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# Use of cyclodextrins in capillary electrophoresis for the chiral resolution of some 2-arylpropionic acid non-steroidal anti-inflammatory drugs

Salvatore Fanali*, Zeineb Aturki

*Istituto di Cromatografia del CNR, Area della Ricerca di Roma, P.O. Box 10, 00016 Monterotondo Scalo (Rome), Italy*

**Abstract**

The enantiomeric separation of racemic compounds of some 2-arylpropionic acid non-steroidal anti-inflammatory drugs (profens), namely fenoprofen, ibuprofen, flurbiprofen, suprofen, ketoprofen and indoprofen, was performed by capillary zone electrophoresis. The separation was obtained by supporting the background electrolyte with derivatized β-cyclodextrins. The type and concentration of cyclodextrin used and the background electrolyte composition (pH and amount of methanol) influenced the complexation and the chiral resolution. All the modified β-cyclodextrins used (heptakis-2,6-di-O-methyl-β-, heptakis-2,3,6-tri-O-methyl- and 6$^{A}$-methylamino-β-cyclodextrin) showed good complexing effects with the profens tested. Tri-O-methyl-β-cyclodextrin proved to be the best stereoselective additive because it allowed the enantiomeric resolution of all the profens studied whereas the dimethylated and methylamino-β-cyclodextrin were able to separate only some of them.

## 1. Introduction

In the last decade, the resolution of racemic compounds has attracted great interest in analytical chemistry, especially in pharmaceutical analysis. Several drugs are administered as racemates, but very often one of the two enantiomers can be pharmacologically more active than its antipode, which might be even toxic. For example, (−)-epinephrine and (−)-terbutaline are ten and four times more potent than their optical antipodes, respectively [1]. The anti-inflammatory activity of flurbiprofen and ibuprofen is mainly ascribed to the (*S*)-(+)-isomer [2] whereas the (*S*)-(−)-thalidomide has teratogenic effects [3]. The aim in the pharmaceutical industry, therefore, is the production and marketing of drugs containing only the active enantiomers. Furthermore, rapid, sensitive and selective analytical methods are required to control the chiral purity of the products.

The separation of a wide variety of enantiomers has been performed predominantly by high performance-liquid chromatography (HPLC), thin-layer chromatography (TLC) and gas chromatography (GC) [4–7]. Recently, capillary electrophoresis (CE) has been used for chiral separations, applying different kinds of resolution mechanisms. The methods include micellar electrokinetic chromatography (MEKC) with chiral additives [8,9], ligand exchange with metal and chiral compound complexes [10,11], affinity electrophoresis with proteins [12,13] and inclu-

* Corresponding author.

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sion–complexation with cyclodextrins or its derivatives and crown ether derivatives [14–18].

Commercially available cyclodextrins (CDs) have been widely employed in CE for the separation of enantiomers, including compounds of pharmaceutical interest. Despite its low solubility [19], β-CD has been used several times in derivatized (methylated, carboxymethylated, hydroxypropylated, soluble β-CD polymer, etc.) forms having higher solubility, different cavity dimensions and different substituent groups on the rim of the molecule as compared with the parent compound [20].

The 2-arylpropionic acid non-steroidal antiinflammatory drugs (2APAs), also known as profens, are used for the treatment of several inflammatory diseases and are often administered as racemic mixtures. The need for the stereoselective methods for the determination of 2-APAs has been demonstrated. Brune et al. [21] used HPLC for a study of pharmacodynamic effects of pure enantiomers of flurbiprofen and of the inversion of (*R*)- to (*S*)-enantiomers of flurbiprofen, ibuprofen and ketoprofen in different species (man, rat, dog, etc.) [21]. The resolution of 2-APA enantiomers can be achieved either after derivatization using a chiral reagent or with a chiral stationary phase using HPLC [22–26] or GC [27]. The enantiomeric separation of fenoprofen, ibuprofen and naproxen by capillary electrophoresis utilizing β-cyclodextrin or hydroxypropyl-β-cyclodextrin [28,29] or maltodextrins [30] added to the background electrolyte (BGE) has been reported.

