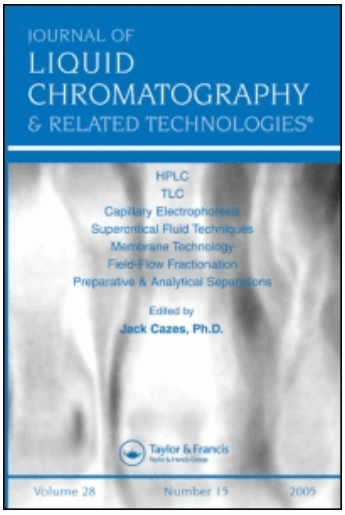

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Use of Video Densitometry and Scanning Densitometry to Study an Impact of Silica Gel and L-Arginine on the Retention of Ibuprofen and Naproxen in TLC Systems

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Abstract: In our earlier articles, we demonstrated the phenomenon of the two-dimensional enantioseparation of the selected 2-arylpropionic acids (2-APAs) in the one-dimensional thin-layer chromatographic mode, yet our measuring results originated from the classical scanning densitometry only. A basic precondition of the discussed phenomenon is the omnipresence of the two-dimensional effective diffusion in planar chromatography. However, one should anticipate an action of the two different–and apparently chiral–elements, one responsible for the vertical enantioseparation (in the direction of the mobile phase migration) and another one responsible for the horizontal enantioseparation (inducing deviation of the chiral analytes' migration tracks from the vertical). In the investigated chromatographic systems two chiral elements are in fact present. One chiral element is the microcrystalline silica gel layer and the other one is L-arginine as the impregnating chiral selector. Upon our earlier results originating from the scanning densitometry, it could be deduced that the crystalline chirality of silica gel is responsible for the horizontal enantioseparation, and the molecular chirality of L-arginine is responsible for the vertical separation. In this study, we confirm our earlier findings in a more immediate way, using the flatbed video densitometry to record the pictures of the whole chromatograms and also those of the individual chromatographic spots of ibuprofen and naproxen. We combine these results with the data obtained from the classical scanning densitometry to monitor the discussed enantioseparations by means of the concentration profiles of the respective antimers. Combination of the results originating from the video and the scanning densitometry allows a deep enough insight in the chromatographic behavior

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of the two selected 2-APAs on the plain silica gel layers and on those impregnated with L-arginine.

Keywords: Ibuprofen, Naproxen, TLC, Chirality of silica gel, 2-Arylpropionic acids (2-APAs), Enantioseparations, Video densitometry, Scanning densitometry

INTRODUCTION

Enantioseparations carried out by means of thin layer chromatography (TLC) used to be considerably less frequent than with the aid of the other separation techniques (like, e.g., high performance liquid chromatography, HPLC, or capillary electrophoresis, CE). At the same time, performance of TLC with densitometric detection is of the same high quality as that offered by the other separation techniques and moreover, one can name some additional advantages that are inherent of TLC alone.

It is obvious that separations performed by means of TLC can be preserved on the chromatographic plates even for long periods of time and the separation results can be checked and confirmed in situ by a vast number of the instrumental–mostly spectroscopic–analytical techniques (the advantages that clearly out perform HPLC and CE). It is equally obvious that TLC does not demand equipment as expensive, as in the case of HPLC or CE, and moreover, the consumption of solvents with TLC is more economic than with the other liquid chromatography techniques.

There is one more significant advantage of TLC in comparison with HPLC, which is a popular usage of silica gel as an adsorbent in the TLC systems (and its practical absence from the HPLC ones). In this paper[1] we published the results from examination of the silica gel samples by means of the spectroscopy of circular dichroism (CD), and it came out that–against a popular and widespread conviction–silica gel is not amorphous, but chiral. Chirality of silica gel combined with the two-dimensional effective diffusion (taking place in the planar chromatography systems and for obvious reasons absent from the chromatographic columns) results in the horizontal contribution to the enantioseparation of the racemic and scalemic mixtures, as it was shown upon the selected examples of 2-arylpropionic acids (2-APAs) in literature.[2–4] In that way, one can obtain the two-dimensional enantioseparations with use of the one-dimensional TLC.

The first example of the two-dimensional enantioseparation in the one-dimensional chiral TLC system was presented in a paper,[5] although it was not commented on by its authors. In Figure 1 of that paper a photograph was given of the one-dimensional chromatogram showing two well separated antimers of ibuprofen visualized in the iodine vapours and one can easily notice two nicely shaped chromatographic spots with slightly different R_F values appearing side by side.

