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RESEARCH PAPER

Effect of Water-Soluble Polymers on Naproxen Complexation with Natural and Chemically Modified β-Cyclodextrins

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ABSTRACT

The combined effect of cyclodextrins (CDs) (β-, methyl-β-, hydroxypropyl-β-cyclodextrins) and water-soluble polymers (sodium carboxymethylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone K30, polyethylene glycol 6000) on naproxen solubility improvement was studied. Phase solubility analysis at 25°C was used to investigate the interaction of the drug with each cyclodextrin (or polymer), alone or in the presence of the different water-soluble polymers (or cyclodextrins). The combined use of polymer and cyclodextrin was always clearly more effective in enhancing the aqueous solubility of naproxen in comparison with the corresponding drug-polymer or drug-cyclodextrin binary systems, and the solubilization enhancement was not simply additive, but synergistic. Water-soluble polymers increased the complexation efficacy of cyclodextrins toward naproxen (as shown by the increased stability constants of the complexes), which resulted in enhanced drug solubility. No previous sonication or heating treatments of the drug-cyclodextrin-polymer suspensions was necessary to obtain this favorable effect. The best results were obtained in ternary systems with β-cyclodextrin, which had a solubilizing effect toward naproxen in the presence of 0.25% w/v of the different hydrophilic polymers examined that was improved from 25% to about 80%, depending on the type of polymer.

Key Words: *Complexation; Cyclodextrins; Naproxen; Polymers; Solubilization*

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INTRODUCTION

Cyclodextrins (CDs) have attracted growing interest in the pharmaceutical technology field due to their ability to form inclusion compounds with a number of guest molecules by incorporating them into their central cavities (1). This phenomenon can be utilized to enhance the dissolution of poorly water soluble drugs and to improve drug stability and bioavailability (2,3). However, due to various reasons (such as their high molecular weight, relatively low water solubility, and possible parenteral toxicity), the amount of cyclodextrin that can actually be used in most solid and liquid drug formulations is limited. Therefore, it would be useful to find methods to enhance the complexation and solubilization efficiency, thus making it possible to reduce the cyclodextrin dose considerably. When a cyclodextrin forms a complex with a drug, the complexation efficiency can be considered equal to the product of the intrinsic solubility of the drug S_0 for the stability constant of the complex K_s (4). Thus, increased complexation efficiency can be obtained by increasing S_0, K_s, or both simultaneously.

Recent works have shown that the presence of various auxiliary substances, such as cellulose derivatives, water-soluble polymers, hydrotropic compounds, surfactants, cosolvents, and the like, can significantly affect cyclodextrin complexation (5). For example, small amphiphilic molecules such as ethanol and propylene glycol can reduce cyclodextrin complexation by acting as competing guest molecules (6,7). Likewise, lipophilic preservative molecules or surfactants have been shown to displace drug molecules from the cyclodextrin cavity (8–11). In contrast, the addition of certain low molecular weight acids or hydroxyacids can enhance the cyclodextrin solubilization of basic drugs by an order of magnitude through the formation of drug-acid-cyclodextrin ternary complexes (12–14). Similarly, addition of small amounts of various water-soluble polymers to the aqueous complexation medium (accompanied by sonication and autoclaving of the suspensions) can significantly increase the cyclodextrin solubilizing efficiency (15–18).

We previously showed that the solubility of naproxen, a nonsteroidal anti-inflammatory drug very poorly water soluble (25 mg/L at 25°C), can be improved by both complexation with β-cyclodextrin and chemically modified β-cyclodextrins (19) or solid dispersion with water-soluble polymers (20,21). Therefore, it seemed of interest to extend our investigation to the study of the combined effect of various hydrophilic polymers (polyvinylpyrrolidone K30 [PVPK30], sodium carboxymethylcellulose [NaCMC], hydroxypropylmethylcellulose [HPMC], polyethylene glycol 6000 [PEG6000]), and cyclodextrins (β-, methyl-β-, hydroxypropyl-β-) on the aqueous solubility enhancement of naproxen. Phase solubility studies of the drug in the presence of cyclodextrins and/or polymers were performed to evaluate and compare both the solubilizing and the complexing efficacy of the different binary and ternary systems.