In this work, we studied the effect of different β-cyclodextrin derivatives, added to the BGE, on the resolution of several 2-APAs with the aim of optimizing the electrophoretic separation and describing the parameters that influence the chiral resolution.

## 2. Experimental

Heptakis-2,6-di-O-methyl-β-cyclodextrin (di-OMe-β-CD) and heptakis-2,3,6-tri-O-methyl-β-cyclodextrin (tri-OMe-β-CD) were purchased from Cyclolab (Budapest, Hungary). Morpholinoethanesulfonic acid (MES), racemic fenoprofen (Fen), ibuprofen (Ibu), ketoprofen (Ket), flurbiprofen (Flu), indoprofen (Ind), suprofen (Sup) and (*S*)-(+)-ibuprofen were obtained from Sigma (St. Louis, MO, USA). $6^A$-Methylamino-β-CD (Me-NH-β-CD) was prepared as described previously [16]. (−)- and (+)-suprofen and (−)- and (+)-flurbiprofen were kindly supplied by Dr. Cecilia Bartolucci (Istituto di Strutturistica Chimica, Consiglio Nazionale delle Ricerche, Montelibretti, Rome, Italy). The optical purity of (−)- and (+)-suprofen was about 98% and that of flurbiprofen was about 99%, as measured by CE (peak-area ratio) using as the BGE 0.1 *M* MES at pH 5 containing 30 m*M* tri-OMe-β-CD.

Electrophoretic experiments were carried out using a Biofocus 3000 apparatus (Bio-Rad Labs., Hercules, CA, USA). The injection of the samples was done by pressure (10 p.s.i. s; 1 p.s.i. = 6894.76 Pa). The separations were performed in a fused-silica capillary of 35 cm (effective length 31.5 cm) × 0.050 mm I.D. (Polymicro Technologies, Phoenix, AZ, USA) coated with polyacrylamide according to the method described by Hjertén [31]. The polyimide coating was removed using hot $H_2SO_4$ in order to prepare a detector window of about 0.5 cm. The capillary assembled in a cartridge (Bio-Rad) was thermostated by circulating liquid at 25°C. Detection was performed with a UV–visible detector at 206 nm. The carousel temperature was kept at 25°C. The high-voltage power supply was operated in the constant-voltage mode, applying 20 kV, and the substances migrated towards the positive pole.

The BGE in the electrophoretic experiments was 0.1 *M* MES (pH adjusted with sodium hydroxide to the desired value between 4 and 7). The appropriate amount of cyclodextrin was dissolved in the BGE before the electrophoretic experiments to yield concentrations in the range 0–30 m*M* (tri-OMe-β-CD) and 0–20 m*M* (di-OMe-β-CD and Me-NH-β-CD). The concentrations of methanol used for the electrophoretic experiments in organic/aqueous BGE were 10, 20, 30 and 40% (v/v).

Stock standard solutions ($10^{-3}$ *M*) of standard racemic 2-APAs and their enantiomers were

prepared in methanol and diluted at the desired concentration with 5 m*M* MES at pH 5.

Two different 2-APA formulations, namely Moment and Orudis, containing ibuprofen (200 mg per tablet) and ketoprofen (50 mg per tablet), respectively, were weighted and triturated separately and methanol was added and stirred at room temperature for 10 min. The mixture was filtered and the volume adjusted in order to obtain two solutions containing about $10^{-3}$ *M* of ibuprofen and ketoprofen. The stock standard solutions were diluted tenfold with 5 m*M* MES at pH 5 and injected for electrophoresis analysis.

The resolution, *R*, was calculated using the following equation:

$$R = \frac{t_2 - t_1}{w_2 - w_1} \cdot 2 \quad (1)$$

where $t_2$, $t_1$ and $w_2$, $w_1$ are the migration times and the widths of the peaks, respectively, measured at the baseline in seconds for the two enantiomers (1 and 2) of the same compound.

## 3. Results and discussion

The enantiomers of several 2-APAs (Fig. 1) were studied in the pH range 4–7 by free solution capillary electrophoresis in the absence or presence of derivatized cyclodextrins. In this pH range the carboxylic group of all 2-APAs is dissociated and thus the analytes migrate as anions [28,29].

