers poly(ethylene glycol)–poly(propylene glycol)–poly(ethylene glycol) (PEG–PPG–PEG) and (2-hydroxypropyl)cyclodextrins. The results with solutions of the individual solubilizers were as expected: the solubility enhancement was much higher with a micelle-forming copolymer than with the non-micellizing one and with (2-hydroxypropyl)-β-cyclodextrin (HPBCD) than with (2-hydroxypropyl)-α-cyclodextrin (HPACD). Although the formation of inclusion complexes between HPACD and PEG and between HPBCD and PPG is well established, the naphthalene solubility in mixed solutions does not significantly deviate from that predicted for a mixture of independent solubilizers. Thus the interactions between HPCD and PEG–PPG–PEG copolymers are not strong enough to disrupt micelles and aggregates formed by those copolymers. In fact, slight synergetic deviations were observed with the micellizing copolymer, indicating the existence of ternary naphthalene/HPCD/copolymer interactions. For pharmaceutical applications, it is important that the solubilization efficacy of PEG–PPG–PEG copolymers and that of cyclodextrins modified by the 2-hydroxypropyl group would not be compromised if these two types of solubilizers were co-administered.

Keywords Naphthalene solubilization · Copolymer micellization · Cyclodextrins

Introduction

The early experiments on main-chain inclusion of water-soluble polymers by cyclodextrins (CDs), leading to formation of pseudopolyrotaxanes, appear to provide a solid framework for interpreting the phenomena. The decisive factor seems to be the fit of the main chain into the central cavity of these oligosaccharides as illustrated by the behavior of poly(alkylene oxides): the smallest cyclodextrin, α-cyclodextrin with six glucose units in the molecule, forms a crystalline complex with poly(ethylene glycol) (PEG) but not with poly(propylene glycol) (PPG). The reverse is true for larger β-cyclodextrin with seven glucose units in the molecule [1]. With triblock copolymers PEG–PPG–PEG, the content of CD in the crystalline complex corresponds to the content of PEG in the case of α-CD and PPG in the case of β-CD [2, 3]. The primary driving force of the inclusion is the relative hydrophobicity of the cavity; however, the binding of the individual CD molecule is rather weak [4]. Inspite of that, the yields of crystalline complexes precipitating from solution are high. The fact that derivatization of CD hydroxy groups, for example, with 2-hydroxypropyl group prevents formation of a solid complex pinpoints the hydrogen bonding between adjacent CD molecules as the main driving force behind the high yields

obtained. Since two free secondary hydroxy groups on each glucose unit are located at the wider rim of CD molecules whereas just one primary group is located at the narrower rim, the regular head-to-head/tail-to-tail arrangement comes as natural. Moreover, the CD size and the complex composition correspond to two monomeric units of PEG or PPG.

The appealing consistency of the outlined picture made it widely accepted even though it simplifies some details and ignores some fundamental questions. The regular head-to-head/tail-to-tail arrangement was shown highly improbable by Monte Carlo simulation [5]. The number of monomer units covered by cyclodextrin is higher than two. However small the found difference may seem, it has significant consequences for the theoretical description of the binding isotherm. The behavior of methylated CDs challenges the role of hydrogen bonding. The fact that 2,6-*O*-dimethyl-*β*-cyclodextrin forms a crystalline complex with PPG can be simply explained if hydrophobic interaction replaces hydrogen bonding as a source of cooperativity, but then the question arises why fully methylated *β*-CD does not form any such complex [6, 7]. It was suggested that the source of high yields may be low solubility of crystalline complexes rather than strong cooperativity in CD threading [4]. The localization of *β*-CD on PPG segment in complexes with PEG–PPG–PEG copolymers basically supports the validity of the size-matching criterion, but at the same time, this fact violates the criterion because *β*-CD has to pass over a PEG segment in order to reach the middle PPG segment, which means that *β*-CD forms complexes with PEG in solution, though weak and soluble. Yet this violation is understandable as the thinner chain gets through the bigger ring. The recent experimental finding that α-CD forms crystalline complexes with PPG–PEG–PPG copolymers [8] is more baffling because molecular modeling showed that a deeper penetration of PPG into the α-CD cavity results in considerable, energetically unfavorable deformation of α-CD macrocycle. This means that even though the crawling of the PPG chain through α-CD cavity is possible in principle, it is not very probable. [9]