EXPERIMENTAL

Materials

Naproxen [(S)-6-methoxy-α-methyl-2-naftalenacetic acid, NAP], recrystallized from ethanol, and β-cyclodextrin (β-CD) were purchased from Sigma Chemical Company (St. Louis, MO). β-Cyclodextrin amorphous derivatives randomly substituted, that is, hydroxypropyl-β-cyclodextrin (HP-β-CD) with an average molar substitution degree per anhydroglucose unit of 0.6 (average molecular weight 1380) and methyl-β-cyclodextrin (Me-β-CD) with an average substitution degree per anhydroglucose unit of 1.8 (average molecular weight 1310), were kindly donated by Wacker-Chemie GmbH (Munich, Germany) and were used as received. Water contents of amorphous β-cyclodextrin derivatives (determined by thermogravimetric analysis) ranged from 6% to 7% (as mass fraction). The following water-soluble polymers were examined: PEG6000 (Merck-Schuchardt, Munich, Germany); and PVP K30, NaCMC, and HPMC (Sigma).

Method

Phase Solubility Studies

Phase solubility equilibrium diagrams (in water at 25°C) were obtained for both binary and ternary systems according to Higuchi and Connors (22). Studies for binary systems were carried out by adding an excess amount of the drug to 10 ml aqueous solutions containing increasing concentrations of cyclodextrin (from 0% to 7.5% w/v for Me-β-CD and HP-β-CD or from 0% to 1.6% w/v for β-CD, i.e., to its aqueous saturation solubility at 25°C) or polymer (from 0% to 0.5% w/v). Experiments for ternary systems were performed analogously to those for binary

systems, but in the presence of a fixed amount of the third component, that is, the polymer (0.25% w/v) or the cyclodextrin (7.5% w/v for HP-β-CD and Me-β-CD and 1.6% w/v for β-CD), respectively. The glass containers were sealed and electromagnetically stirred (500 rpm) at a constant temperature (25°C) until equilibrium was reached (48 h). An additional series of suspensions, containing an excess drug in the presence of 0.25% w/v polymer and 7.5% w/v HP-β-CD or Me-β-CD or 1.6% w/v of β-CD, was sonicated 1 h in an ultrasonic bath, heated 2 h in an oven at 90°C, and then equilibrated under electromagnetic stirring (500 rpm) at 25°C for 48 h. All the suspensions were then filtered through a 0.45-μm membrane filter (Sartorius AG, Goettingen, Germany) and assayed for drug concentration by second-derivative ultraviolet (UV) spectroscopy (19) using a Perkin Elmer model 552 S spectrophotometer (Norwalk, CT). The presence of cyclodextrin and/or polymer did not interfere with the spectrophotometric assay. Each test was repeated four times (coefficient of variation [CV] < 3%).

The apparent 1 : 1 stability constants of NAP-CD complexes were calculated from the slope of the initial straight portion of the phase solubility diagrams and the determined drug solubility in water S_0 (22):

$$K_c = \text{Slope}/[S_0(1 - \text{Slope})]$$

Viscosity Determinations

Bulk viscosity measurements (Rheomat model 108 Contraves viscometer) were performed in triplicate at 25° ± 0.3°C on 100 ml of aqueous solution by the continuous shear method (0–150–0 s^{-1} shear cycle).

RESULTS AND DISCUSSION

Influence of Polymers

Several papers have reported the solubilizing effect of hydrophilic polymers toward a number of drugs through the formation of water-soluble complexes (23–25). Therefore, equilibrium solubility studies were performed in aqueous solutions to determine the solubilizing effect of the different polymers examined on NAP. In all cases, an initial increase in drug solubility was observed, but it was rapidly followed by a plateau that was achieved in the presence of relatively low polymer concentrations (0.25–0.5% w/v) (Fig. 1).

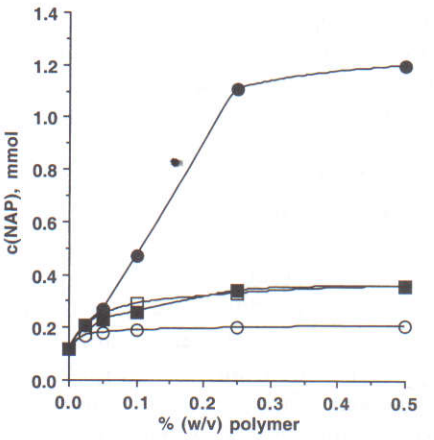

Figure 1. The effect of increasing concentrations of ○ PEG6000, ■ PVP K30, □ HPMC, or ● NaCMC on the aqueous solubility of NAP (naproxen) at 25°C. Each point represents the mean of four determinations (coefficient of variation [CV] < 3%).