In the absence of cyclodextrins no resolution of enantiomers was obtained, which is in accordance with the fact that the enantiomers of the same compound possess similar physico-chemical properties and similar electrophoretic mobilities. The direct resolution method [32], introducing stereoselective interactions, was used for the enantiomeric separation of the six 2-APAs, using several modified β-CDs, such as heptakis-2,6-di-O-methyl-β-CD, heptakis-2,3,6-tri-O-methyl-β-CD and $6^A$-methylamino-β-CD.

β-CD and hydroxypropyl-β-CD in the presence of hydroxypropylcellulose were used by Rawjee and Vigh [29] for the separation of the enantiomers of naproxen and fenoprofen.

Modified β-CDs can give several advantages over the native compounds for enantiomeric separations by CE, e.g., higher solubility in the BGE, different depth of the cavity and different stereoselective interactions due to the presence of different substituents on the rim of the CD (di-OMe-β-CD and tri-OMe-β-CD). The utility of chargeable groups on the CD structure (MeNH-β-CD) when CE separation is per-

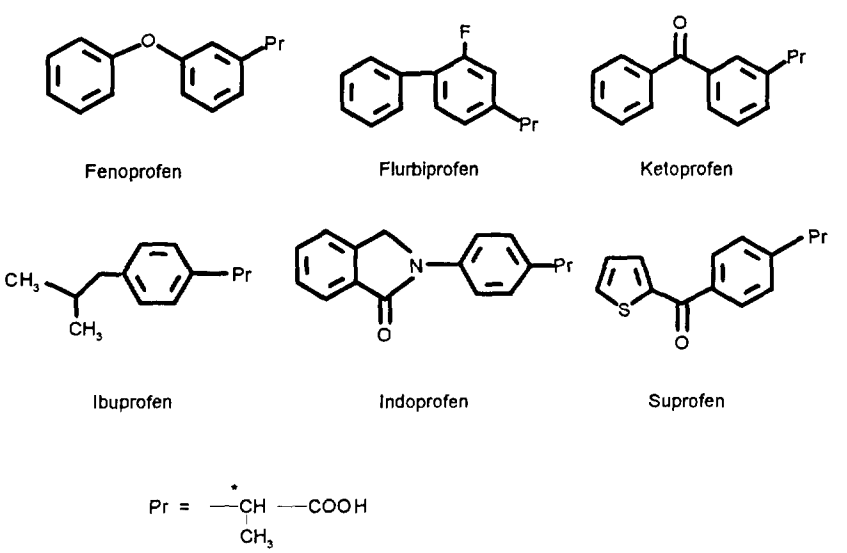


Fig. 1. Structures of the non-steroidal anti-inflammatory drugs studied.

formed should be noted. In fact, the CD can move in the opposite direction to the analytes (in coated capillaries) and can show capability as an ion-pairing agent and thus enhance the resolution of the enantiomers.

Fig. 2a and b show the effect of tri-O-methyl-β-cyclodextrin concentration on the migration times of 2-APAs at pH 5. Higher concentrations of the modified CD caused a decrease in the effective mobilities (increased migration times) of all the 2-APAs investigated except ketoprofen. This increase in migration time was due to the complex formation between CD and the analytes with a probable complexation order Ibu > Indo ≈ Flu > Fen > Sup > Ket.

The migration order of the separated enantiomers was verified for ibuprofen, flurbiprofen and suprofen by spiking the racemic samples with the pure optical isomers. In all instances the (*R*)-(−)-isomer moved with a lower velocity than the (*S*)-(+)-isomer, indicating that the (*R*)-(−)-isomers form more stable inclusion complexes than their optical antipodes with tri-OMe-β-CD.

In order to explain the different stabilities of the diastereomers formed during the electrophoretic runs, we may consider the data on the crystal structures of the flurbiprofen enantiomers complexed with tri-OMe-β-CD [33]. In this case, the fluorobiphenyl groups of the (*R*)-(−) and (*S*)-(+)-isomers are included similarly in the cavity of the modified CD stabilized by hydrophobic interactions, but the carboxyl group of the (*S*)-(+)-isomer forms a hydrogen bond with the oxygen at position 2 of the CD molecule, whereas the (*R*)-(−)-isomer is linked to the adjacent tri-OMe-β-CD by the –COOH–water–O(6) hydrogen-bond bridge. As a result of such complexation, two diastereomers with different mass-to-charge ratios are formed, which are then separable by CE.