Under the circumstances when the interactions of CDs and water-soluble polymers are not fully understood, additional data on the subject are required, especially because both CDs and PEG–PPG–PEG copolymers were proposed or even used as solubilizers in various biomedical and industrial applications [10, 11]. The solubilizing power of PEG–PPG–PEG copolymers is derived from their ability to form micelles with a relatively hydrophilic PEG corona and more hydrophobic PPG core in which a sparingly soluble compound can dwell. However, it was shown that the solubilizing effect of both CDs and micellar solubilizer can decrease if administered together. Thus the solubility of benzo[*a*]pyrene in a micellar bile acid salt solution (15 mM sodium taurocholate) decreases after addition of (2-hydroxypropyl)-*β*-cyclodextrin (HPBCD) because a strong inclusion complex forms between HPBCD and a bile acid and, consequently, the number of micelles into which benzo[*a*]pyrene can enter decreases. Also HPBCD is consumed in the complexation of bile acid salt, and the solubility of benzo[*a*]pyrene starts to grow again only after an excess of HPBCD is added [12].

Therefore, we decided to verify whether a similar detrimental effect on solubilizing power is also caused by interactions between CDs and PEG–PPG–PEG copolymers. As a sparingly soluble solute, we chose naphthalene, a popular model compound frequently used to investigate the solubilizing power both of PEG–PPG–PEG copolymers [13–15] and cyclodextrins [12, 16, 17]. Naphthalene is a representative of polycyclic aromatic hydrocarbons, highly carcinogenic pollutants, and naphthalene rings are present in molecules of some drugs, for example nonsteroidal anti-inflammatory drug Naproxene. The water solubility of naphthalene, which is about 30 mg/l [18], is 25 times greater in 5% solution of HPBCD [12] and an even higher increase (∼100 times in 5% solution) is observed with some micellizing PEG–PPG–PEG copolymers [13–15]. For comparison, the increase in naphthalene solubility in 5% methanol is as low as 40%. [19]

We carried out a series of experiments on solubility of naphthalene in solutions of (2-hydroxypropyl)cyclodextrins, PEG–PPG–PEG triblock copolymers, and their mixture. The 2-hydroxypropyl derivatization of CDs ensures good solubility, not only of CDs but also of their complexes with naphthalene and polymers.

Experimental

Materials

Samples of PEG–PPG–PEG triblock copolymers were of commercial origin. Their composition was determined by ^{1}H-NMR and their molecular weight by MALDI-TOF mass spectrometry. Detailed results of the copolymer characterization, summarized in Table 1, show that the first sample (copolymer I) corresponds to Pluronic L64 and the second one (copolymer II) is between Pluronics L83 and L93 in the nomenclature introduced by BASF Co.

(2-Hydroxypropyl)-α-cyclodextrin (HPACD), purchased from Fluka, has an average degree of substitution 0.6 and (2-hydroxypropyl)-*β*-cyclodextrin (HPBCD), from Aldrich, has an average degree of substitution 0.8. Prior to use, both modified cyclodextrins were dried overnight under reduced presure at 40 °C.

Table 1 Characterization of PEG–PPG–PEG copolymers

Sample	M_n [a]	M_w [b]	w_{PEG} [c]	N_{PPG} [d]	N_{PEG} [e]
Copolymer I	2,680	2,860	0.403	28	2×12
Copolymer II	3,880	4,020	0.336	44	2×15

[a]Number-average molecular weight determined by MALDI-TOF mass spectrometry
[b]Weight-average molecular weight determined by MALDI-TOF mass spectrometry
[c]Weight fraction of PEG determined by ^{1}H-NMR
[d]Approximate number of monomeric units in the PPG block
[e]Approximate number of monomeric units in the PEG blocks

Solubility determination

The inner surface of 1.5 ml vials was precoated with naphthalene by allowing a naphthalene solution in tetrahydrofuran to evaporate while slowly rotating the vials. Water or a solubilizer(s) solution (1 ml) was added and vials were gently shaken at 25 °C for 3 days. Preliminary experiments showed that after 3 days, equilibrium was attained because prolonged dissolution did not increase the amount of solubilized naphthalene. Samples were shortly centrifuged, diluted first 1:1 with methanol, and then with methanol/H_2O 1:1 to final concentrations giving acceptable reading on a UV/VIS spectrophotometr at 275 nm.

For each solubilizer, three series of naphthalene solubilization experiments were carried out in which the concentration of the solubilizer was varied from 2% to 8% (w/w). In the basic series, no other solubilizer was added, while 4% of a solubilizer of the other type (i.e., CDs for PEG–PPG–PEG copolymers and *vice versa*) was present in the second and third series.