It is evident that, as a consequence of drug-carrier interactions, all the examined polymers showed a more or less marked solubilizing effect toward NAP, which had a solubility that was doubled or tripled in the presence of PEG6000 or HPMC and PVP K30, respectively, and it increased up to 10 times in the presence of NaCMC. Hydrophilic polymers mainly interact with drug molecules by electrostatic bonds (ion-to-ion, ion-to-dipole, and dipole-to-dipole bonds), even though other types of forces, such as van der Waals forces and hydrogen bridges, can frequently participate in the complex formation (26). The nature of the interactions in solution between NAP and PVP or PEG, as well as the consequent drug solubility improvement have been previously investigated (20,21,27,28). Differences of conformational structure, degree of polymerization, charge density, accessibility, and type of functional groups on the polymer chain could account for the different solubilizing power toward NAP as presented by the considered macromolecules (26). In particular, it should be underlined that NaCMC is an ionizable polysaccharide, whereas all the other examined macromolecules are neutral polymers that have little or no effect on the pH of the aqueous solution. In particular, the pH of aqueous solutions of NAP ($pK_a = 4.15$) (29) remained practically unvaried (pH ≈ 5) after addition of the different polymers, except in the case of NaCMC, which caused an increase of pH of about 1 unit (pH ≈ 6). Therefore,

the increased drug ionization (more than 95%, calculated on the basis of the drug pK_a value) can concur to explain the higher increase in NAP solubility observed in the presence of such polymer.

Influence of the Association Polymer-Cyclodextrin

Phase solubility diagrams of NAP in ternary systems obtained by adding an excess of drug to aqueous solutions containing increasing amounts of polymers and a constant amount of cyclodextrin (Fig. 2) showed a behavior rather similar to that of the corresponding binary systems without cyclodextrin. In fact, in most cases, a plateau was rapidly established, even though it was at a higher NAP concentration level owing to the presence of the cyclodextrin. Moreover, NaCMC, which exhibited the highest solubilizing effect in binary systems, likewise showed the largest enhancing effect on cyclodextrin NAP solubilization with all the tested cyclodextrins. In contrast, the other considered polymers showed a different order in their promoting effect, depending on the type of cyclodextrin present in the aqueous solution.

The more or less intense interactions between the polar groups of each polymer and those of NAP, CD, and NAP-CD molecules are responsible for the different trends shown by the polymers in combination with the various cyclodextrins. In any case, solubility experiments showed that the optimal polymer concentration always ranged between 0.1% and 0.25% w/v since further addition of polymer to the aqueous cyclodextrin solutions led to no further increase, and sometimes even to some decrease, in drug solubility. Such an effect, which was particularly evident in the case of ternary systems with PEG6000 and HP-β-CD, has already been observed by other authors (16,30,31) and attributed, in the case of PEG, to the properties of this polymer that can strengthen intermolecular hydrogen bonding in water, thus making the solvent more hydrophobic and therefore the inclusion into the cyclodextrin cavity less attractive for the hydrophobic drug molecule (8,31).

Rheological Studies

Rheological studies showed that only cellulose ethers had an appreciable effect on the viscosity of the aqueous solutions, giving typical non-Newtonian flow curves (Fig. 3). Addition of cyclodextrins caused