The higher complexation of ibuprofen and indoprofen compared with the other compounds analysed is probably due to the *para* position of the substituent (containing the chiral centre) on the aromatic ring. Earlier data have already shown that *para*-substituted aromatic rings can fit properly into the CD cavity [34,35]. The relatively low complexation of the modified CD with ketoprofen is, therefore, easily understandable if we consider that the analyte can be oriented in an unfavourable way in the CD cavity owing to its substituent in the *meta* position.

Fig. 3a and b show the resolution (*R*) of the enantiomeric pairs of the 2-APAs as a function of the tri-O-methyl-β-CD concentration at pH 5. The resolution increased with increasing amount of CD. Baseline separation ($R \geq 1$) of the enantiomers was obtained at different tri-OMe-β-

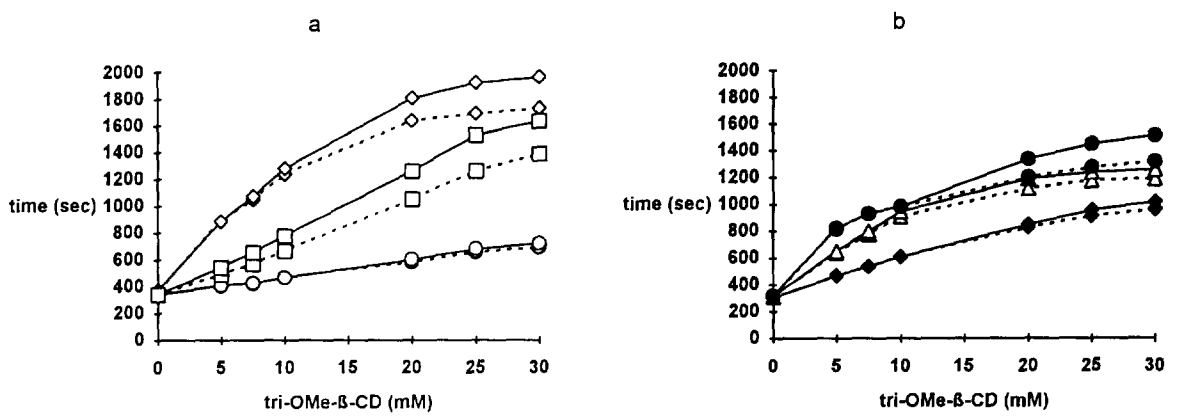


Fig. 2. Effect of the heptakis-tri-O-methyl-β-cyclodextrin (tri-OMe-β-CD) concentration on the migration time of the profens studied. Capillary 35 (31.5) cm × 0.050 mm I.D., coated; background electrolyte, 100 m*M* MES at pH 5 with the appropriate amount of CD; applied voltage, 20 kV, 6.6 μA; pressure injection, 10 psi s; sample concentration, $5 \times 10^{-5}$ *M* fenoprofen, flurbiprofen and ketoprofen, $10^{-4}$ *M* suprofen, ibuprofen and indoprofen. □ = Indoprofen; ○ = ketoprofen; ◇ = ibuprofen; △ = fenoprofen; ● = flurbiprofen; ◆ = suprofen.

