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Prediction of selectivity for enantiomeric separations of uncharged compounds by capillary electrophoresis involving dual cyclodextrin systems

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Abstract

The single-isomer polyanionic cyclodextrin (CD) derivative heptakis-6-sulfato-β-cyclodextrin (HSβCD) has been tested as chiral additive for the enantioseparation of non-steroidal anti-inflammatory drugs, such as fenoprofen, flurbiprofen, ibuprofen and ketoprofen, in capillary electrophoresis, using a pH 2.5 phosphoric acid–triethanolamine buffer in the reversed polarity mode. In most cases, the enantiomers of these acidic compounds, present in uncharged form at that pH, were only poorly resolved with HSβCD alone. However, the use of HSβCD in combination with the neutral CD derivative, heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMβCD), which has a particularly high enantioselectivity towards these compounds, has led to complete enantioresolution in reasonably low migration times in most cases. Affinity constants for the enantiomers with the two cyclodextrins were determined, using linear regression in a two-step approach. Affinity constants with the charged HSβCD were first calculated in single systems while those with the neutral TMβCD were determined in dual systems. Selectivity for the enantiomeric separation of these compounds in dual CD systems could be predicted using recently developed mathematical models. © 2002 Elsevier Science B.V. All rights reserved.

Keywords: Enantiomer separation; Pharmaceutical analysis; Selectivity; Mathematical modelling; Cyclodextrins; Profens; Nonsteroidal anti-inflammatory drugs

1. Introduction

The enantioseparation of chiral compounds is of great importance in the pharmaceutical field, where a wide number of drugs have one or more chiral centers and are used as racemic mixtures. Very often, the pharmacological activity and metabolism of the two enantiomers are different, therefore, appropriate analytical methods are required for their individual determination. Over the past few years, capillary electrophoresis (CE) has been proved to be a powerful tool for chiral analysis, as it provides high separation efficiencies together with rapid method development and low consumption of additives [1–8].

A number of chiral compounds have been enantioseparated using various kinds of chiral selectors in CE. Among these selectors, cyclodextrins (CDs) have been shown to be broad spectrum chiral selectors due to their physicochemical properties and commercial availability in native and derivatized forms [9–11]. However, the use of single cyclo-

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dextrin systems has sometimes shown difficulties for the enantioseparation of some compounds. Therefore, a combination of cyclodextrins in dual systems has been introduced in order to enhance both selectivity and resolution. Such a combination can lead to higher resolution due to the differences in the complexation mechanisms of the two cyclodextrins with the analyte enantiomers, regarding stability of complexation, chiral recognition pattern and effect on analyte mobility [12–14].

Several studies have demonstrated the interest of dual cyclodextrin systems, using mixtures of anionic and neutral cyclodextrins, Lurie et al. [12] have used combinations of neutral and anionic CDs for the chiral analysis of basic drugs of forensic interest.

Anigbogu et al. [15] reported the use of dual CD systems for the enantioresolution of aminoglutethimide in uncharged form.

Fillet et al. [16,17] investigated the enantiomeric separation of a series of acidic drugs in uncharged form and neutral compounds using mixtures of anionic and neutral CDs.

In contrast to neutral CDs, charged CDs have their own electrophoretic mobility, which gives them the advantage that they can be used as carriers in electrokinetic chromatography for the separation of uncharged compounds [18–20].

Some other studies have shown the importance of the combination of two cyclodextrins referring to the principle that the mobility difference between the enantiomers of certain analyte will be higher when one of the CDs accelerates one enantiomer while the other CD decelerates the opposite enantiomer [19]. Also when the two CDs have an opposite chiral recognition to a given analyte, it can lead to improvement of enantiomeric separation [13,21]. It is also possible that both chiral selectors accelerate or decelerate the analyte and that the same chiral recognition pattern will be in some cases required for both selectors for the enhancement of selectivity [22].

Several studies have achieved complete resolutions of the enantiomers of some of the arylpropionic acid nonsteroidal anti-inflammatory drugs (NSAIDs) such as fenoprofen, ibuprofen, flurbiprofen, and ketoprofen by CE using native cyclodextrins, hydroxypropyl-, dimethyl-, trimethyl-β-cyclodextrins or positively charged CD derivatives as additives to the background electrolyte (BGE) [4,23–32].

On the other hand, some papers have explored the advantages of using dual cyclodextrin systems, based on the combination of charged and neutral cyclodextrins, for the enantioseparation of the NSAIDs, showing high resolution values and low migration times [13,16–18].