Theory

Solubilization with a single solubilizer

The overall solubility of a sparingly soluble compound (solute) can be appreciably increased in the presence of a compound (solubilizer) with which it forms a soluble complex. For the 1:1 stoichiometry, the complexation equilibrium can be described by

$$K_C = \frac{[CS - S]}{[S][CS]}, \quad (1)$$

where K_C is binding constant [CS−S], [CS], and [S] are equilibrium molar concentrations of the complex, complex-forming solubilizer, and solute. In the presence of a solid solute, the concentration of a free solute in solution is constant and equal to its solubility in water, S_0. Total solute solubility in a solution of complex-forming solubilizer, $S = S_0 + [CD-S]$, can be then expressed as

$$\frac{S}{S_0} = 1 + K_C[CS]. \quad (2)$$

Taking into account that the total concentration of the complex-forming solubilizer, $c_{CS} = [CS-S] + [CS]$, Eq. 2 can be recast as [16]

$$\frac{S}{S_0} = 1 + \frac{K_C}{1 + K_C S_0} c_{CS} = 1 + K'_C c_{CS}. \quad (3)$$

Equation 3 shows that using the overall molar concentration of the complex-forming solubilizer, c_{CS}, instead of the equilibrium value [CS] we underestimate the binding constant unless $K_C S_0 << 1$. However, the calculation of a true binding constant from the apparent one, K_C', is quite straightforward.

Formally, Eq. 3 describes solubilization also as partition of the solute between solvent and the pseudophase formed by a complex-forming solubilizer, in which the solute concentration is proportional to $(S-S_0)/c_{CS}$. In this context, K_C' correspond to a partition coefficient, K_P, rather than to a binding constant [16]. To identify the pseudophase with, for example, inner cavities of cyclodextrins would be far-fetched; however, the existence of pseudophase can be postulated for a second class of solubilizers considered in this paper, namely micelle-forming solubilizers, for which the increase in the overall solute concentration is achieved by sequestering solute into the micellar cores [20]. The concentration of pseudophase is not proportional to the total concentration of a micelle-forming solubilizer, c_{MS}, because micelles are in equilibrium with (ideally) molecularly dissolved solubilizer at a concentration equal to the so called critical micellar concentration, cmc. Thus, Eq. 3 becomes

$$\frac{S}{S_0} = 1 + K_P(c_{MS} - cmc) = 1 - K_P cmc + K_P c_{MS}. \quad (4)$$

Obviously, Eq. 4 is valid only for solubilizer concentrations above cmc where the relative solubility enhancement is a linear function of the solubilizer concentration, similarly as in Eq. 3 but with the intercept $(1-K_P\ cmc) < 1$. Equation 4 gives $S = S_0$ at cmc and hence assumes no solubilization below cmc. Frequently, however, micelle-forming solubilizers display a solubilizing effect also in sub-micellar concentrations, with Eq. 3 applicable. Thus for $c_{MS} >$ cmc, this has to be accounted for. The straightforward way to do that is simply to combine Eqs. 3 and 4 [20]

$$\begin{aligned}\frac{S}{S_0} &= 1 + K'_C cmc + K_P(c_{MS} - cmc) \\ &= 1 + (K'_C - K_P) cmc + K_P c_{MS}. \end{aligned} \quad (5)$$

Thus, Eqs. 5 and 3 together describes the effect of a micelle-forming solubilizer in a whole concentration range with two linear branches. Equation 5, however,

neglects the fact that a part of the micelle-forming solubilizer is consumed in the complex. The correct equation should read, using a true complexation constant K_C rather than the apparent one K_C',

$$\frac{S}{S_0} = 1 + \frac{K_C \text{cmc}}{1 + K_C S_0} + K_P[c_{MS} - \text{cmc}(1 + K_C S_0)]$$
$$= 1 + \left[\frac{K_C}{1 + K_C S_0} - K_P(1 + K_C S_0)\right]\text{cmc} + K_P c_{MS}. \quad (6)$$

Equation 6 gives also the solubility at high concentrations of a micelle-forming solubilizer as a linear function of the total solubilizer concentration but the important difference is that the crossover point is not at cmc but at a higher concentration, cmc $(1 + K_C S_0)$. Below this concentration, the solubility is described by Eq. 3.

In any case, the above equations should be used as semiempirical because some assumptions can be violated in practice. For example, solute/solubilizer complexes with stoichiometry different from 1:1 can be formed or micellization can be promoted by solute.

Solubilization with a pair of solubilizers

In general, the solubility of a sparingly soluble compound in solution of two solubilizers can be assumed to be additive as long as there are no other significant interactions except those between the solute and individual solubilizers. The total solubility is then given by solubilizing powers of individual solubilizers, denoted as A and B,

$$\frac{S}{S_0} = \left(\frac{S}{S_0}\right)_A + \left(\frac{S}{S_0}\right)_B - 1 \quad (7)$$

where the terms for individual solubilizers are assessed either experimentally or obtained with an appropriate equation, for example those given in the preceding section.

