J Incl Phenom Macrocycl Chem (2007) 59:307–313
DOI 10.1007/s10847-007-9329-9

ORIGINAL PAPER

The influence of chitosan on cyclodextrin complexing and solubilizing abilities towards drugs

Paola Mura · Giovanna Corti · Francesca Maestrelli · Marzia Cirri

Received: 17 January 2007 / Accepted: 24 April 2007 / Published online: 6 June 2007

Abstract The present work was performed to investigate the effect of chitosan, a well known hydrophilic polymer with both enhancer and solubilizing properties, on the solubilizing and complexing abilities of cyclodextrins towards drugs. With this aim, phase-solubility studies were carried out with a series of model drugs, both of acid and basic nature and with different water-solubility and lipophilicity values, in the presence of chitosan and cyclodextrin (ß- or hydroxypropyl-ß-cyclodextrin), both separately (binary systems) and in combination (ternary systems). Unexpectedly, differently from the favorable effect reported in literature for various hydrophilic polymers, the addition of chitosan to the cyclodextrin complexation medium caused a decrease in the cyclodextrin complexing power towards all the examined drugs, independent from their very different physicochemical properties. On the contrary, the influence of the polymer on the cyclodextrin solubilizing efficiency was found to be dependent on the type of drug and both positive, or negative or non-significant effects were observed. The overall results are explained in terms of a common basic mechanism due to the presence of chitosan–cyclodextrin interactions, which hindered the drug–cyclodextrin complex formation, thus causing the binding constant reduction; the simultaneous presence of drug–chitosan and/or chitosan–(drug–cyclodextrin complex) interactions, different from drug to drug, were considered responsible for the distinct (and sometimes opposite) effects observed in the drug solubilizing efficiency of ternary systems.

P. Mura (✉) · G. Corti · F. Maestrelli · M. Cirri
Department of Pharmaceutical Sciences, University of Florence, via U. Schiff 6, 50019 Sesto Fiorentino, Florence, Italy
e-mail: paola.mura@unifi.it

Keywords Chitosan · Cyclodextrins · Complexing and solubilizing abilities · Phase-solubility studies · Stability constants of complexes

Introduction

Complexation with cyclodextrins has been extensively employed to improve the physicochemical properties of various drugs. Their ability to form inclusion compounds with a number of guest molecules by incorporating them into their central cavities can be in fact successfully exploited to enhance the dissolution of poorly water-soluble drugs and/or to improve their stability and bioavailability [1–3]. However, the use of cyclodextrins in most pharmaceutical formulations is limited for a series of reasons, such as, in particular, formulation problems due to their high molecular weight, possible parenteral toxicity and relatively high cost [4]. Therefore, it is important to find methods to enhance the complexation and solubilization efficiency of cyclodextrins, by making it possible to considerably reduce their dose and thus extend their possible applications in the pharmaceutical field.

The complexation efficiency of a given drug–cyclodextrin complex can be considered as the product of the intrinsic solubility of the drug and the stability constant of the drug–cyclodextrin complex [5]. Therefore, an improvement of complexation efficiency can be obtained by increasing either the drug intrinsic solubility, or the binding constant, or both simultaneously. In this regard, the positive effect of the addition of small amounts of various hydrophilic polymers, such as PVP, NaCMC, HPMC, PEG, etc., to the complexation medium has recently been reported [5–9]. The phenomenon of improved drug solubilization capacity of the cyclodextrin, induced by the

hydrophilic polymer, is interpreted in terms of enhanced complexation power, as demonstrated by the concomitant increase in the complex stability constant [6–9].

Chitosan is a cationic natural polymer which is receiving increasing attention in the pharmaceutical domain due to its several favorable biological properties such as non-toxicity, biocompatibility, biodegradability, and good enhancer properties, accompanied by wide availability in nature, low cost and high flexibility in use [10–12]. Furthermore, its effectiveness in enhancing the dissolution properties of poorly-soluble drugs has been proven [13–16].