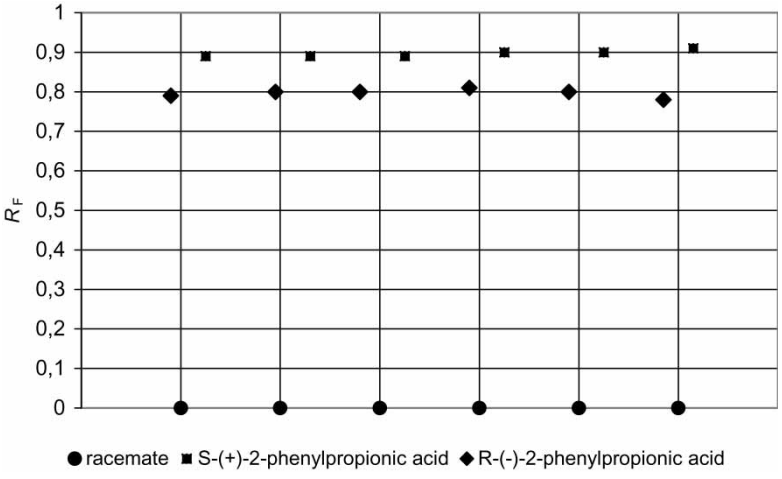

Figure 1. Schematic representation of the deviation from the vertical of the migration tracks of the enantiomers of 2-phenylpropionic acid on silica gel 60 F_{254} impregnated with L-arginine. The mobile phase was acetonitrile–methanol–water, $5 + 1 + 0.75$, v/v (originally published in [2]).

In our own studies on the enantioseparation of the selected 2-APAs,[2–4] the assessment of the chromatograms was carried out by means of the scanning densitometry only. Quite soon, however, it became clear that the migration tracks of the individual optically pure enantiomers from a racemic or scalemic mixture deviate to the right or to the left from the vertical (depending on the analyte considered and on its chiral configuration) and for this particular reason we scanned our chromatograms along the tracks 35 mm wide, at parallel in the 1.5 mm intervals per one chromatographic spot. The results of our scrutiny have been presented in the form of the diagrams, like that given in Figure 1, and taken from literature.[2] Although we felt that these diagrams did not provide realistic enough pictures of the horizontal (i.e., sidewise) enantioseparations, at that time we lacked a flatbed video densitometer to take the pictures of the whole chromatogram and of the individual chromatographic spots in UV light. Purely visual assessment of the chromatograms in UV light was inadequate in the sense that the chromatographic spots were too small and not distinct enough to allow drawing of the respective diagrams by hand.

The goal of this paper is to confirm the impact of the crystalline chirality of the plain silica gel and of the molecular chirality of L-arginine (applied as chiral selector) on the enantioseparation of ibuprofen and naproxen by a combined use of the flatbed video densitometer and the classical scanning densitometer. Upon our earlier results obtained with use of the scanning densitometer and presented in papers,[1,2] it could be concluded that the main effect of the silica gel chirality was the horizontal enantioseparation of the

two antimers, and the main effect of L-arginine was the vertical enantioseparation thereof. We felt that a deeper insight in our earlier findings with a combined use of video densitometry and scanning densitometry is needed as an important step forward in our study.

EXPERIMENTAL

S-(+)-Ibuprofen and *S*-(+)-Naproxen as the Test Analytes

In our study, we used *S*-(+)-ibuprofen and *S*-(+)-naproxen, manufactured by Sigma-Aldrich (St Louis, MO, USA; cat. nos I-106 and 28,478-5, respectively). As it has been shown in our earlier papers,[6–8] solutions of *S*-(+)-ibuprofen and *S*-(+)-naproxen undergo, in the course of a prolonged storage, a spontaneous (and oscillatory) in vitro transenantiomerization to form the scalemic mixtures of the two respective antimers. In our present experiments, we used solutions of *S*-(+)-ibuprofen and *S*-(+)-naproxen in 70% ethanol after their storage for at least two weeks in the sealed vessels at ambient temperature. Even without measuring the quantitative ratio of the two ibuprofen and naproxen antimers in these relatively long stored solutions, their presence in each individual solution was guaranteed (as it comes out from the results of our earlier studies).[6–8] Concentration of ibuprofen in the solution was equal to 5 mg mL^{-1} (ca. 2.2×10^{-2} mol L^{-1}) and that of naproxen was equal to 1 mg mL^{-1}(ca. 4.3×10^{-3} mol L^{-1}). The 5 μL volumes of these solutions were then applied to the chromatographic plates.