Strong mutual interactions between solubilizers can decrease the total solubilization effect. If a complex between solubilizers is formed, portions of solubilizers consumed in this way are excluded from the solubilization. This can be accounted for if stochiometry and a binding constant are known—the conservation relationship for both solubilizers and solute has to be combined together with appropriate binding isotherms. For the case of 1:1 complex formed both between the solute and each solubilizer as well as between solubilizers themselves, the relevant equations are

$$\frac{S}{S_0} = 1 + K_{C,A}[A] + K_{C,B}[B], \quad (8a)$$

$$c_A = [A] + K_{C,A}[A]\, S_0 + K_{AB}[A][B], \quad (8b)$$

$$c_B = [B] + K_{C,B}[B] S_0 + K_{AB}[A][B] \quad (8c)$$

where c_A, c_B are total and [A], [B] equilibrium molar concentrations of solubilizer A and B, respectively.

Equations 8a, 8b, 8c can be used for micellizing solubilizers at concentrations not high enough for micelles to be formed. In order to modify Eqs. 8a, 8b, 8c for the solutions in which one solubilizer (e.g., solubilizer B) forms micelles, an assumption has to be made that the solubilizer A binds only with molecularly dissolved solubilizer B. Denoting the concentration of solubilizer B participating in the micelle formation as $c_{B,M}$ we have

$$\frac{S}{S_0} = 1 + K_{C,A}[A] + K_{C,B}\text{cmc} + K_{P,B} c_{B,M}, \quad (9a)$$

$$c_A = [A] + K_{C,A}[A]\, S_0 + K_{C,A}[A]\text{cmc}, \quad (9b)$$

$$c_B = \text{cmc} + K_{C,B}\text{cmc}\, S_0 + K_{AB}[A]\text{cmc} + c_{B,M}. \quad (9c)$$

By this procedure (i.e., by solving Eqs. 9a, 9b, 9c), solubilization of benzo[*a*]pyrene in a mixture of HPBCD and bile acid salt (sodium taurocholate) was successfully predicted knowing both behavior of individual solubilizers and their interactions [12].

Solubilization with polymeric solubilizers

The polymeric nature of a solubilizer does not invalidate the scheme outlined above for solubilization with one solubilizer. With micellizing solubilizers, the molecular weight has no qualitative effect on the relation between the solubilizer concentration and the amount of pseudophase formed. It is true that the existence of several solute binding sites per molecule can be expected for high-molecular-weight complexing solubilizers but still the use of 1:1 stoichiometry is quite appropriate—multiplicity of binding sites can be hidden in the binding constant because of a very low solute concentration resulting in low saturation of solubilizer binding sites by the solute. Due the low saturation, complicating factors such as delocalization and/or cooperativity of binding can be neglected as well. On the other hand, the nature of solute binding below cmc is more obscure with polymeric solubilizers than with low-molecular-weight ones, aggregation and solute-induced micellization being more probable. However, such phenomena may operate also with low-molecular-weight solubilizers and are of no concern as long as Eq. 5 is used as semi-empirical, without aspirations to establish solubilization mechanism. [20]

Polymeric nature becomes important if the solubilizer is used in conjunction with another solubilizer, which can be of low molecular weight, and the two solubilizers interacts. For one, low saturation cannot be a priory assumed in solubilizer/solubilizer binding. On the other

hand, the consequences of solubilizers binding for solubilizing or micellizing ability of the polymeric micellizing solubilizer are not clear and, in fact, neither of these abilities needs to be hampered. For such limiting case, when a low-molecular-weight solubilizer A binds to both molecular and micellar forms of a polymeric solubilizer B, and only the solubilizing power of a low-molecular-weight solubilizer A is affected by this binding, we get

$$\frac{S}{S_0} = 1 + K_{C,A}[A] + K_{C,B}\text{cmc} + K_{P,B}(c_B - \text{cmc}), \quad (10a)$$

$$c_A = [A] + K_{C,A}[A]\, S_0 + K_{AB}[A][B], \quad (10b)$$

$$c_B = [B] + K_{C,B}\text{cmc}\, S_0 + K_{AB}[A][B]. \quad (10c)$$

.