In this work, recently developed mathematical models were used for the prediction of selectivity for the enantioseparation of a series of NSAIDs, namely fenoprofen, flurbiprofen, ibuprofen, and ketoprofen, in dual cyclodextrin systems, by employing the single-isomer polyanionic cyclodextrin derivative heptakis-6-sulfato-β-cyclodextrin (HSβCD) in combination with heptakis-(2,3,6-tri-*O*-methyl)-β-cyclodextrin (TMβCD) in a pH 2.5 phosphoric acid–triethanolamine buffer.

The calculation of affinity constants for the two cyclodextrins towards the enantiomers of these drugs was obtained through a two-step approach using linear regression.

2. Experimental

2.1. Apparatus

All experiments were carried out on a SpectraPhoresis ULTRA CE instrument (ThermoQuest, San José, CA, USA) equipped with an automatic injector, an autosampler, a variable-wavelength UV–visible absorbance detector (190–800 nm) and a temperature control system (15–60°C). The pH of running buffers were measured by means of a Delta 345 pH meter from Mettler (Halstead, UK).

2.2. Chemicals and reagents

TMβCD was obtained from Sigma (St. Louis, MO, USA). HSβCD was kindly provided by Professor Gyula Vigh (Texas A&M University, Texas, TX, USA). Phosphoric acid (85%) and triethanolamine were of analytical reagent grade and methanol of HPLC grade from Merck (Darmstadt, Germany). Water was of Milli-Q quality (Millipore, Bedford, MA, USA). Fenoprofen, flurbiprofen, ibuprofen, ketoprofen and pure S-(+) enantiomer of ibuprofen were obtained from Sigma. Dextroketoprofen was obtained from Laboratories Manirini (Barcelona, Spain). The pure enantiomers of fenoprofen and

flurbiprofen were kindly provided by Professor Bezhan Chankvetadze (University of Münster, Münster, Germany). The standard solutions were prepared by dissolving each compound at a concentration of about $5 \cdot 10^{-5}$ M (20 μg/ml) in a mixture of water–methanol (9:1). In all cases, the racemic mixture was spiked with an excess amount of S-(+) enantiomer.

2.3. Electrophoretic technique

Electrophoretic separations were performed with uncoated silica capillaries of 45 cm (40.3 cm to detector) ×50 μm I.D., provided by Supelco (Bellefonte, PA, USA). At the beginning of each working day, the capillary was pretreated successively with alkaline solutions (1 M NaOH, 0.1 M NaOH), water and running buffer for 5 min each. Between each injection, the capillary was rinsed with buffer for 3 min. The applied voltage was −25 kV (reversed polarity mode). UV detection was performed at 214 nm and injections were made in hydrodynamic mode for a period of 5 s. The capillary was thermostated at 25°C. For most electrophoretic experiments, a buffer made of 100 mM phosphoric acid adjusted to pH 2.5 with triethanolamine was used. For the determinantion of the enantiomer migration order of the compounds studied in the presence of TMβCD, a pH 4.5 phosphoric acid–triethanolamine buffer was employed.

The resolution (R_s) and plate number (N) were calculated according to the standard expressions based on peak width at half height [33]. The selectivity (α) was calculated [34] by the ratio of the effective mobilities of the separated enantiomers, μ_A/μ_B, where μ_A is the effective mobility of enantiomer A (first peak) and μ_B is the effective mobility of enantiomer B (second peak).

3. Results and discussion

3.1. Single CD systems containing a single-isomer anionic CD derivative as chiral selector

In preliminary experiments, the highly pure single isomer, HSβCD was tested as a chiral additive for the enantioseparation of profens at pH 2.5. This CD derivative (cf. Fig. 1) has a sulfate group on the

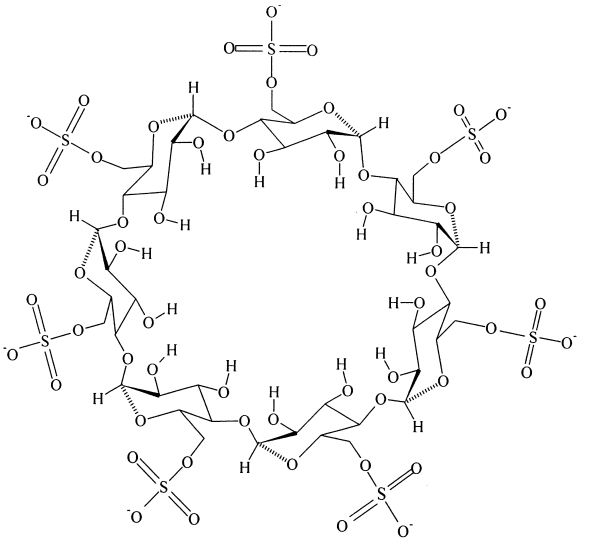

Fig. 1. Structure of heptakis-6-sulfato-β-cyclodextrin.