Ethanol used for preparation of the ibuprofen and naproxen solutions was of the HPLC grade (Merck, Darmstadt, Germany) and water was double distilled in our laboratory.

Commercial TLC Silica Gel Layers and Their Pretreatment

TLC was performed on commercial glass plates (20 cm × 20 cm) precoated with 0.25 mm layers of silica gel 60 F_{254} (Merck KGaA, Darmstadt, Germany; cat. no. 1.05715). Before use, the plates were carefully washed by predevelopment with methanol and then dried at ambient temperature for 3 h. Methanol used for prewashing was of the HPLC grade (Merck).

Then the prewashed plates were divided into two groups. Group 1 plates were directly used in the chromatographic experiment. Group 2 plates were impregnated with a 3×10^{-2} mol L^{-1} solution of L-arginine (analytical reagent grade, Merck) in methanol by conventional dipping for 2 s. The concentration of the impregnating solution was calculated as that depositing 0.5 g of L-arginine per 50 g of the dry silica gel adsorbent layer. Finally, the

washed and impregnated adsorbent layers from group 2 were ready for chromatography.

Mobile Phase and Development of Thin Layer Chromatograms

Development of the ibuprofen and the naproxen samples was carried out at $22 \pm 2^{\circ}C$ for a distance of 15 cm, using the following mobile phases: (a) With the non-impregnated chromatographic plates (group 1) ethanol was used as a pure monocomponent eluent (in order to avoid demixing of the multicomponent mobile phase); and (b) with the impregnated chromatographic plates (group 2) ethanol was also used as eluent, but it contained an extra addition of several drops of glacial acetic acid, in order to protonate the amino group of L-arginine acting as chiral selector.

Sample application to the plates was made with the use of an autosampler (the AS 30 model autosampler manufactured by Desaga, Heidelberg, Germany). The ibuprofen and naproxen solutions were applied to the plate 1.5 cm above the lower edge of the plate. Nine samples (samples 1–5: ibuprofen; samples 6–9: naproxen) in the equal distance of 2 cm from one another were applied, one per plate, and then the chromatogram was developed. After development, the plates were dried at ambient temperature for 3 h, and then the chromatograms were evaluated by means of the flatbed video densitometry and the scanning densitometry.

Densitometric Assessment of the Chromatograms

The Flatbed Video Densitometry

The chromatograms were scanned at the wavelength $\lambda = 254$ nm with use of the Chromimage flatbed scanner (manufactured by AR2i, Le Plessis Robinson, France), to save the pictures of the whole chromatogram and of the individual chromatographic spots. Each experiment was carried out on at least three plates.

The Classical Scanning Densitometry

Densitograms were acquired with a Desaga (Heidelberg, Germany) Model CD 60 densitometer equipped with Windows compatible ProQuant software. The track, 20 mm wide, was scanned densitometrically for each individual chromatographic spot in the 1 mm intervals. Concentration profiles of the scanned lines were recorded in UV light from the deuterium lamp (in the reflectance mode) at 210 nm. The dimensions of the rectangular light beam were 2.0 mm $\times$ 0.1 mm. The maxima of the 2-APA concentration profiles were used for calculation of the respective R_F values.

RESULTS AND DISCUSSION

In order to demonstrate intermolecular interactions between the chiral elements of stationary phase and the chiral analytes that result in the two-dimensional separations of the scalemic (or racemic) mixtures of ibuprofen and naproxen (as discussed, e.g., in papers),[1,2,5] we selected among the simplest chromatographic systems possible. Two different stationary phases were used in our experiment, namely (i) plain silica gel and (ii) silica gel impregnated with L-arginine. In the first case, we intended to demonstrate the impact of the crystalline chirality of silicon dioxide alone on the migration tracks of the ibuprofen and naproxen antimers. In the second case, we deposited L-arginine on the silica gel layer with an intent to demonstrate the combined impact of the molecular chirality of this optically pure amino acid and of the crystalline chirality of silica gel on the investigated enantioseparations.

Selecting the mobile phase, we ignored the long established and very efficient ternary mobile phases used in the experiments described in papers[5–8] and instead we applied ethanol as a monocomponent eluent (when using silica gel impregnated with L-arginine, several drops of glacial acetic acid were added to ethanol, in order to protonate the amino group of L-arginine acting as chiral selector). The applied mobile phase proved excellent in exposing the main features of the impact exerted by the two stationary phases on the retention of the test analytes. Using this simple mobile phase, we attempted to avoid any problems resulting from a possible multicomponent eluent demixing.