Result and discussion

Naphthalene solubilization with individual solubilizers

Although we are primarily interested in the interactions between PEG–PPG–PEG block copolymers and CDs, i.e., in naphthalene solubilization with mixtures of solubilizers, the solubilizing power of all individual solubilizers had to be established at first. The reason was not only to obtain the data not available in the literature or to verify those available, but also to establish a reliable basis for the interpretation of solubilization by mixed solubilizers because a significant difference can exist between samples classified under the same general name, both in the case of CD derivatives and PEG–PPG–PEG copolymers. The results on solubilization with individual solubilizers are collected in Fig. 1.

The solubility of naphthalene in solutions of HPBCD and of HPACD appreciably increased. The value of the binding constant K_{CD} = 840 dm^3/mol for HPBCD agrees reasonably well with literature data [12, 21]. No such data are available on solubilization of naphthalene by HPACD but the observation reported in the literature that naphthalene is about six times more soluble in 25 mM HPBCD than in 25 mM α-CD corroborates the value K_{CD} = 131 dm^3/mol found for HPACD by us. The linear increase in naphthalene solubility both with HPACD and HPBCD concentration agrees with the observation that 2-hydroxypropyl derivatives of cyclodextrins form only a 1:1 complex with naphthalene and not some higher complexes observed with natural CDs [21].

A higher solubilizing power is expected for the PEG–PPG–PEG triblock copolymers that form micelles under given conditions. The results of characterization of our samples of PEG–PPG–PEG triblock copolymers, together with literature data on micellization of PEG–PPG–PEG triblock copolymers imply that only polymer II can be expected to form micelles at 25 °C and at the concentrations used. This is corroborated by our measurement of naphthalene solubility which is substantially higher in solutions of polymer II than in solutions of copolymer I; however, naphthalene solubility increased even in the latter.

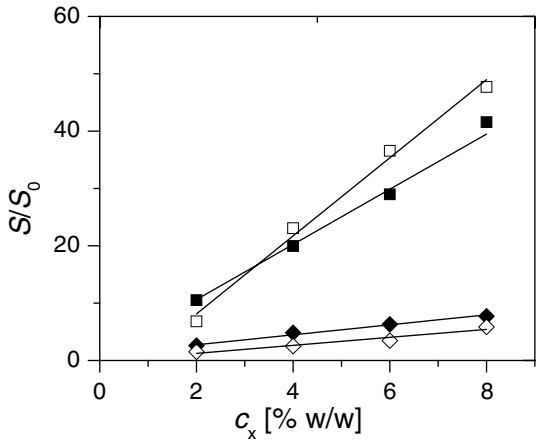

Fig. 1 Solubility of naphthalene in solutions of individual solubilizers relative to the solubility in pure water. Solubilizers: HPACD (*filled diamond*), HPBCD (*filled square*), copolymer I (*open diamond*), copolymer II (*open square*)

The solubility of naphthalene increases linearly with the concentration of copolymer I with no apparent break. The value of the intercept close to 1 implies that cmc of copolymer I at 25 °C is above the concentrations used by us, which means that the slope of the dependence corresponds to K'_C, the value being 192 dm^3/mol. Paterson et al. [13] proposed a linear bivariate correlation between K'_C and molecular weights of PEG and PPG blocks forming the PEG–PPG–PEG triblock copolymer. We found that a better fit to their data is obtained if the correlation is made for log K'_C. Thus the obtained correlation predicts K'_C = 260 dm^3/mol for copolymer I giving the support to our experimental data.

The linear dependence of naphthalene solubility on the solubilizer concentration was also found for copolymer II, but with a large negative intercept, which means that the concentrations used are above cmc for copolymer II and therefore the slope of the dependence is not equal to $K_{C'}$ but to K_P (Eq. 4 or Eq. 5). The value found, 2,700 dm^3/mol, is somewhat lower than that reported for P84 [13], the Pluronic most similar to copolymer II for which literature data are available. The difference is not surprising because significant differences in composition between copolymer II and Pluronic P84 still exist.

Solubilization with a pair of solubilizers

The solubility of naphthalene in solutions containing two solubilizers was measured for all four pairs combining one of HPCDs and one of PEG–PPG–PEG copolymers. Two series were measured for each pair: the HPCD concentration was varied from 2% to 8% (w/w) while the concentration of a PEG–PPG–PEG copolymer was kept at 4% in the first series whereas the PEG–PPG–PEG copolymer concentration was varied and that of HPCD kept constant in the second one. In order to assess mutual interactions of solubilizers, the results were compared with some theoretical predictions, generally discussed here before proceeding with the presentation of the results for each pair.