On this basis, we considered it a promising idea to take advantage of the combined use of chitosan and cyclodextrin, with the aim of not only simultaneously exploiting their known beneficial effects on both dissolution and permeability properties of drugs, but also of improving the cyclodextrin complexation efficiency by virtue of the presence of the hydrophilic polymer.

Previous preliminary studies performed using glyburide as a model drug actually showed a synergic enhancer effect of cyclodextrin and chitosan, when used in combination, on the drug permeability; however, unexpectedly, a decrease of the cyclodextrin solubilizing and complexing efficiency towards the drug was found [17]. An analogous negative effect on the cyclodextrin complexation due to the presence of chitosan was observed also in the case of other hydrophobic drugs such as triclosan and furosemide, in spite of the favorable effect of the polymer on the dissolution properties of both these drugs [18]. A possible competition between polymer and drug for the interaction with the macrocycle was hypothesized to explain this phenomenon [17, 18].

Therefore, it seemed worthy of interest to extend our investigations in order to obtain more insight about the influence of chitosan on the complexing and solubilizing effectiveness of cyclodextrins towards drugs. With this aim, in the present work we selected a series of model drugs, both of acid and basic nature, with different water-solubility and lipophilicity values, in order to evaluate the role played by the drug physicochemical properties in the interactions with chitosan and cyclodextrin, both separately and in combination. Phase-solubility studies were performed for both binary (drug–chitosan or drug–cyclodextrin, at increasing amounts of each carrier) and ternary (drug–chitosan–cyclodextrin at increasing amounts of cyclodextrin) systems. The influence of chitosan on the cyclodextrin complexation power towards the examined drugs was evaluated by determining the solubilizing efficiency of the different binary and ternary systems and the apparent stability constants of the related complexes.

Experimental

Materials

Glyburide (GLY) was obtained from Guidotti Laboratori S.p.A., Pisa, Italy; econazole (ECO) was a gift from Italfarmaco, Genova, Italy; triclosan (TRI) was provided by Bottega Verde, Milan, Italy; naproxen (NAP), ketoprofen (KETO), flufenamic acid (FLU) and Chitosan (CS) (molecular weight 150,000, deacetylation degree 75–85%) were purchased from Sigma Chem. Co., St. Louis, USA; Hydroxypropyl-β-Cyclodextrin MS 0.9 (HPβCD) and β-Cyclodextrin (β-CD) were gifts from Roquette, Lestrem, France.

Phase-solubility studies

Phase-solubility studies were performed by adding an excess of drug to phosphate buffer solutions (pH 5.5) containing increasing concentrations of CS (0–0.5% w/v) or CD (0–25 mM) (binary systems) or a fixed amount of CS and increasing amounts of CD (0–25 mM for HPßCD or 0–13 mM for ßCD) (ternary systems). The vials were sealed and the suspensions were electromagnetically stirred (500 rpm) at constant temperature (25 °C) until equilibrium (2 day). An aliquot of solution was then withdrawn with a filter-syringe (pore size 0.45 μm), and the concentration of each examined drug was spectrometrically determined (UV/Vis 1601 Shimadzu) at the respective λ_{max}. The presence of CD and/or CS did not interfere with the spectrophotometric assay of the different drugs. Each experiment was performed in triplicate (C.V. <2.5%). The apparent stability constants of the drug–CD complexes were calculated from the slope of the phase-solubility diagrams and the drug solubility in the dissolution medium [19]:

$$K_s = \frac{\text{slope}}{s_0(1 - \text{slope})}$$

Partition coefficient measurement

The apparent partition coefficients between *n*-octanol and pH 5.5 phosphate buffer solution, were determined at 25 °C following the procedure of Fujita et al. [20]. The organic and aqueous phases were reciprocally saturated before partitioning by shaking together for 5 h and then fragmented by centrifugation. 10 mL of organic phase containing 10 mg mL^{-1} of drug were added to 10 mL of aqueous phase and shaken for 24 h. The phases were equilibrated and separated by centrifugation, and the drug concentration was determined in the aqueous phase by UV

spectroscopy as in Phase-solubility studies. The apparent partition coefficient was obtained from the ratio between the total amount of drug in the organic and aqueous phases. The experiments were carried out in triplicate (coefficient of variation C.V. < 6%).