Video Densitometry

The results obtained with the aid of the flatbed video densitometer are presented in Figures 2 and 3. First, let us focus on Figures 2a and 3a, showing the pictures of the typical chromatograms of the scalemic mixtures of ibuprofen and naproxen on the non-impregnated (Figure 2a) and the impregnated with L-arginine (Figure 3a) silica gel layer. With the non-impregnated silica gel layer, the positions of ibuprofen and naproxen on the chromatogram did not differ among themselves (Figure 2a). This result points to the same energetics of the retention with the two investigated 2-APAs. Apparently, this is the pure adsorption mechanism of retention that involves carboxylic groups of 2-APAs on the one hand and the silanol groups of silica gel on the other.

With the impregnated silica gel layer, the retention mechanism of the test analytes is mixed. It is quite obvious that physical adsorption of 2-APAs on the silanol active sites of the stationary phase is inevitable. The complementary retention mechanism consists in the ion pair formation between the impregnating L-arginine in the cationic form and each of the two 2-APA antimers in the

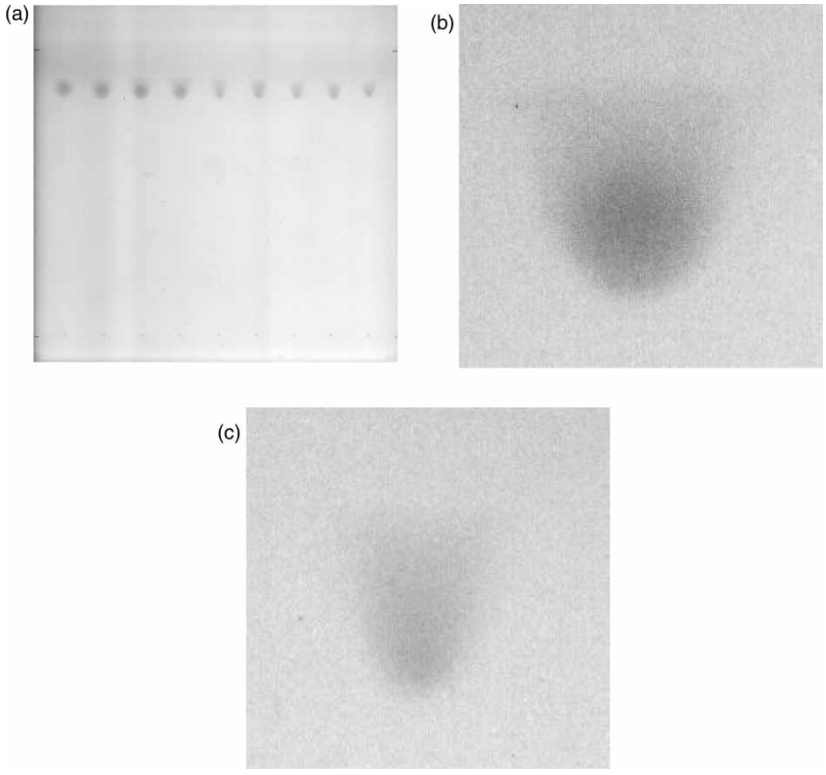

Figure 2. Video images obtained from the non-impregnated chromatographic plate precoated with silica gel 60 F_{254} and developed with ethanol. (a) The whole chromatogram (spots 1–5: ibuprofen; spots 6–9: naproxen); (b) Enlargement of a typical chromatographic spot of ibuprofen; (c) Enlargement of a typical chromatographic spot of naproxen.

anionic form. The combined energetic effect of these two retention mechanisms is higher than in the case of the plain silica gel layer, which results in considerably lower positions of ibuprofen and naproxen on the chromatogram (and also in the differentiated positions of these two compounds) in comparison with the non-impregnated silica gel layer (Figure 3a).