6-carbon atom of each of the glucopyranose subunits of the CD, which gives it a strongly negative charge at any pH commonly used in CE.

As can be seen in Table 1, the addition of HSβCD at different concentrations to a pH 2.5 phosphoric acid–triethanolamine buffer leads to no enantiomeric resolution for fenoprofen, a slight separation of the enantiomers of ibuprofen and flurbiprofen, and to an almost complete resolution of ketoprofen enantiomers. A 2 mM concentration of HSβCD was found to be the most suitable for the resolution of ketoprofen enantiomers and a 3 mM HSβCD concentration was selected for the other three profens (fenoprofen, flurbiprofen, and ibuprofen) as it gave them adequate mobility, although the slight enantioresolution observed at lower HSβCD concentrations for flurbiprofen and ibuprofen was completely lost (cf. Table 1). These concentrations of HSβCD were kept constant in further experiments involving the use of dual CD systems.

3.2. Dual CD systems for the enantioseparation of profens

In order to be able to enhance selectivity and resolution in the CE enantioseparation of profens, dual CD systems were employed. TMβCD was added at different concentrations (0–25 mM) to the pH 2.5 phosphoric acid–triethanolamine buffer con-

Table 1
Influence of the concentration of HSβCD on the chiral resolution of profens in single CD systems

Analyte	R_s				
	0.75 (mM)	1.0 (mM)	1.5 (mM)	2.0 (mM)	3.0 (mM)
Fenoprofen	–	–	–	–	–
Flurbiprofen	1.0	0.9	0.7	0.6	–
Ibuprofen	0.9	0.8	–	–	–
Ketoprofen	1.3	1.3	1.3	1.4	1.3

All conditions as described in Sections 2.2 and 2.3.

taining HSβCD. As can be seen in Table 2, selectivity and resolution were significantly increased for the enantiomers of all profens tested by the simultaneous addition of the neutral TMβCD, resulting in complete enantioseparation in all cases. This can be explained by a high chiral recognition ability of TMβCD towards profen enantiomers in their uncharged forms.

The concentrations of TMβCD given in Table 2 correspond to those which were found to lead to the highest selectivity and resolution values. The corresponding electropherograms for each of the profens studied are shown in Figs 2–6. They are compared to those obtained in single systems containing HSβCD. In all cases, non-racemic mixtures, containing an excess of the *S* isomer were used. The highest resolution in the dual systems was obtained for ketoprofen enantiomers but their migration times were rather long (more than 30 min), indicating a particularly strong complexation of these enantiomers with the neutral TMβCD (cf. Fig. 3 and Table 3). Much shorter analysis times (8–16 min) were obtained for the other three profens (cf. Figs. 4–6). In the case of fenoprofen, dual CD systems containing HSβCD and TMβCD were especially favourable since a resolution value higher than 4 could be obtained while no enantioresolution was observed in the presence of the anionic CD derivative alone (cf. Fig. 6, Table 1).

Table 2
Enantioseparation of profens using dual CD systems containing HSβCD–TMβCD in different concentration ratios

Analyte	[CD] (HSβCD–TMβCD, mM)	α	R_s
Fenoprofen	3/20	1.098	4.3
Flurbiprofen	3/10	1.045	2.9
Ibuprofen	3/10	1.061	3.3
Ketoprofen	2/20	1.280	6.1

All conditions as described in Sections 2.2 and 2.3.