Results and discussion

The main physicochemical parameters of the series of model drugs, selected to investigate the influence of CS on the CD complexation efficiency, are collected in Table 1, together with their solubility values determined in phosphate buffer solution at pH 5.5. Due to the different acidic or basic nature of the considered drugs, in order to obtain comparable data, unaffected by pH variations, all solubility studies (of both drugs alone and in the presence of the different carriers and carrier combinations) were performed in phosphate buffer solution at pH 5.5.

Effect of chitosan alone

First of all, equilibrium solubility studies were carried out in the presence of increasing concentrations of CS, in order to determine its possible effect towards the solubility of the examined drugs (Fig. 1). In fact, the solubilizing power of various hydrophilic polymers, including CS, has been reported [13–16, 21–24] and has been attributed to the formation of weak water-soluble complexes.

In the case of ECO, no significant variations of its solubility were observed in the presence of the polymer, while, on the contrary, an almost linear solubility increase was found, with all the other examined drugs as a consequence of drug–carrier interactions (Fig. 1). No attempt was made to calculate the apparent stability constants of the drug–CS complexes, since the exact stoichiometric ratio between the two components should be known. However, a qualitative comparison of the degrees of interaction was possible. In fact, the relative affinity of the different drugs for the polymer was evaluated by comparing the slopes of the straight-line relationships of the phase-solubility diagrams [25] and it varied in the order FLU > NAP > GLY > TRI ≈ KETO > >ECO. No relation was found with the drug lipophilicity, which, according to the log *P* values, varied in the order ECO > GLY > TRI > FLU > NAP > KETO (Table 1).

The high effectiveness of CS towards FLU and NAP could be attributed to the formation of ion-to-ion drug-to-polymer electrostatic bonds, considering the cationic nature of CS and the acidic nature of these drugs. However, even though such interaction surely plays a role, it is not the only factor responsible for such a result. In fact, regardless of the common acidic character of KETO, NAP and FLU, they showed varying degrees of affinity and different solubility improvements in the presence of CS. While, on the contrary, similar solubility increases were obtained for KETO and TRI, despite their opposite acidic or basic nature (as indicated by their pKa values). Therefore, other kinds of drug–CS interactions, such as ion-to-dipole or dipole-to-dipole electrostatic bonds, van der Waals dispersion forces and hydrogen bridge formation [26] probably concur in determining the CS promoting effect.

Table 1 Main physicochemical parameters of the examined drugs

Drug	P.M	Log *P*	pKa[a]	Solubility (mM) at pH 5.5
Glyburide	494.0	3.8	5.3	0.016
Naproxen	230.3	2.2	4.2	0.12
Ketoprofen	245.3	1.9	4.5	0.54
Flufenamic ac.	281.2	2.9	4.0	0.05
Econazole	381.8	4.3	7.3	0.013
Triclosan	317.7	3.5	7.9	0.081

[a] Data from Clarke's Analysis of drugs and poisons, 3rd Ed., London, Pharm. Press, 2003

Effect of cyclodextrin, alone or in the presence of chitosan

In the following step, phase solubility studies were carried out with the various drugs in the presence of increasing concentrations of ßCD or HPßCD, alone or in the presence of a fixed amount of CS (0.0625% w/v). This latter amount was selected in view of possible future permeability studies through Caco-2 cells to carry on with such systems, in order to evaluate their enhancer properties. According to our previous studies [17], 0.0625% w/v was the highest CS concentration with acceptable cytotoxicity towards Caco-2 cells.

The phase-solubility diagrams of all the investigated drugs with the two different CDs, both in the absence and in the presence of CS, were all of Higuchi's A_L-type [19], i.e. characterized by a linear drug solubility increase with increasing the CD concentration, indicative of the formation of water-soluble complexes of 1:1 mol:mol stoichiometry (Figs. 2 and 3). Only in the case of TRI in the presence of ßCD was a plateau observed, after the initial linear portion, indicative of the achievement of the saturation solubility of the complex [19]. The values of the apparent 1:1 mol:mol stability constants of the different drug–CD complexes, both in the absence and in the presence of CS, are presented in Table 2, while the drug solubility values obtained with binary (drug–CD or drug–CS) and ternary (drug–CD–CS) systems and the relative solubility ratios are collected in Table 3.