The first prediction used (procedure 1), assuming no significant interaction between solubilizers, is given by Eq. 7 with each term corresponding to the solubility in the absence of the other solubilizer. In the second prediction (procedure 2), we utilize our knowledge on interactions between CDs and PEG–PPG–PEG copolymers and use Eqs. 10a, 10b, 10c, i.e., assume that HPCD binds both to molecularly dissolved and micellar PEG–PPG–PEG copolymer without affecting the copolymer ability to participate in micelle formation or the ability of micelles to solubilize naphthalene. An experimental naphthalene solubility lower than the first prediction would indicate some binding between HPCD and copolymer and if lower than the second prediction, it would indicate that the interactions between HPCD and copolymer are strong enough to interfere with copolymer micellization and/or solubilizing power.

The first pair was HPACD and copolymer I, for which the complexation is expected to occur on PEG blocks. According to the competitive spectrophotometry, the binding constant for binding of an isolated HPACD molecule to PEG is approximately 2.5 dm^3/mol [4]. This value is based on a binding site corresponding to two monomeric units and we used this definition and this value of the binding constant in calculating the theoretical solubility according to procedure 2 with the polymeric solubilizer concentration expressed as the concentration of EG doublets. Copolymer I does not form micelles at the concentrations and temperature used by us and, therefore, no drastic reduction in the naphthalene solubility caused by micelle destruction can be expected. Moreover, solubilization with a molecularly dissolved copolymer may be expected to involve a more hydrophobic inner PPG block rather than outer PEG blocks on which HPACD would reside. Thus only a small effect of interactions between HPACD and copolymer I on total naphthalene solubility in mixture of these two solubilizers is to be expected. As seen from Fig. 2, this is really the case. In fact, the naphthalene solubility corresponds to the predictive procedure 1 for measurements at a constant content of copolymer I

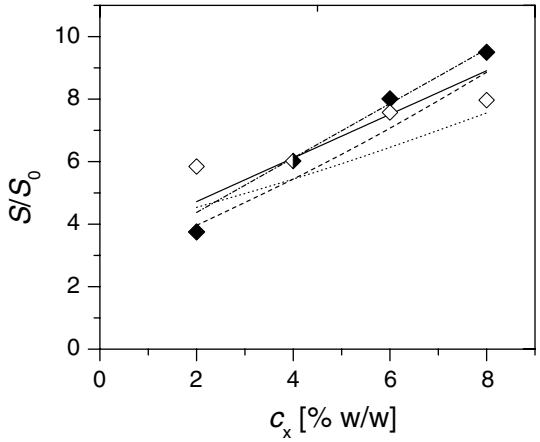

Fig. 2 Solubility of naphthalene in mixed solutions of HPACD and copolymer I relative to the solubility in pure water. Either the concentration of HPACD was kept at 4% while concentration of copolymer I was varied (*filled diamond*, *dashed and full lines*, $c_x = c_I$) or the concentration of copolymer I was kept at 4% while the concentration of HPACD was varied (*open diamond*, *dotted and dash-dotted lines*, $c_x = c_{HPACD}$). Symbols depict experimental data, and the point common to both series is given as *Half filled diamond*. The *lines* indicate solubility predicted from the behavior of individual solubilizers assuming either complete additivity (*dash-dotted and full lines*) or a contribution of HPACD decreased due to interactions between HPACD and PE blocks of copolymer I (*dotted and dashed lines*), see text

almost perfectly, although one would expect that the data will rather match the predicting procedure 2. However, to interpret this finding as an indication or even as a proof of the absence of significant interactions between HPACD and copolymer I would be shortsighted as can be seen from the behavior of the following pair of solubilizers.

Figure 3 shows the results of naphthalene solubilization in mixtures of HPACD with the other PEG–PPG–PEG copolymer, micelle-forming copolymer II, which has a much higher solubilizing power than copolymer I. Consequently, the effect of copolymer II is dominant in the mixtures with HPACD and the difference in predictions by the procedure 1 or 2 is relatively small. It is worth noting that some synergetic effect appears at higher concentrations of HPACD where a naphthalene solubility higher than that predicted by procedure 1 was found. The source of the synergy remains obscure. The experiments of Loftsson [22], who observed enhancement of the dissolution efficiency of CDs by addition of neutral polymers, are probably not relevant here because rather harsh dissolution methods were required. Rather, the explanation may be similar as in the case of HPBCD and sodium taurocholate [12] for which enhanced benzo[*a*]pyrene solubility at high HPBCD concentrations was adequately described only assuming the formation of an additional complex. Regardless of the origin, the synergetic effect might