In order to confirm these observations, equilibrium constants for the complexation between the enantiomers of these compounds and each of the two CD derivatives used in combination were determined and

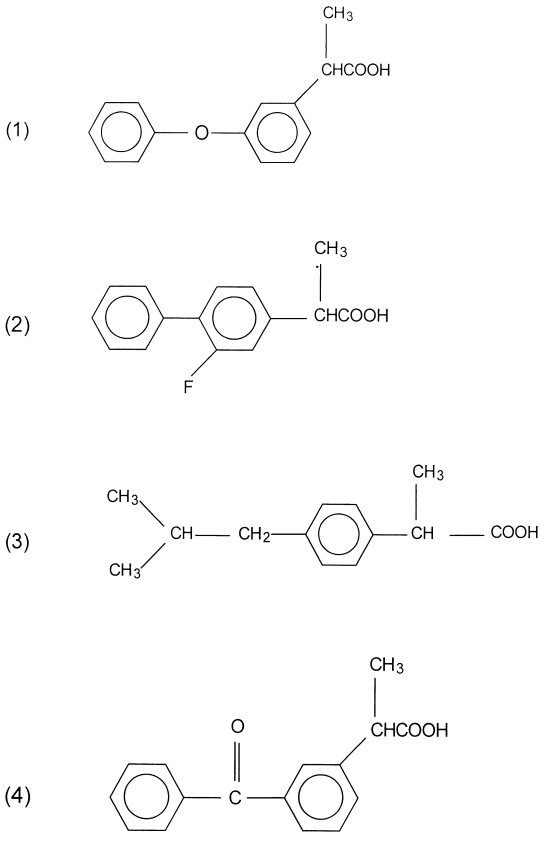

Fig. 2. Structures of profens: (1) fenoprofen; (2) flurbiprofen; (3) ibuprofen; (4) ketoprofen.

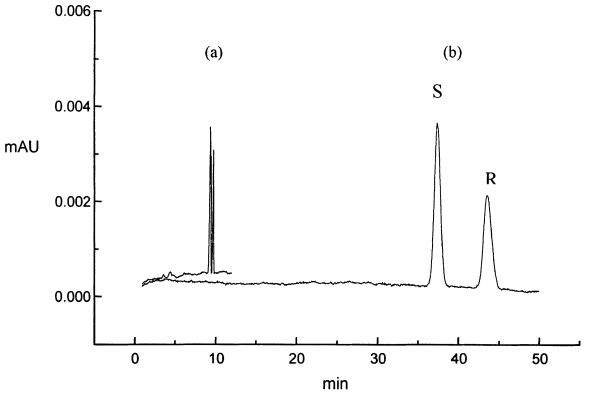

Fig. 3. Enantioseparation of ketoprofen. Buffer: 100 mM phoshoric acid adjusted to pH 2.5 with triethanolamine, containing: (a) 2 mM HSβCD, (b) dual system with HSβCD–TMβCD (2/20 mM), other conditions as in Section 2.2.

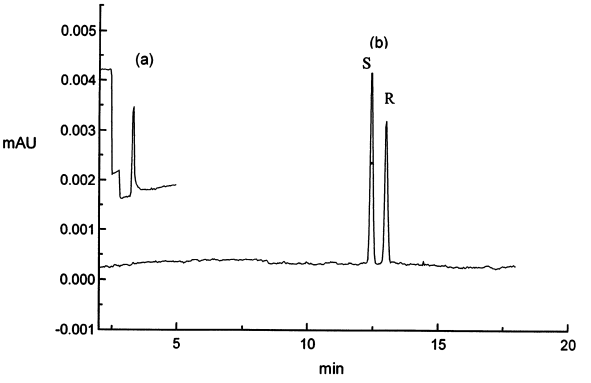

Fig. 5. Enantioseparation of flurbiprofen. Buffer: 100 mM phosphoric acid adjusted to pH 2.5 with triethanolamine, containing: (a) 3 mM HSβCD, (b) dual system with HSβCD–TMβCD (3/10 mM), other conditions as in Section 2.2.

the possibilities of predicting selectivity for the CE enantioseparation in these dual CD systems using mathematical models were investigated.

3.3. Theoretical approach

Several equations have been developed to express the effective mobilities of the analyte enantiomers A and B, μ_A and μ_B, and the corresponding selectivity of the enantioseparation, α, usually defined as the ratio μ_A/μ_B, when two complexing agents, and in particular cyclodextrins, are used in combination [12,13,18].

These equations are usually based on the same assumptions: they are valid if only 1:1 complexation occurs between the analyte enantiomers and the CDs, if the two CDs lead to independent complexation (no mixed complexes) and if there is no mobility difference for the complexes formed between the enantiomers and a given CD. In addition, the electroosmotic flow is assumed to be negligible and the CDs are considered to be pure, well characterised compounds, which is unfortunately not so often the case in practice, except for the native CDs, TMβCD and some charged derivatives, such as the single-isomer CD sulfates developed by Vigh and Sokolowski [35].