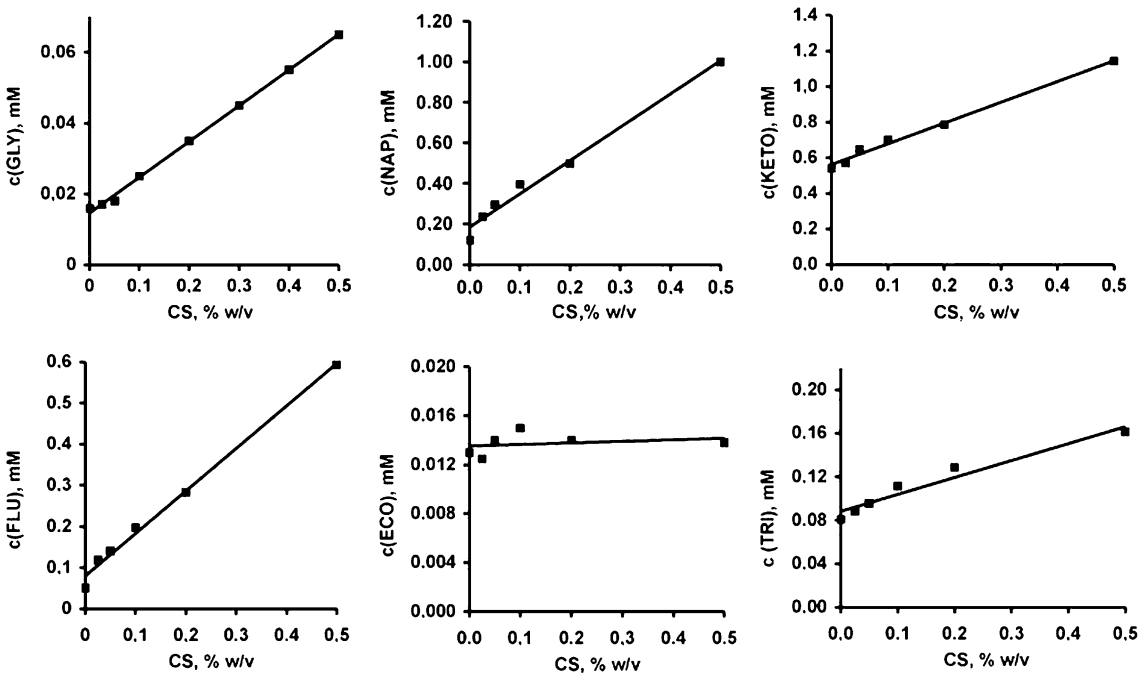

Fig. 1 The effect of increasing concentrations of chitosan (■) on the solubility of different drugs in pH 5.5 phosphate buffer solutions at 25 °C. Each point represents the mean of three determinations (C.V. <2.5%)