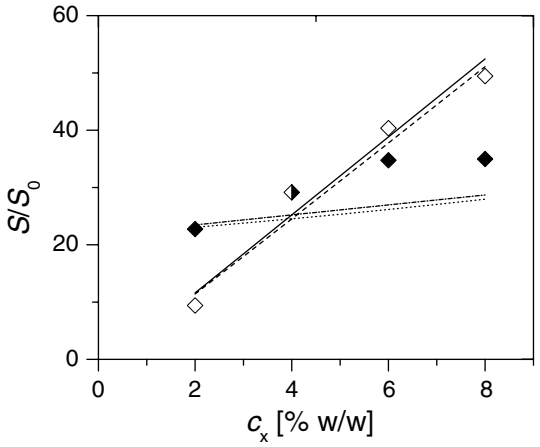

Fig. 3 Solubility of naphthalene in mixed solutions of HPACD and copolymer II relative to the solubility in pure water. Either the concentration of HPACD was kept at 4% while concentration of copolymer II was varied (*filled diamond*, *dashed and full lines*, $c_x = c_{II}$) or the concentration of copolymer II was kept at 4% while the concentration of HPACD was varied (*open diamond*, *dotted and dash-dotted lines*, $c_x = c_{HPACD}$). Symbols depict experimental data, and a point common to both series is given as *Half filled diamond*. *Lines* indicate solubility predicted from the behavior of individual solubilizers assuming either complete additivity (*dash-dotted and full lines*) or a contribution of HPACD decreased due to interactions between HPACD and PE blocks of copolymer II (*dotted and dashed lines*), see text

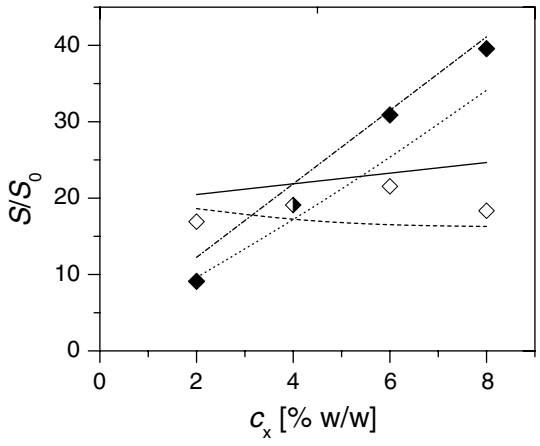

Fig. 4 Solubility of naphthalene in mixed solutions of HPBCD and copolymer I relative to the solubility in pure water. Either the concentration of HPBCD was kept at 4% while concentration of copolymer I was varied (*filled diamond, dashed and full lines*, $c_x = c_I$) or the concentration of copolymer I was kept at 4% while the concentration of HPBCD was varied (*open diamond*, *dotted and dash-dotted lines*, $c_x = c_{HPBCD}$). Symbols depict experimental data, and a point common to both series is given as *half filled diamond*. *Lines* indicate solubility predicted from the behavior of individual solubilizers assuming either complete additivity (*dash-dotted and full lines*) or a contribution of HPBCD decreased due to interactions between HPBCD and a PP block of copolymer I (*dotted and dashed lines*), see text

compensate the decrease in solubility expected for HPACD/copolymer I and explain the observed agreement between the experiments and the prediction by procedure 1. The reason why the synergetic effect is distinct with copolymer II is probably caused by a lower PEG content but also by worse PEG accessibility due to micellization.

In the combination of HPBCD and copolymer I (Fig. 4), the dominant solubilizer is HPBCD. It is known that HPBCD threads on PPG [1] but the quantitative information on interactions of an isolated HPBCD molecule with PPG is missing. Therefore in predictive procedure 2, we used the same value of the binding constant as for HPACD/PEG. Although the naphthalene solubility observed is somewhat lower than those predicted by the procedure 1, they are generally above those predicted by procedure 2. Even though this may be caused by overestimating the value of the binding constant used in procedure 2, synergetic effects may also play some role.

The synergetic effect is apparent in the last pair of solubilizers—HPBCD and copolymer II (Fig. 5), since the observed naphthalene solubility is well above the prediction of procedure 1. Obviously, the interactions of HPBCD and the PPG block are not strong enough to disrupt significantly micelles or even to thread onto micellized copolymer extensively. This contradicts the results obtained with PEG containing octadecyl groups