Now, let us discuss the shapes of the chromatographic spots of the scalemic mixtures of ibuprofen and naproxen obtained on the plain silica gel layer (as shown in Figures 2 a–c). These spots are typical of the discussed test analytes and of the chromatographic system involved. With both analytes they are V-shaped (see Figures 2 b, c) and show the front tailing that is somewhat split, with the resulting two front tails deviating to the left and to the right from the vertical direction of the mobile phase flow. The front tailing is indicative of the anti-Langmuir-type adsorption

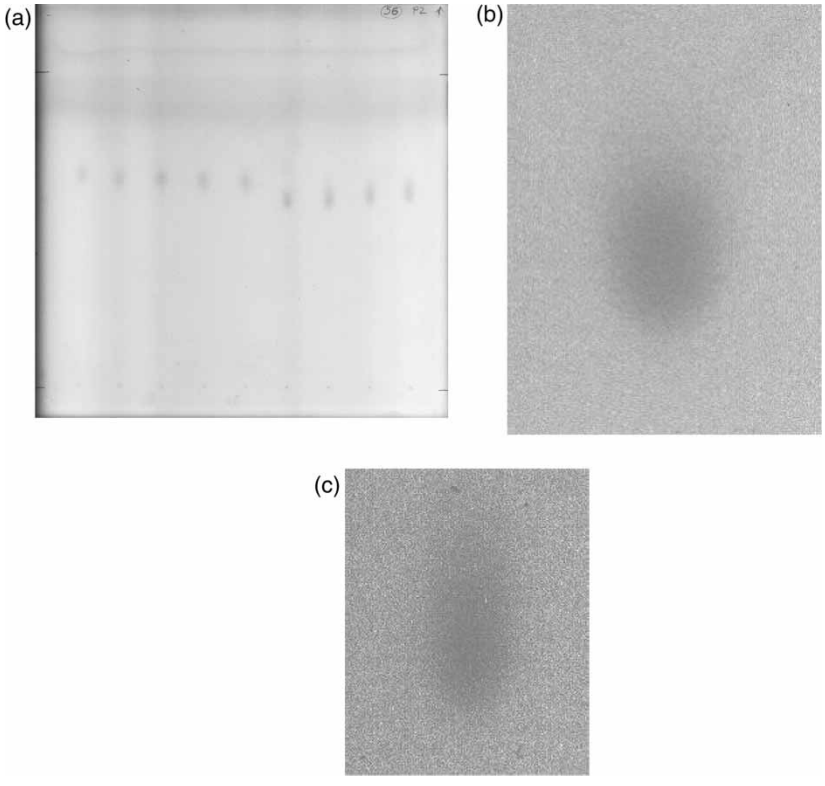

Figure 3. Video images obtained from the silica gel 60 F_{254} precoated chromatographic plate, impregnated with L-arginine and developed with ethanol (plus several drops of glacial acetic acid). (a) The whole chromatogram (spots 1–5: ibuprofen; spots 6–9: naproxen); (b) Enlargement of a typical chromatographic spot of ibuprofen; (c) Enlargement of a typical chromatographic spot of naproxen.

isotherm, typical of the presence of the lateral (i.e., analyte–analyte) interactions among the molecules of ibuprofen and naproxen, respectively. The left handed and the right handed orientation of the two tails is indicative of the horizontal separation of the two antimers of each investigated 2-APA on the plain silica gel layer. Thus, it can be concluded that the crystalline chirality of silicon dioxide induces horizontal enantioseparation of the two 2-APA antimers.

The shapes of the chromatographic spots of the scalemic mixtures of ibuprofen and naproxen, obtained on the silica gel layer impregnated with L-arginine look different from the previous ones (as shown in Figures 3b and 3c, respectively). Contrary to the V-shaped spots originating from the plain silica gel layer, these spots are oblong with the slight front tailing, again indicative of the anti-Langmuir-type adsorption isotherm. The oblong

shapes of the chromatographic spots announce the vertical separation of the antimer pairs under the influence of the molecular chirality of L-arginine as the chiral selector deposited on the silica gel layer.

Scanning Densitometry

As mentioned in Experimental, the tracks 20 mm wide were scanned densitometrically for each individual chromatographic spot in the 1 mm intervals and the concentration profiles of the scanned lines were recorded. The obtained results were fully analogous in the qualitative terms for the ibuprofen and the naproxen samples and, therefore, for the sake of brevity, we are going to discuss our results upon the example of the two randomly selected naproxen spots only, one obtained on the plain silica gel layer (Figure 2c) and the other originating from the silica gel layer impregnated with L-arginine (Figure 3c).

In Figures 4a and 5a, we presented two video densitograms of the naproxen spots (their pictures are shown in Figures 2c and 3c, respectively). These two densitograms cut the chromatographic spots approximately along their vertical axis. As can be observed from Figure 4a, no separation in the vertical direction was observed on the plain silica gel layer. From Figure 5a, it is evident that on the impregnated silica gel layer an incomplete separation was obtained. To get a better insight in the mass distribution of naproxen in these two chromatographic spots, the 3D densitograms were pieced together from all 21 scans per each 20 mm wide track (see Figures 4b and 5b).