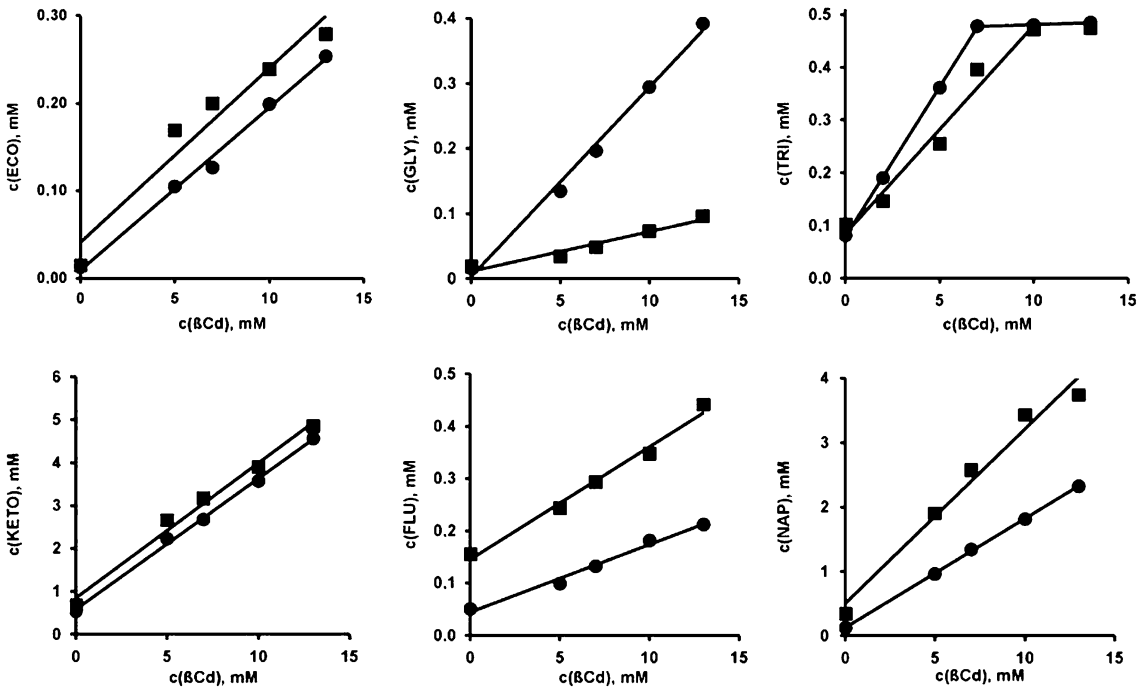

Fig. 2 The effect of increasing concentrations of ßCD alone (●) or in the presence of 0.0625% w/v of chitosan (■) on the solubility of different drugs in pH 5.5 phosphate buffer solutions at 25 °C. Each point represents the mean of three determinations (C.V. <2.5%)

Differently from that observed with most hydrophilic polymers (such as PVP, NaCMC, HPMC, PEG) whose presence gives rise to an improvement in the stability constant of drug–CD complexes [5–9], an opposite effect was observed for CS. In fact, the addition of CS caused a decrease in the complexation ability of both ßCD and HPßCD towards all the examined drugs, in spite of their different nature. The same trend was substantially obtained