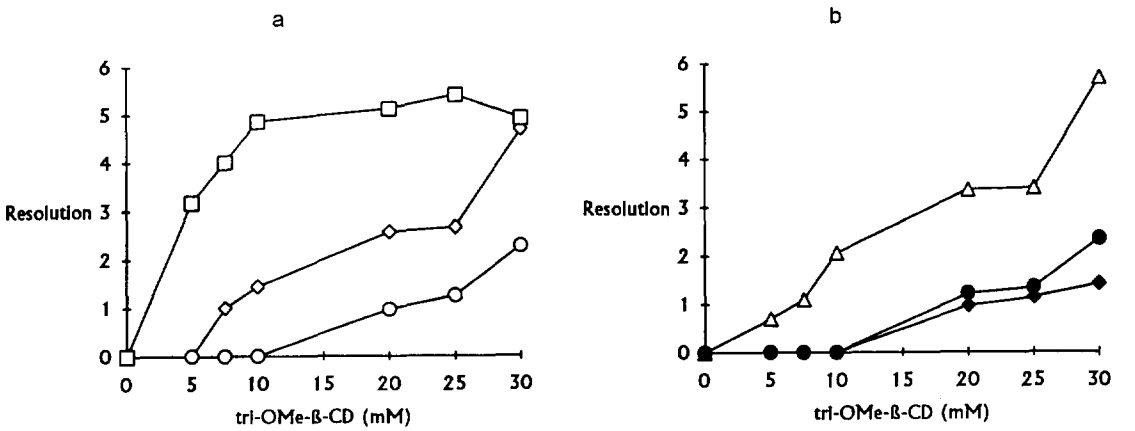


Fig. 3. Effect of the amount of 2,3,6-heptakis-tri-O-methyl-β-cyclodextrin on the enantiomeric resolution of 2-APAs. Experimental conditions and symbols as in Fig. 2.

CD concentrations: indoprofen (<5 m*M*), fenoprofen and ibuprofen (7.5 m*M*) and suprofen, flurbiprofen and ketoprofen (20 m*M*).

### 3.1. Effect of the pH of the background electrolyte on the resolution

Experiments performed using the BGE at different pH values in the range 4–7, in the absence of a chiral additive, showed a general decrease in the migration time for all the compounds analysed with increase in pH owing to the increased dissociation of the carboxylic group on the analytes. In order to verify the effect of pH on the resolution of the enantiomers of the 2-APAs studied, the same amount of tri-OMe-β-CD (25 m*M*) was added to the BGE at pH 4, 5, 6 and 7.

Fig. 4a and b show the effect of pH on the chiral resolution of fenoprofen, flurbiprofen, suprofen, ibuprofen, ketoprofen and indoprofen. At pH 4 it was possible to record the chiral separation of suprofen and indoprofen only because the other racemic compounds were moving too slowly owing to the strong complexation with the chiral selector. These findings were confirmed using a smaller amount of tri-OMe-β-CD (0.5–2.5 m*M*) that allowed the detection of the analyte compounds and the resolution of flurbiprofen, indoprofen and ketoprofen (at 2.5 m*M* of CD, $R = 1.77$, 1.74 and 0.5, respectively) (results not shown).

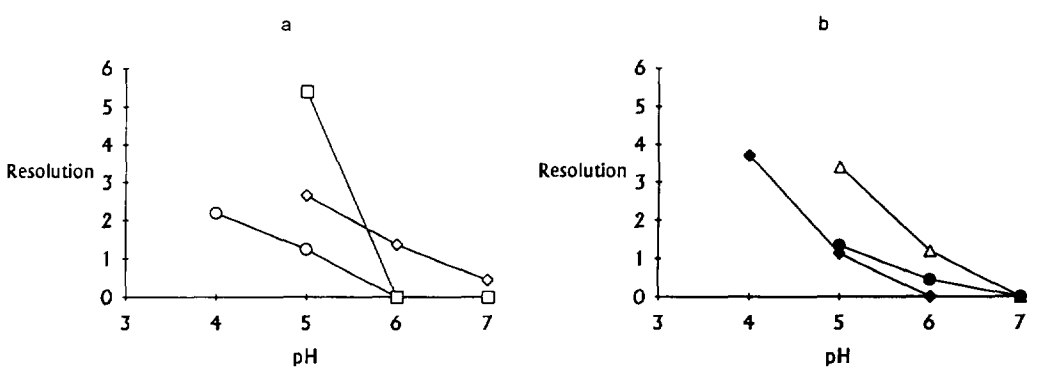


Fig. 4. Effect of the pH of the background electrolyte of the resolution of the compounds studied. The content of cyclodextrin in the background electrolyte was 25 m*M*; applied voltage, 20 kV, 2–35 μA. Other experimental conditions and symbols as in Fig. 2.