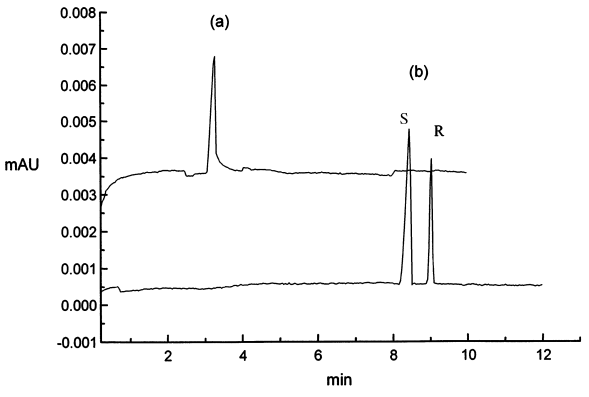

Fig. 4. Enantioseparation of ibuprofen. Buffer: 100 mM phosphoric acid adjusted to pH 2.5 with triethanolamine, containing: (a) 3 mM HSβCD, (b) dual system with HSβCD–TMβCD (3/10 mM), other conditions as in Section 2.2.

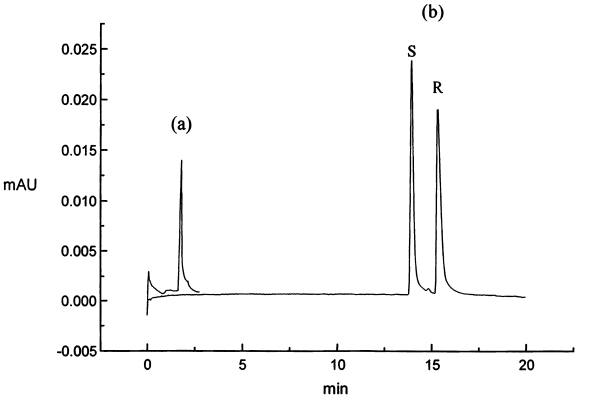

Fig. 6. Enantioseparation of fenoprofen. Buffer: 100 mM phosphoric acid adjusted to pH 2.5 with triethanolamine, containing: (a) 3 mM HSβCD, (b) dual system with HSβCD–TMβCD (3/20) mM), other conditions as in Section 2.2.

Table 3
Binding constants and intrinsic selectivities of HSβCD and TMβCD towards profen enantiomers

Analyte	Enantiomer	HSβCD		TMβCD	
		K_1 (M^{-1})	α_1	K_2 (M^{-1})	α_2
Fenoprofen	S	130±13		176±28	0.889
	R	130±13	1.000	198±36	(α^{-1}=1.125)
Flurbiprofen	S	190±19		180±52	0.957
	R	185±18	1.027	188±57	(α^{-1}=1.044)
Ibuprofen	S	634±8		427±30	0.936
	R	617±7	1.028	456±32	(α^{-1}=1.068)
Ketoprofen	S	360±34		500±12	0.820
	R	337±35	1.068	610±21	(α^{-1}=1.220)

Intrinsic selectivity $(\alpha_n) = K_{A.Cn}/K_{B.Cn} = K_{n,S}/K_{n,R}$.
All conditions as described in Sections 2.2 and 2.3.

The following equation can be used to express the effective mobility of enantiomer A (μ_A) in dual CD systems [18]:

$$\mu_A = \frac{1}{1 + K_{A.C_1}[C_1] + K_{A.C_2}[C_2]} \cdot (\mu_f + \mu_{C_1} K_{A.C_1}[C_1] + \mu_{C_2} K_{A.C_2}[C_2]) \quad (1)$$

where $[C_1]$, $[C_2]$: concentrations of the two CDs C_1 and C_2; μ_f: mobility of the analyte in free form; μ_{C_1}, μ_{C_2}: mobilities of analyte-CD complexes A.C_1 and A.C_2, respectively; $K_{A.C_1}$, $K_{A.C_2}$: equilibrium constants for the formation of complexes between enantiomer A and C_1 or C_2, respectively.

An analogous equation can be derived for the effective mobility of enantiomer B (μ_B). Eq. (1) is applicable to all kinds of dual systems, containing ionic and/or uncharged CDs, and to charged or neutral analyte enantiomers. Using this kind of equations, the changes of selectivity obtained in dual systems by altering the CD concentrations can in principle be predicted, provided the equilibrium constants for the complexation of both enantiomers A and B with the two CDs are known, as well as the mobilities of the analyte in free and complexed forms, and that the hypotheses mentioned above are valid. Under these conditions, the optimisation of dual CD systems with respect to the migration times and the separation of the analyte enantiomers should be greatly facilitated.