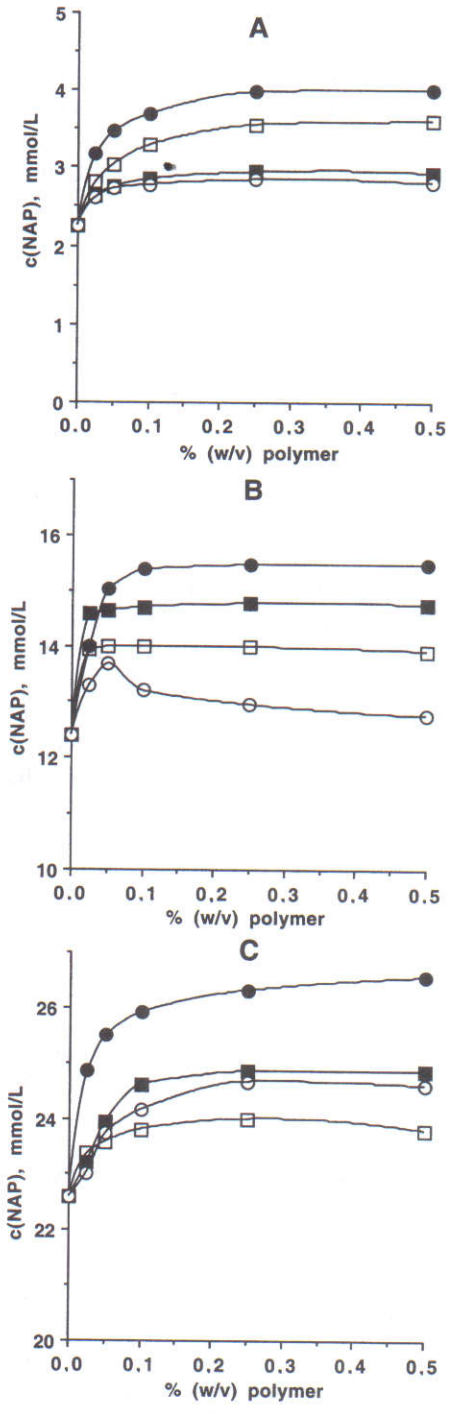

Figure 2. The effect of increasing concentrations of ○ PEG6000, ■ PVP K30, □ HPMC, or ● NaCMC on the aqueous solubility of NAP (naproxen) in the presence of (A) 1.6% w/v β-CD (saturation solubility), (B) 7.5% w/v HP-β-CD, or (C) 7.5% w/v Me-β-CD at 25°C. Each point represents the mean of four determinations (coefficient of variation [CV] < 3%).

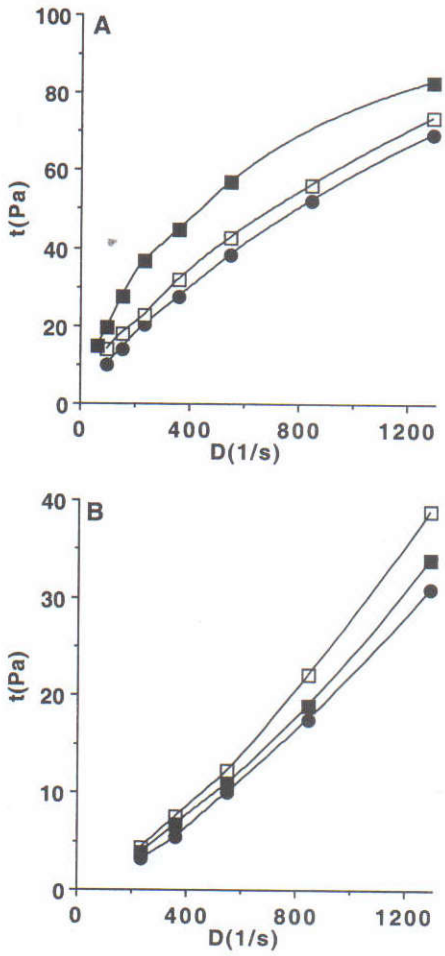

Figure 3. Rheograms obtained for 1.5% w/v aqueous solutions of (A) HPMC or (B) NaCMC, ● alone or in the presence of 1.5% w/v of □ β-CD or ■ HP-β-CD.

changes in the course of flow curves, suggesting the occurrence of physicochemical interactions between the components. Similar effects have been observed by other authors and attributed to the formation of molecular associations between the polymer and the CD, which were confirmed by laser light-scattering spectrometry and were of the "side-to-side" type in the case of NaCMC and of the "end-to-end" type in the case of HPMC (32). However, no relationship was found between the intensity of these changes in flow curves and the extent of the positive effect of the polymers on NAP solubility improvement.

Effect of Polymers on the Stability Constants of Complexes

The phase solubility diagrams of NAP in aqueous solutions at 25°C of the three different cyclodextrins, with or without 0.25% w/v of polymer, were all of Higuchi's A_L type; that is, a linear increase of drug concentration was observed as a function of cyclodextrin concentration, independent of the presence of the polymer. The slopes in all cases were less than unity, thus confirming the formation of 1 : 1 complexes (22).

The values of the apparent stability constants of NAP-CD complexes, both when no polymer was present or in the presence of 0.25% w/v polymer are shown in Table 1. Addition of polymer to the cyclodextrin solutions always resulted in a stability constant increase that varied from a minimum of 6% to a maximum of 50%, depending on the cyclodextrin and polymer considered. Therefore, the improved cyclodextrin solubilizing efficiency can be attributed to the increase of the cyclodextrin com-

Table 1

Effect of Polymers (0.25% w/v) on the Stability Constant K_s of Naproxen (NAP) Complexes with Different Cyclodextrins in Aqueous Solutions at 25°C