An increase in the pH of the BGE caused a decrease in the resolution for all the 2-APAs studied; at pH 5 complete enantiomeric resolution was obtained for all the compounds investigated whereas at pH 6 the resolution was lost ($R = 0$) for suprofen, indoprofen and ketoprofen but was satisfactory for the other compounds, and at pH 7 only ibuprofen was poorly resolved into its enantiomers. Based on our results, it appears that the optimum experimental conditions for the enantiomeric separation of the six 2-APAs can be obtained if the pH of the BGE is adjusted to 5. An increase in pH is not convenient for chiral resolution, probably owing to the higher dissociation of the carboxylic group and to the shorter migration time. The time spent by the analytes in the cavity of the CD is, of course, shortened with a decrease in resolution, and further, the dissociation of the carboxylic group will probably influence the stereoselective hydrogen bonds between this group and the substituents on the CD's rim.

As an example, Fig. 5 shows the electropherogram for the separation of ketoprofen, flurbiprofen, fenoprofen and ibuprofen into their enantiomers in a BGE at pH 5 containing 30 m*M* tri-OMe-$\beta$-CD.

### *3.2. Effect of the cyclodextrin type on the enantiomeric resolution*

In order to verify the influence of the CD type on the resolution of the enantiomers of the 2-APAs, pH 5 was selected for the experiments and the BGE was supported with $\beta$-CD derivatives, namely $6^{A}$-methylamino-$\beta$-CD or heptakis-2,6-di-O-methyl-$\beta$-CD.

For methylated CDs, the substituent groups at positions 2, 3 and 6 are the same in all seven glucose molecules whereas in MeNH-$\beta$-CD all the substituents are of hydroxy type and only glucose (A) at position 6 is substituted with a methylamino group. The methylated CDs are not charged at the operating pH (5) whereas MeNH-$\beta$-CD is positively charged and thus moving towards the cathode (in the opposite direction to the analytes).

Both modified CDs were added to the BGE at concentrations of 2.5, 5, 10 and 20 m*M*. An increasing amount of the CDs cause a general

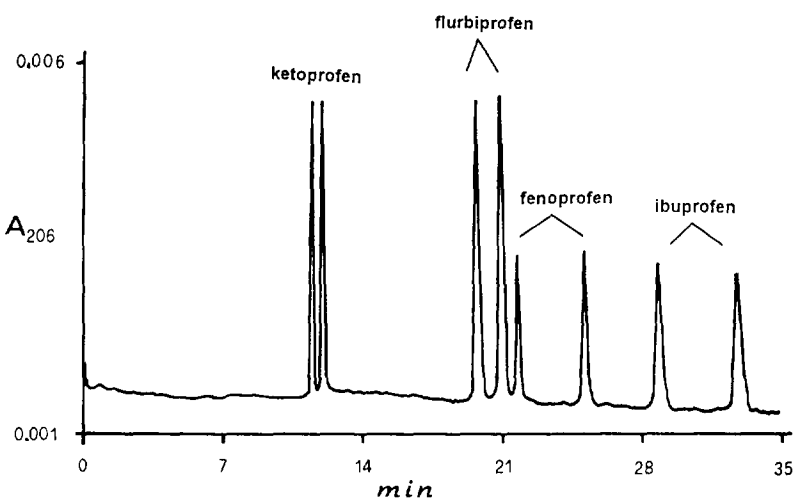


Fig. 5. Electropherogram of the enantiomeric separation of ibuprofen, fenoprofen, ketoprofen and flurbiprofen. Background electrolyte, 100 m*M* MES (pH 5) and 30 m*M* tri-O-methyl-$\beta$-CD; applied voltage, 20 kV, 6.6 $\mu$A; sampling: pressure, 10 psi s of a mixture of $10^{-4}$ *M* ibuprofen, $10^{-5}$ *M* fenoprofen, ketoprofen and flurbiprofen $5 \times 10^{-5}$ *M*. Other experimental conditions as in Fig. 2.

increase in the migration times for all the 2-APAs, but this was more evident for di-OMe- and MeNH-β-CD, showing a higher complexing effect of the former CD.

Table 1 shows the effect of the concentration of the two CDs on the resolution at pH 5.