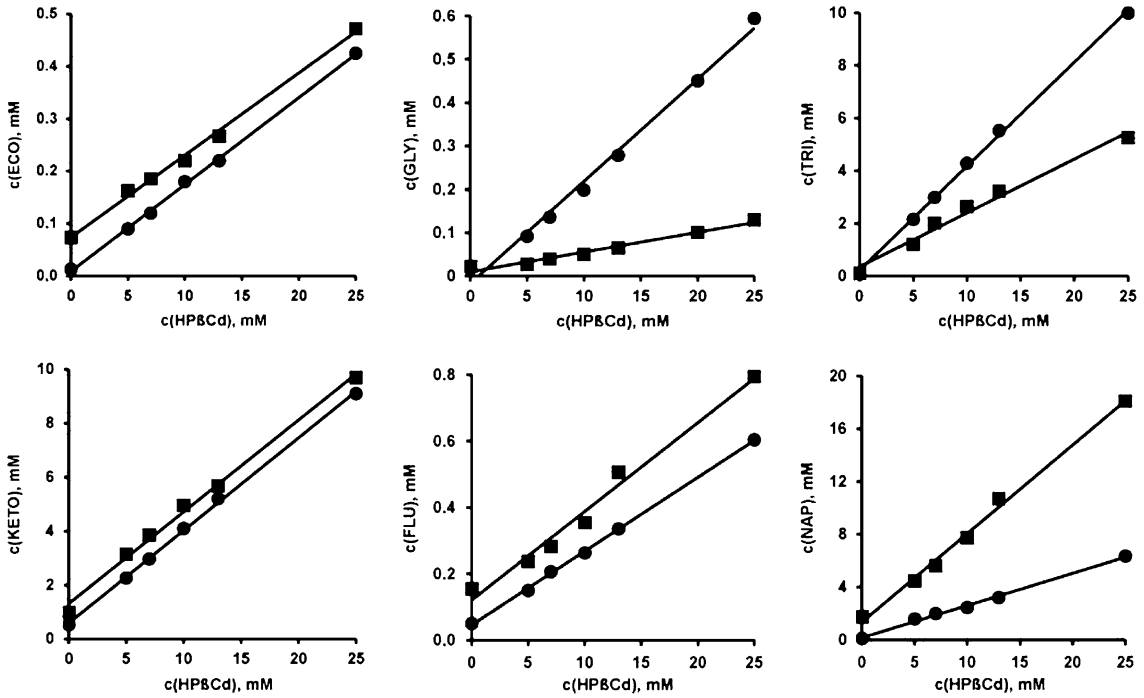

Fig. 3 The effect of increasing concentrations of HPßCD alone (●) or in the presence of 0.0625% w/v of chitosan (■) on the solubility of different drugs in pH 5.5 phosphate buffer solutions at 25 °C. Each point represents the mean of three determinations (C.V. <2.5%)

Table 2 Stability constant values (Ks, M^{-1}) of drug–CD complexes in the presence or not of 0.0625%w/v chitosan (CS), in aqueous CD solutions at pH 5.5

Drug	Drug–ßCD	Drug–ßCD–CS	Tern/bin	Drug–HPßCD	Drug–HPßCD–CS	Tern/bin
Glyburide	1873	396	0.21	1,510	295	0.20
Naproxen	1695	1088	0.64	2,632	1,536	0.58
Ketoprofen	810	680	0.84	970	800	0.82
Flufenamic	260	142	0.55	456	178	0.39
Econazole	1450	1350	0.93	1,293	1,145	0.88
Triclosan	743	405	0.54	8,090	2,530	0.31

Table 3 Effect of chitosan (CS) on the solubilization of drugs in aqueous cyclodextrin (CD) solutions at pH 5.5

Drug	S_{CS}[a]	$S_{ßCD}$[b]	$S_{ßCD+CS}$[c]	$S_{ßCD+CS}/S_{ßCD}$[d]	$S_{HPßCD}$[e]	$S_{HPßCD+CS}$[c]	$S_{HPßCD+CS}/S_{CD}$[d]
Glyburide	0.022	0.39	0.10	0.26	0.59	0.13	0.22
Naproxen	0.287	2.32	3.74	1.61	6.35	9.51	1.50
Ketoprofen	0.634	4.56	4.85	1.06	9.10	9.70	1.06
Flufenamic	0.144	0.21	0.44	2.10	0.60	0.79	1.32
Econazole	0.013	0.25	0.28	1.12	0.42	0.45	1.07
Triclosan	0.102	0.48	0.39	0.83	9.98	5.15	0.52

[a] Solubility in the presence of 0.0625% w/v CS

[b] Solubility in the presence of 13 mM ßCD

[c] solubility in the presence of both CD and CS

[d] solubility ratio

[e] solubility in the presence of 25 mM HPßCD

with both native ßCD and its hydroxypropyl-derivative: the only observable difference was a slightly more marked negative effect in the case of ternary systems with HPßCD (Table 2). Such results seem to indicate a common mechanism of interaction between CS and the different host–guest substrates. Since the physicochemical properties of the selected guests, i.e. the drugs, are remarkably different, such a common mechanism cannot be associated with the guest structure, but instead to that of the host, i.e. the CD molecule. Thus, it is reasonable to hypothesize the possible formation of CS–CD interactions, which could give rise to a reduced affinity of CD for the drug. On the other hand, with those guest molecules able to interact with the polymer, the additional presence of drug–CS interactions, competing with the drug–CD inclusion complex formation, should be taken into account. Furthermore, even the possible role of CS–(drug–CD complex) interactions, which could reduce the above destabilizing effects on the CD complexing ability, cannot be excluded. Both these latter phenomena could concur in determining the different degrees of reduction of the complex binding constants observed with the various drugs.