3.4. Determination of affinity constants and effective mobilities of the complexes

Equilibrium constants for the complexation of the enantiomers of the four profens studied, present in uncharged form at pH 2.5, with the anionic CD derivative HSβCD and the mobility of the corresponding complexes were first determined by CE, using the effective mobilities obtained for profen enantiomers in single systems with HSβCD at different concentrations in the 0.5–5 mM range. Under these conditions Eq. (1) can be simplified as follows since the mobility of the analyte in free form is equal to zero and C_2 is not present:

$$\mu_A = \frac{\mu_{C_1} K_{A.C_1}[C_1]}{1 + K_{A.C_1}[C_1]} \quad (2)$$

The same kind of equations can be deduced for enantiomer B. Binding constants for both enantiomers with HSβCD (C_1) and the mobility of the corresponding complexes (μ_{C_1}) can easily be calculated by linear regression using the following equation obtained by inverting Eq. (2):

$$\frac{1}{\mu_A} = \frac{1}{\mu_{C_1}} + \frac{1}{\mu_{C_1} K_{A.C_1}} \cdot \frac{1}{[C_1]} \quad (3)$$

By plotting $1/\mu_A$ or $1/\mu_B$ versus $1/[C_1]$, the mobility of the complex with HSβCD could be obtained from the intercept and the corresponding affinity constant from the intercept/slope ratio of the regression line (cf. Table 3).

Binding constants for profen enantiomers with the neutral derivative TMβCD, C_2, were then determined indirectly by CE at pH 2.5 in dual CD systems in which HSβCD and TMβCD were used in combination.

However, the affinity pattern of TMβCD towards the profen enantiomers was first investigated at pH 4.5 by introducing non-racemic mixtures of these compounds in a phosphoric acid–triethanolamine buffer containing only TMβCD as chiral selector. At the latter pH, profens were partly dissociated and had their own electrophoretic mobility towards the detector, situated at the anodic side of the capillary in the reversed polarity mode. Under these conditions, TMβCD had a decelerating effect on the mobility of the profen enantiomers. For all profens tested, the *S* enantiomer was always migrating faster than the *R* isomer in these systems, indicating that the latter was more strongly bound to TMβCD than the former.

In HSβCD/TMβCD dual systems at pH 2.5, the mobilities of the profens in free form and as complexes with TMβCD were both equal to zero, which again allows a simplification of Eq. (1) in the following way:

$$\mu_A = \frac{\mu_{C_1} K_{A.C_1}[C_1]}{1 + K_{A.C_1}[C_1] + K_{A.C_2}[C_2]} \quad (4)$$

By inverting Eq. (4), a linear relationship can be obtained between $1/\mu_A$ or $1/\mu_B$ and $[C_2]$, the concentration of TMβCD in the dual systems (0–25 mM), the HSβCD concentration ($[C_1]$), being kept constant in all these experiments (3 mM for fenoprofen, flurbiprofen and ibuprofen and 2 mM for ketoprofen):

$$\frac{1}{\mu_A} = \frac{1 + K_{A.C_1}[C_1]}{\mu_{C_1} K_{A.C_1}[C_1]} + \frac{K_{A.C_2}}{\mu_{C_1} K_{A.C_1}[C_1]} \cdot [C_2] \quad (5)$$

A further simplification of Eq. (5) can be obtained if conditional equilibrium constants for profen enantiomers with TMβCD valid in the presence of a given concentration of HSβCD are introduced. These conditional equilibrium constants can be defined as follows:

$$K'_{A.C_2} = \frac{K_{A.C_2}}{1 + K_{A.C_1}[C_1]} \quad (6)$$

If μ'_A or μ'_B represent the effective mobilities of profen enantiomers in the presence of HSβCD alone at a fixed concentration, Eq. (5) can be rewritten in the following way:

$$\frac{1}{\mu_A} = \frac{1}{\mu'_A} + \frac{K'_{A.C_2}}{\mu'_A} \cdot [C_2] \quad (7)$$

Conditional binding constants for profen enantiomers with TMβCD could be calculated from the slope/intercept ratios of the regression lines and the corresponding affinity constants with TMβCD could be deduced from Eq. (6) by introducing the previously determined binding constants with HSβCD (cf. Table 3).