Baseline resolution of the enantiomers was obtained for ibuprofen, suprofen and indoprofen whereas fenoprofen and flurbiprofen were poorly resolved and no resolution was achieved for ketoprofen when the BGE was supported with different amounts of MeNH-β-CD. An increase in the CD concentration increased the resolution for ibuprofen, suprofen and indoprofen and the best resolution was obtained for ibuprofen and suprofen at 20 m*M* ($R = 1.23$ and 1.12, respectively), whereas at 10 m*M* for indoprofen $R = 2.1$.

When di-OMe-β-CD was used as a chiral selector at pH 5, baseline enantiomeric resolution was obtained for ibuprofen and indoprofen; flurbiprofen, ketoprofen and suprofen were poorly resolved ($R < 0.5$) and fenoprofen was not resolved.

From these results, we can conclude that the positively charged CD, being useful for the enantiomeric separation of three of the six 2-APAs studied, showed a higher resolving power than di-OMe-β-CD but lower than tri-OMe-β-CD, except for suprofen. In fact, even relatively small amounts of positively charged CD (2.5–5 m*M* MeNH-β-CD) allowed the enantiomeric resolution of suprofen. The higher stereoselective effect of this modified CD in comparison with the methylated compound may be due to the charged group on the CD structure. In fact, the neutral CD acts as a quasi-stationary phase whereas the charged CD is moving in the opposite direction to the analytes, enhancing the complexation equilibria. Anyway, the inclusion–complexation power of the charged CD is lower than that of the methylated CDs. This behaviour is probably due to the structures of the CDs, in which the depth and the substituent groups on the rim play a very important role in inclusion–complexation. The depth of MeNH-β-CD cavity is probably similar to that of the β-CD (only one hydroxy group is substituted) and smaller than that of di-OMe-β-CD owing to the presence of methoxy groups on the rim, and thus the cavity of methylated CDs is more hydrophobic.

### 3.3. Effect of methanol on the resolution

The effect of the addition of methanol to the BGE on the enantiomeric resolution was studied for fenoprofen, ibuprofen, ketoprofen and flurbiprofen at pH 5. Experiments were performed at a low concentration of tri-OMe-β-CD (5 m*M*) where no or poor enantiomeric resolution was

Table 1
Effect of the amount of modified β-cyclodextrin on the enantiomeric resolution of profens

| Profen | Cyclodextrin (m*M*) | | | | | | | |
|---|---|---|---|---|---|---|---|---|
| | 2.5 | | 5 | | 10 | | 20 | |
| | $R_{di\text{-}OMe}$ | $R_{MeNH}$ | $R_{di\text{-}OMe}$ | $R_{MeNH}$ | $R_{di\text{-}OMe}$ | $R_{MeNH}$ | $R_{di\text{-}OMe}$ | $R_{MeNH}$ |
| Fenoprofen | 0 | <0.5 | 0 | <0.5 | 0 | <0.5 | 0 | <0.5 |
| Ibuprofen | 0.7 | <0.5 | 0.8 | 0.6 | 1.1 | 0.9 | 1.3 | 1.2 |
| Ketoprofen | 0 | 0 | 0 | 0 | 0 | 0 | <0.5 | 0 |
| Flurbiprofen | <0.5 | 0 | <0.5 | 0 | 0 | <0.5 | 0 | <0.5 |
| Suprofen | 0 | <0.5 | <0.5 | 0.8 | 0 | 0.9 | 0 | 1.1 |
| Indoprofen | 1.0 | 0.8 | 1.7 | 1.9 | 2.0 | 2.1 | 2.2 | 2.0 |

$R_{di\text{-}OMe}$ and $R_{MeNH}$ = resolution in presence of dimethylated and methylamino-β-cyclodextrin, respectively.

obtained and the methanol content in the BGE was chosen between 10 and 40% (v/v).

As expected, an increase in the methanol concentration in the BGE (containing the chiral selector) caused an increase in the migration times for the four 2-APAs. When 5 m*M* tri-OMe-β-CD was used in the absence of methanol we obtained enantiomeric resolution for fenoprofen and flurbiprofen ($R = 0.7$ and $<0.5$, respectively), whereas ibuprofen and ketoprofen showed no resolution. The addition of methanol did not influence the chiral resolution of ketoprofen and ibuprofen but slightly improved that for fenoprofen ($R = 0.82$ at 40% of methanol). In the absence of methanol, the flurbiprofen enantiomers were poorly separated, but baseline resolution was obtained by increasing the content of the organic additive in the BGE ($R = 1.4$ at 20% of methanol, increasing to 2.5 at 40%).