As for the influence of CS on the CD solubilizing effect, different results were observed with the different drugs, showing an apparently undefined trend (Table 3). The solubilizing efficiency of CDs towards NAP and FLU was strongly improved by the presence of CS, and such an effect can be attributed to the strong solubilizing power of the polymer towards these drugs, which can more than counterbalance the reduced complexation efficiency of CD. This same phenomenon could explain the not significant variation, which was instead observed in the case of KETO, by considering the lower solubilizing effect of CS towards this drug. However, a negative effect on drug solubility was observed in ternary systems with both GLY and TRI, despite the CS solubilizing effect towards these drugs, which can be considered rather similar to that for KETO. Moreover, insignificant solubility reduction was found in ternary systems with ECO, despite the lack of a favorable solubilizing effect of the polymer.

However, the above results about the CD solubilizing efficiency towards the drugs are only apparently contradictory and they are substantially in good agreement with our previous hypothesis. In fact, the different effects observed on the solubility variation of the various examined drugs are due to the contemporaneous and combined influence of the negative effect played by CD–CS interactions, which lower the CD complexation ability, and the positive effects due to the solubilizing power of CS towards the drug and/or the formation of CS–(drug–CD complex) interactions, influencing the intensity of reduction of the drug–CD binding constant. Indeed, the final effect on the drug solubility in the ternary system depended on the relative importance of these three factors.

Previous NMR spectroscopic studies of drug–CD interactions in solution [27–30] indicated, accordingly with the results of the present study, the formation of equimolar drug–CD complexes for the examined drugs. These studies provided interesting information about the modalities of inclusion of the examined drug molecules into the CD cavity, but they did not give any useful additional insight to explain the different effects observed in the presence of CS. More interesting information could be probably achieved by performing an in-depth NMR spectroscopic study of the interactions between drug and CS and drug and CD in the presence of CS. However, such a study should be performed separately for each examined drug; in fact, the study of a single drug could give insight about the specific system investigated, but the obtained results could not be extended to the other considered drugs, since there is not a general common behavior.

Conclusion

The addition of CS to the CD complexation medium, differently from that observed with other hydrophilic polymers such as PVP, HPMC, NaCMC, PEG [5–9], gave rise to a decrease of the stability constants of the various drug–CD complexes examined, independent of the very different nature of the selected model drugs. Such a result suggested the presence of a common mechanism based on the formation of CS–CD interactions which could hinder the drug–CD complex formation.

On the contrary, the influence of CS on the solubilizing efficiency of CDs was found to be dependent on the type of drug, and both positive or negative or non-significant effects were observed. These results were explained in terms of the presence, in addition to the CS–CD interactions, of drug–CS and CS–(drug–CD complex) interactions, influencing respectively the drug solubility and the stability constant of the drug–CD complex, and, consequently, the final drug solubility in the ternary system.

Due to the complexity of these concomitant interactions, it was not possible, at least for now, to predict the variation in the CD complexing and solubilizing ability towards a given drug as a consequence of CS addition, but it has to be determined case by case. The study will be then extended to a larger number of drugs, to obtain more insight about the relative importance of the different interactions (CS–CD, drug–CS, drug–CD and CS–(drug–CD)) in determining the final result. Moreover, spectroscopic NMR studies will be performed on selected systems in the attempt to clarify the role of CS in affecting drug–CD interactions

However, the combined use of CD and CS appears to be of particular interest for improving drug bioavailability, in particular when the final drug solubility in the ternary system is improved. In fact, the destabilizing effect of CS on the drug–CD complex cause, as a positive consequence, an increase of the free drug amount available for permeation; then it should render more effective the permeation enhancer properties of CS, as was actually observed for glyburide [17]. Therefore, permeation studies through Caco-2 cells will be performed on these and other binary (drug–CD) and ternary (drug–CD–CS) systems, with the aim of verifying this hypothesis and evaluating a possible synergistic effect of CD and CS in improving drug permeability.

Acknowledgment Financial support from MIUR is gratefully acknowledged

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