All determination coefficients for the regression lines were in the range from 0.992 to 0.997.

3.5. Affinity patterns and intrinsic selectivities of HSβCD and TMβCD towards profen enantiomers

Binding constants for each enantiomer of the four profens studied with the anionic HSβCD and the neutral TMβCD, respectively, are presented in Table 3. It is worth noting that the affinity patterns of HSβCD (C_1) and TMβCD (C_2) towards profen enantiomers are always opposite, the *S* and *R* isomers being the most strongly bound with HSβCD and TMβCD, respectively. No chiral discrimination was observed, however, for fenoprofen with HSβCD as selector. The presence of opposite affinity patterns has been mentioned earlier as a necessary condition for significant selectivity enhancement in dual systems in which charged and neutral CDs are used in combination [13,16–18]. It is therefore not surprising that the use of dual systems containing these two CDs has led to high selectivity and resolution for profen enantiomers (cf. Table 2).

Binding constants given in Table 3 also confirm that HSβCD has a particularly high affinity for ibuprofen enantiomers while TMβCD is very strongly bound to ketoprofen enantiomers.

As expected, the intrinsic selectivity of TMβCD towards profen enantiomers, i.e. the ratio of the affinity constants obtained for the two enantiomers of the same compound, is always much higher than that exhibited by HSβCD. α_2 values are however to be inverted in order to be higher than one since the affinity pattern of TMβCD is reversed compared to that of HSβCD. Intrinsic selectivities of TMβCD (α_2^{-1}) towards fenoprofen and especially ketoprofen enantiomers are remarkably high, which is quite in accordance with the results presented in Table 2.

3.6. Comparison between found and predicted selectivities

The calculated affinity constants for both CDs and the mobilities of the complexes with HSβCD were then introduced in expressions such as Eq. (1) [18]. From these kind of expressions, selectivity values for the enantioseparation of profens in HSβCD–TMβCD dual systems could be predicted for any concentrations of the two CDs in the range studied. These predicted selectivity values were compared with those obtained experimentally at the same concentrations. As can be seen in Table 4, a very good agreement was achieved between the predicted and found selectivity values for three compounds (ibuprofen, fenoprofen and flurbiprofen). However in the case of ketoprofen, the agreement was less good, except at higher concentrations of the neutral CD (TMβCD). This seems to indicate that the assumptions made are valid and that the model developed is appropriate for this kind of dual systems.

It is interesting to note that the selectivity values obtained in these dual CD systems sometimes exceed the intrinsic selectivities given in Table 3, clearly illustrating the high potential of this kind of systems for enantiomeric separations in capillary electrophoresis.

Table 4
Comparison between found and predicted selectivities for profens in dual systems (HSβCD–TMβCD)

HSβCD (mM)	TMβCD (mM)	α_{found}	$\alpha_{predicted}$
Fenoprofen			
3	5	1.049	1.048
3	7.5	1.068	1.068
3	10	1.080	1.070
3	15	1.085	1.082
3	20	1.098	1.090
3	25	1.086	1.094
Flurbiprofen			
3	7.5	1.040	1.043
3	10	1.045	1.047
3	15	1.047	1.052
3	20	1.052	1.056
3	25	1.055	1.058
Ibuprofen			
3	5	1.037	1.047
3	7.5	1.056	1.056
3	10	1.061	1.062
3	15	1.081	1.070
3	20	1.084	1.075
3	25	1.084	1.080
Ketoprofen			
2	7.5	1.10	1.23
2	10	1.15	1.23
2	12.5	1.16	1.24
2	15	1.21	1.25
2	17.5	1.25	1.26
2	20	1.28	1.27

All conditions as described in Sections 2.2 and 2.3.

4. Conclusions

Dual cyclodextrin systems containing the anionic HSβCD and the neutral TMβCD were found to be very effective for the enantiomeric separation of acidic drugs by capillary electrophoresis at low pH. In these systems, the anionic CD can provide these compounds with suitable mobility while the neutral CD can give them high enantioselectivity. High selectivity and resolution values were obtained for most compounds studied in relatively low migration times. Binding constants for the compounds studied with the two CDs were determined by using linear regression through a two-step approach. These affinity constants could then used to predict conditions for obtaining high selectivity and resolution for the CE enantioseparation of profens in HSβCD–TMβCD dual systems applying recently developed mathematical models.