	β-CD		Me-β-CD		HP-β-CD	
Polymer	K_s (M^{-1})	K_{St}/K^a_{Sb}	K_s (M^{-1})	K_{St}/K^a_{Sb}	K_s (M^{-1})	K_{St}/K^a_{Sb}
No polymer	1700	—	6950	—	2080	—
HPMC	2240	1.32	7390	1.06	2850	1.37
NaCMC	2310	1.36	7835	1.13	3100	1.49
PVP K30	2050	1.20	7690	1.11	2990	1.44
PEG6000	1990	1.17	7520	1.08	2570	1.23

[a]Ratio between the stability constants of ternary (K_{St}) and binary (K_{Sb}) systems.

plexing power toward NAP. Addition of polymers can contribute to favoring the complexation ability of cyclodextrins by establishing interactions such as hydrophobic bonds, van der Waals dispersion forces, or hydrogen bonds and/or by promoting the release of the high-energy water molecules present in their cavity (33).

Solubility studies on binary systems showed definite interactions both between NAP and each CD (which was of the inclusion type) and between NAP and each examined polymer, suggesting in this case the formation in solution of polymer-(NAP)*n* soluble complexes. Therefore, possible interactions in the ternary systems, in addition to those already present in binary systems [i.e., NAP-CD and polymer-(NAP)*n*], are in regard to NAP-CD–polymer, polymer–(NAP)*n*–CD systems and, moreover, possible interpolymer complexation between polymer and CD.

The presence of this last type of interaction has been confirmed by the solubilizing effect of hydrophilic polymers (such as PVP or HPMC) toward β-CD (4,34). Moreover, the possible complex formation between PEGs and cyclodextrins has been documented (35,36). Significant variations in thermodynamic parameters of drug-CD interaction on addition of a hydrophilic polymer to the complexation medium accounted for a specific role of the polymer in the complexation process (our unpublished data; 15). Furthermore, the formation of the ternary complexes ("cocomplexes") drug-CD-polymer has been reported (37). However, at present, there is no definite information about the special structural arrangement of the polymers in these ternary systems, and further studies will be necessary to gain insight.

Effect of Polymers, Cyclodextrins, and Their Combinations on Drug Solubility

The effect of the different polymers, cyclodextrins, and their combinations on the aqueous solubility of NAP is presented in Table 2. Solubility of NAP in aqueous solutions at 7.5% w/v β-CD derivatives or 1.6% w/v native β-CD was from 20 (for β-CD) to about 200 times (for Me-β-CD) higher than in water. The addition of 0.25% w/v of water-soluble polymers to the solution medium improved the drug solubility even further. As previously seen, polymers as well showed a solubilizing effect on NAP. However, when polymer and cyclodextrin are present together in solution, one achieves an extent of drug solubilization greater than when they are used separately. Therefore, the solubilization enhancement was more than simply

Table 2

Effect of Polymers on the Solubilization of Naproxen (NAP) in Aqueous Cd Solutions at 25°C

Cyclodextrin	Polymer	S^{a}_{CD} (mg/L)	S^{b}_{pol} (mg/L)	S^{c}_{CD+pol} (mg/L)	S_{CD+pol}/S^{d}_{CD} (mg/L)
β-CD	NaCMC	518	270	945	1.82
	HPMC		80	835	1.61
	PVP		78	685	1.32
	PEG		50	650	1.25
HP-β-CD	NaCMC	2840	270	3580	1.26
	HPMC		80	3290	1.16
	PVP		78	3420	1.20
	PEG		50	3130	1.10
Me-β-CD	NaCMC	5140	270	6220	1.21
	HPMC		80	5820	1.13
	PVP		78	5920	1.15
	PEG		50	5880	1.14

HPMC, hydroxypropylmethylcellulose; NaCMC, sodium carboxymethylcellulose; PEG, polyethylene glycol; PVP, polyvinylpyrrolidone.
[a]Solubility in aqueous solution containing 1.6% w/v β-CD or 7.5% w/v β-CD derivatives.
[b]Solubility in aqueous solution containing 0.25% w/v polymer.
[c]Solubility in aqueous solution containing both polymer and cyclodextrin.
[d]Solubility ratio.

additive; it was synergistic for all the examined polymers.