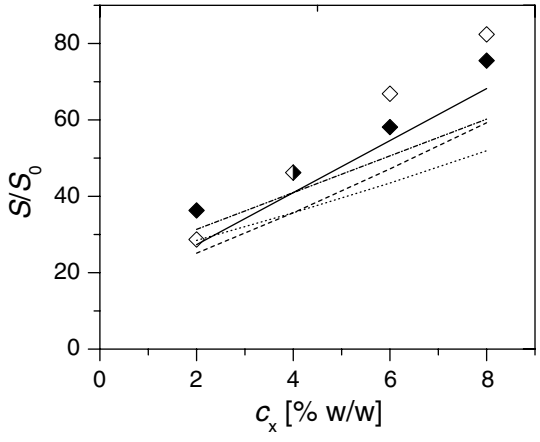

Fig. 5 Solubility of naphthalene in mixed solutions of HPBCD and copolymer II relative to the solubility in pure water. Either the concentration of HPBCD was kept at 4% while concentration of copolymer II was varied (*filled diamond, dashed and full lines*, $c_x = c_{II}$) or the concentration of copolymer II was kept at 4% while the concentration of HPBCD was varied (*open diamond*, *dotted and dash-dotted lines*, $c_x = c_{HPBCD}$). Symbols depict experimental data, and a point common to both series is given as *half filled diamond*. *Lines* indicate solubility predicted from the behavior of individual solubilizers assuming either complete additivity (*dash-dotted and full lines*) or a contribution of HPBCD decreased due to interactions between HPBCD and a PP block of copolymer II (*dotted and dashed lines*), see text

at both ends whose solution rheology in the presence of HPBCD was explained by the model in which HPBCD destroys micelle-like junction points [23]. However, HPBCD binding to alkane is much stronger than to oxoalkane, in fact by three orders of magnitude, and moreover rheology is sensitive to release of individual chains, more precisely their end groups, from junctions, whereas the solubility is affected by destruction of whole micelles.

Conclusion

Naphthalene solubilization in solutions of HPCD and PEG–PPG–PEG copolymers confirms HPCD/copolymer interactions for the non-micellizing copolymer. It could not be decided whether similar interactions exist also in solutions of the micellizing copolymer and whether these interactions are strong enough to interfere with micellization at comparable HPCD and copolymer weight concentrations since the existence of synergetic interactions enhancing naphthalene solubility can mask such a destructive effect. Regardless of the nature of interactions operating in naphthalene/HPCD/copolymer solutions, overall naphthalene solubility does not deviate significantly from a prediction for independent solubilization with HPCD and PEG–PPG–PEG copolymer. Consequently, the solubilization efficiency of HPBCD and PEG–PPG–PEG copolymers may be expected not to be compromised upon their co-administration.

Acknowledgements The project was supported by the Grant Agency of the Academy of Sciences of the Czech Republic (grant A1050101).

References

1. Harada A (2001) Acc Chem Res 34:456
2. Panova IG, Gerasimov VI, Tashlitskii VN, Topchieva IN, Kabanov VA (1997) Polym Sci A 39:452
3. Fujita H, Ooya T, Yui N (1999) Macromolecules 32:2534
4. Horsky J (1998) Eur Polym J 34:591
5. Horsky J (2000) Macromol Theor Simul 9:759
6. Okada M, Kamachi M, Harada A (1999) J Phys Chem B 103:2607
7. Gaitano GG, Brown W, Tardajos G (1997) J Phys Chem B 101:710
8. Li J, Ni X, Zhou Z, Leong KW (2003) J Am Chem Soc 125:1788
9. Mayer B, Klein CT, Topchieva IN, Köhler G (1999) J Comput Aided Mol Des 13:337
10. Uekama K (2002) J Inclusion Phenom Macrocycl Chem 44:3
11. Kabanov AV, Batrakova EV, Alakhov VYu (2002) J Control Release 82:189
12. Horsky J, Pitha J (1996) J Pharm Sci 85:96
13. Paterson IF, Chowdhry BZ, Leharne SA (1999) Langmuir 15:6187
14. Lebens PJM, Keurentjes TF (1996) Ind Chem Res 35:3415
15. Hurter PN, Hatton TA (1992) Langmuir 8:1291
16. Wang X, Brusseau ML (1993) Environ Sci Technol 27:2821
17. Male KB, Brown SR, Luong JHT (1995) Enzyme Microb Technol 17:607
18. May WE, Wasik SP, Freeman DH (1978) Anal Chem 50:997
19. Perez-Tejeda P, Yanes C, Maestre A (1990) J Chem Eng 35:244
20. Guha S, Jaffé PR, Peters CA (1998) Environ Sci Technol 32:930
21. Sau S, Solanki B, Oprecio R, van Stam J, Evans HC (2004) J Inclusion Phenom Macrocycl Chem 48:173
22. Loftsson T (1998) Pharmazie 53:11
23. Horský J, Mikešová J, Quadrat O, Šňupárek J (2004) J Rheol 48:23