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References

[1] H. Nishi, S. Terabe, J. Chromatogr. A 694 (1995) 245.
[2] B.A. Ingelse, F.M. Eveaerts, J.Z. Stansky, S. Fanali, J. High Resolut. Chromatogr. 18 (1995) 348.
[3] B. Chankvetadze, G. Endresz, G. Blaschke, Electrophoresis 15 (1994) 804.
[4] A. Guttman, Electrophoresis 16 (1995) 1900.
[5] D. Belder, G. Schomburg, J. Chromatogr. A 666 (1994) 351.
[6] M. Fillet, I. Bechet, P. Chiap, Ph. Hubert, J. Crommen, J. Chromatogr. A 717 (1995) 203.
[7] R. Vespalec, P. Bocek, Electrophoresis 20 (1999) 2579.
[8] B. Chankvetadze, Trends Anal. Chem. 8 (1999) 485.
[9] S. Fanali, J. Chromatogr. A 875 (2000) 89.
[10] B. Chankvetadze, G. Pintore, N. Burjanadze, D. Bergenthal, K. Bergander, J. Breitkrenuz, C. Muhlenbrock, G. Blaschke, J. Chromatogr. A 875 (2000) 455.
[11] B. Chankvetadze, Capillary Electrophoresis in Chiral Analysis, Wiley, Chichester, 1997.
[12] I.S. Lurie, R.F. Klein, T.A. Dal Cason, M.J. LeBelle, R. Brenneisen, R.E. Weinberger, Anal. Chem. 66 (1994) 4019.
[13] F. Lelièvre, P. Gareil, Y. Bahaddi, H. Galons, Anal. Chem. 69 (1997) 393.
[14] M. Fillet, L. Fotsing, J. Crommen, J. Chromatogr. A 817 (1998) 113.
[15] N.C. Anigbogu, C.L. Copper, M.J. Sepaniak, J. Chromatogr. A 705 (1995) 343.
[16] M. Fillet, I. Bechet, G. Schomburg, Ph. Hubert, J. Crommen, J. High Resolut. Chromatogr. 19 (1996) 669.
[17] M. Fillet, Ph. Hubert, J. Crommen, Electrophoresis 18 (1997) 1013.
[18] M. Fillet, Ph. Hubert, J. Crommen, J. Chromatogr. A 875 (2000) 123.
[19] M. Fillet, B. Chankvetadze, J. Crommen, G. Blaschke, Electrophoresis 20 (1999) 2691.
[20] S. Terabe, M.Y. Miyashita, O. Shibata, J. Chromatogr. 636 (1994) 47.
[21] J. Wang, I.M. Warner, J. Chromatogr. A 711 (1995) 297.
[22] B. Chankvetadze, J. Chromatogr. A 792 (1997) 269.
[23] C. Desiderio, S. Fanali, Z. Aturki, J. Chromatogr. A 716 (1995) 183.
[24] S. Fanali, Z. Aturki, J. Chromatogr. A 694 (1995) 297.
[25] Y.Y. Rawjee, G. Vigh, Anal. Chem. 66 (1994) 619.
[26] C. Quang, M.G. Khaledi, J. High Resolut. Chromatogr. 17 (1994) 609.
[27] E. Tesarova, M. Gilar, A. Jegorov, M. Uhrova, Z. Deyl, Biomed. Chromatogr. 11 (1997) 321.
[28] J.L. Haynes, S.A. Shamsi, F. Okeefe, R. Darcey, I.M. Warner, J. Chromatogr. A 803 (1998) 261.
[29] S. Fanali, C. Desiderio, Z. Aturki, J. Chromatogr. A 722 (1997) 185.
[30] F. Wang, M.G. Khaledi, J. Chromatogr. A 817 (1998) 121.
[31] M. Blanco, J. Coello, H. Iturriaga, S. Maspoch, C. Perez-Masada, J. Chromatogr. A 793 (1998) 165.
[32] X. Zhu, B. Lin, U. Epperlein, B. Koppenhoefer, Chirality 11 (1999) 56.
[33] The European Pharmacopeia, Part 2.2.2, Council of Europe, Strasbourg, 3rd Edition, 1996.
[34] E. Kenndler, in: M.G. Khaledi (Ed.), High Performance Capillary Electrophoresis (Chemical Analysis Series), Vol. 146, Wiley, New York, 1998.
[35] G. Vigh, A.D. Sokolowski, Electrophoresis 18 (1997) 2305.