The highest enhancements were obtained for ternary systems with β-CD, with a solubilizing effect toward NAP that improved 25%, 30%, 60%, or 80% when 0.25% w/v of PEG6000, PVP K30, HPMC, or NaCMC, respectively, was present. On the contrary, lower increments, ranging from 10% to 25% were obtained with β-CD derivatives, which always maintained the best solubilizing efficacy, however. Similar favorable effects on cyclodextrin solubilization of various hydrophobic drugs have already been reported by other authors for various water-soluble polymers; however, it should be underlined that, in our case, this effect was observed without previous sonication and/or heating of the aqueous suspensions, which is different from that described by such other authors (16,30,37–39). In this regard, it was considered interesting to compare the relative NAP solubility increases obtained in binary and ternary systems with and without sonicating and heating the suspensions (Fig. 4A and 4B).

It was found that the sonication-heating treatment actually enabled further improvement of the solubilizing efficacy, but this effect was very limited; moreover, it was clearly more marked for binary systems without polymer (Fig. 4B). In fact, whereas in ternary systems the improvement varied from a minimum of 5% to a maximum of 15% for the Me-β-CD–PEG6000 and β-CD-NaCMC combinations, respectively, it ranged from 10% (Me-β-CD) to 30% (β-CD) when only cyclodextrin was present. It is therefore evident that this particular treatment led to an improvement of the cyclodextrin solubilizing power, but it had no effect on the synergistic action of the polymer.

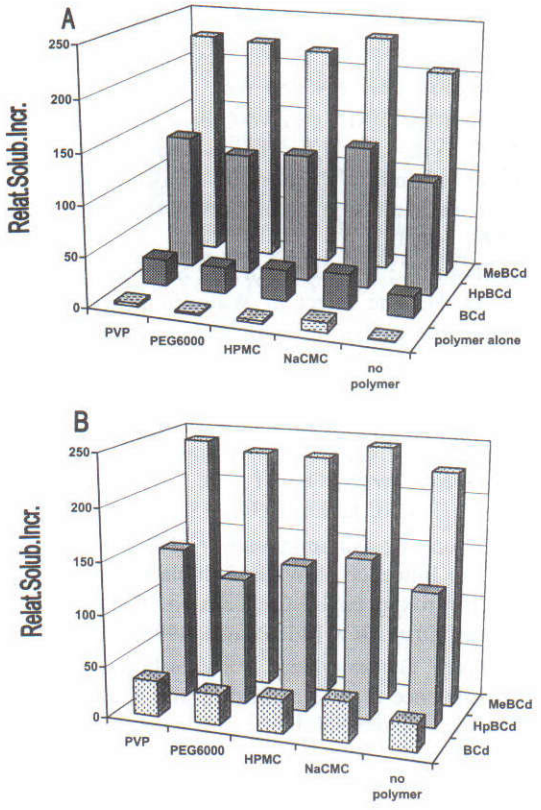

Figure 4. Relative solubility increase of NAP (naproxen) in aqueous solutions at 25°C containing 7.5% w/v HP-β-CD or Me-β-CD or 1.6% w/v βCD (saturation solubility), alone or in the presence of 0.25% w/v of the different polymers, (A) without and (B) with previous sonication-heating treatment.

CONCLUSION

Cyclodextrins are rapidly becoming an essential part of the formulator's options in drug development as a result of their extreme usefulness as pharmaceutical excipients, their increasing availability in highly pure form at an ever more reasonable cost, and their gradual acceptance by various regulatory agencies. However, pharmaceutical formulations should contain as little cyclodextrin as possible since excess cyclodextrin can reduce drug bioavailability, preservative efficacy, or give problems of formulation bulk or potential toxicity (5).

Our study confirmed that the addition of small amounts of hydrophilic polymers is a useful strategy for improving the solubilizing and complexing ability of cyclodextrins, thus allowing less cyclodextrin to be needed to solubilize a given amount of drug, offering an evident economic advantage as well. All the examined polymers (PVP K30, NaCMC, HPMC, and PEG6000) in fact showed an evident synergistic effect on NAP cyclodextrin solubilization by increasing complexation efficacy. It has been found that the best combination for optimal drug solubilization can be determined only on the basis of experimental observations. The highest solubility improvement was obtained for β-CD ternary systems, which had a solubilizing effect toward NAP that was improved up to a maximum of 80% when 0.25% w/v of NaCMC was present. Such a result

can probably be attributed to the contemporaneous favorable effect of the polymers on the aqueous solubility of β-CD (4,34).

Finally, the possibility of obtaining significant improvement of the cyclodextrin solubilizing effect by simply adding the polymer to their aqueous solutions without sonicating and heating the solutions at high temperatures suggests the possibility of extending this methodology further to the solubilization of thermolabile drugs.

ACKNOWLEDGMENT

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