Fig. 6 shows the enantiomeric separation of racemic flurbiprofen with 5 m*M* tri-OMe-β-CD in the absence and presence of 10–40% (v/v) methanol.

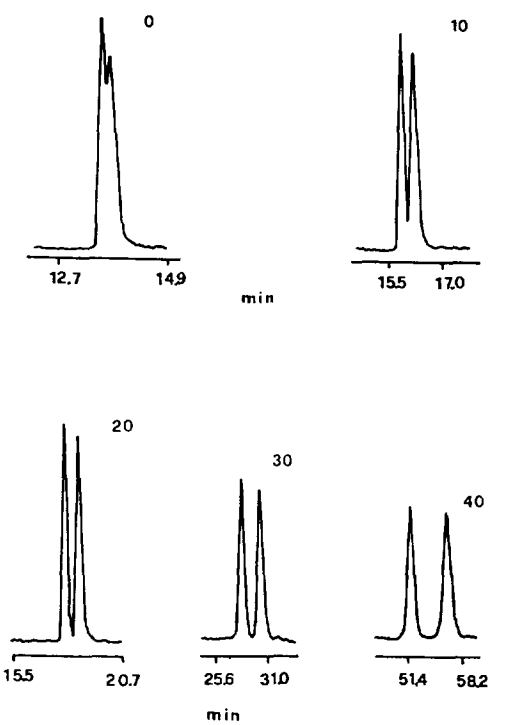


Fig. 6. Electropherograms of the enantiomeric separation of flurbiprofen in the absence and presence of an organic additive to the background electrolyte containing CD. Background electrolyte, 100 m*M* MES (pH 5) and 5 m*M* of tri-OMe-β-cyclodextrin and different concentrations of methanol (0–40%). Applied voltage, 20 kV. 6.6–3.5 μA.

### *3.4. Qualitative analysis of pharmaceutical preparations*

Two samples containing about $10^{-4}$ *M* ibuprofen and ketoprofen were analysed using 50 m*M* MES (pH 5) supported with 20 and 30 m*M* tri-OMe-β-CD, respectively. The electropherograms showed the presence of the two enantiomers in both samples (results not shown), indicating that the two drugs are administered as racemic compounds. The presence of the two enantiomers was confirmed by spiking the two solutions with standard mixtures containing racemic ibuprofen and ketoprofen.

## 4. Conclusions

It has been demonstrated that capillary electrophoresis can be successfully used for the resolution of enantiomers of several 2-arylpropionic acid non-steroidal anti-inflammatory drugs when charged or uncharged cyclodextrin derivatives are added to the background electrolyte as a chiral selector. The chiral resolution is based on the inclusion–complexation between the CD used and the analytes, which causes selective retardation of enantiomers, allowing their separation. The tested modified cyclodextrin derivatives (heptakis-2,6-di-O-methyl-β-CD, heptakis-2,3,6-tri-O-methyl-β-CD and $6^{A}$-methylamino-β-CD) proved to be good complexing agents for the racemic compounds analysed and the most useful chiral selector was tri-OMe-β-CD. The chiral discrimination was influence by the CD type, its concentration, the pH of the BGE and the content of organic solvent.

Capillary electrophoresis can be considered as complementary to other analytical techniques, such as HPLC, for the separation of enantio-

mers. We can outline the following advantages: (i) the amounts of samples and separation buffer are much less than those used in HPLC (in general, nanolitre and microlitre volumes, respectively are used); (ii) usually the chiral selector is dissolved in the BGE and thus the use of expensive chiral columns is not required, (iii) relatively high efficiencies are obtained (more than 100 000 theoretical plates); (iv) the capillary is equilibrated in a few minutes and, owing to the use of small amounts of BGE, environmental pollution is reduced. The disadvantages of CE in comparison with HPLC are the lower sensitivity in terms of concentrations, the lower reproducibility and the smaller possibility of preparative applications.

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