Then, we made different use of these 21 densitograms per one chromatographic spot of naproxen; namely we used them to draw the diagrams presenting the maximum R_F values for each individual densitometric scan in the function of the spot width (see Figure 6). In that way we managed to build a kind of 'watershed' for the obtained chromatographic spots that pinpoint the ranges with the highest amounts of the analyte. The idea of these diagrams is similar to that of the 3D densitograms, they also emphasize the fact that there is no vertical enantioseparation on the plain silica gel layer and that such separation is possible on the silica gel layer impregnated with L-arginine. Other information can also be extracted from Figure 6, namely that the chromatographic spot of naproxen on the plain silica gel layer was V-shaped (this could be seen, although less distinctly, from Figure 2c). In the case of the impregnated silica gel layer, the upper (not fully separated) spot was rather symmetrical and the lower one was again V-shaped (this could not be seen from Figure 3c).

There is still one piece of information missing, namely that of mass distribution of the analyte in the chromatographic spots given in Figures 2c and 3c. To fill this gap, in Figure 7 we presented the 3D pictures showing the heights of the peak maxima (i.e., the amounts of the analyte in the

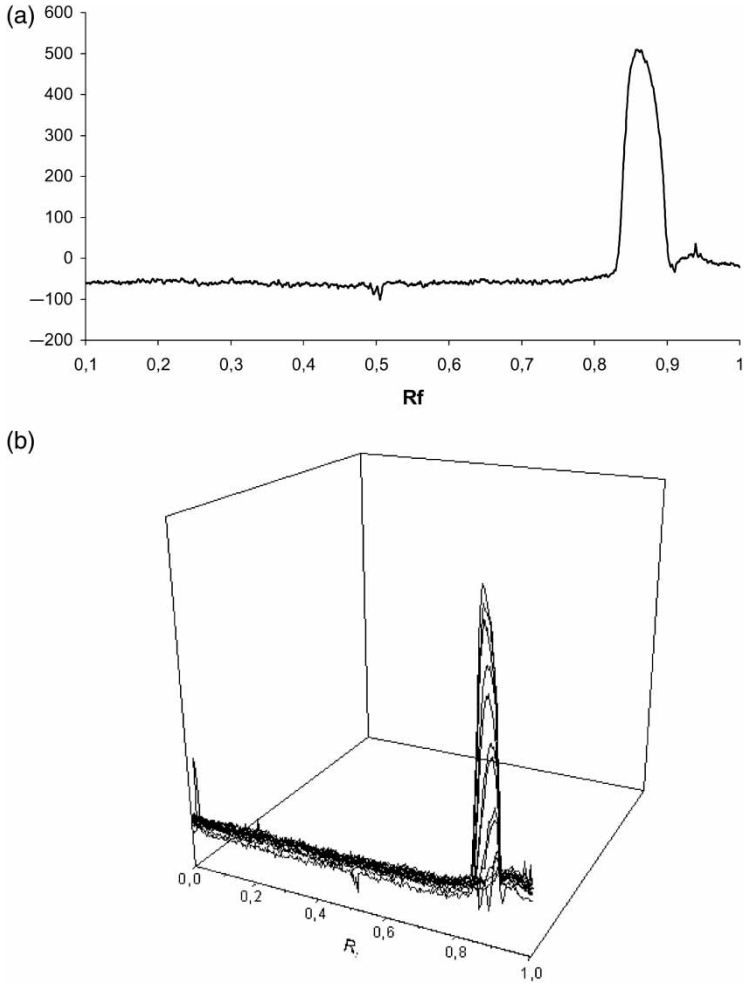

Figure 4. Densitograms of the naproxen sample (for the chromatographic spot shown in Figure 2c) chromatographed on the plain silica gel 60 F_{254} layer by means of ethanol as mobile phase at 22 $\pm$ 2°C. (a) Single scan along the vertical axis of symmetry of the spot; (b) 3D densitogram of the whole spot.

"watershed" points shown in Figures 6a and 6b) for 21 densitometric scans per one spot. As it can be seen from Figure 7a, the greatest amount of naproxen is centered at the bottom of the V-shaped spot (the same can roughly be gathered from Figure 2c) and the split double front tailing is also visible, with the mass of the sample gradually diminishing toward the front of each tail. The R_F value at the bottom of the V character is equal to 0.86 and the maximum deviation of the two separated arms of the V character from the vertical is $\pm$ 6 mm (thus, the maximum distance between these two arms equals 12 mm). It is

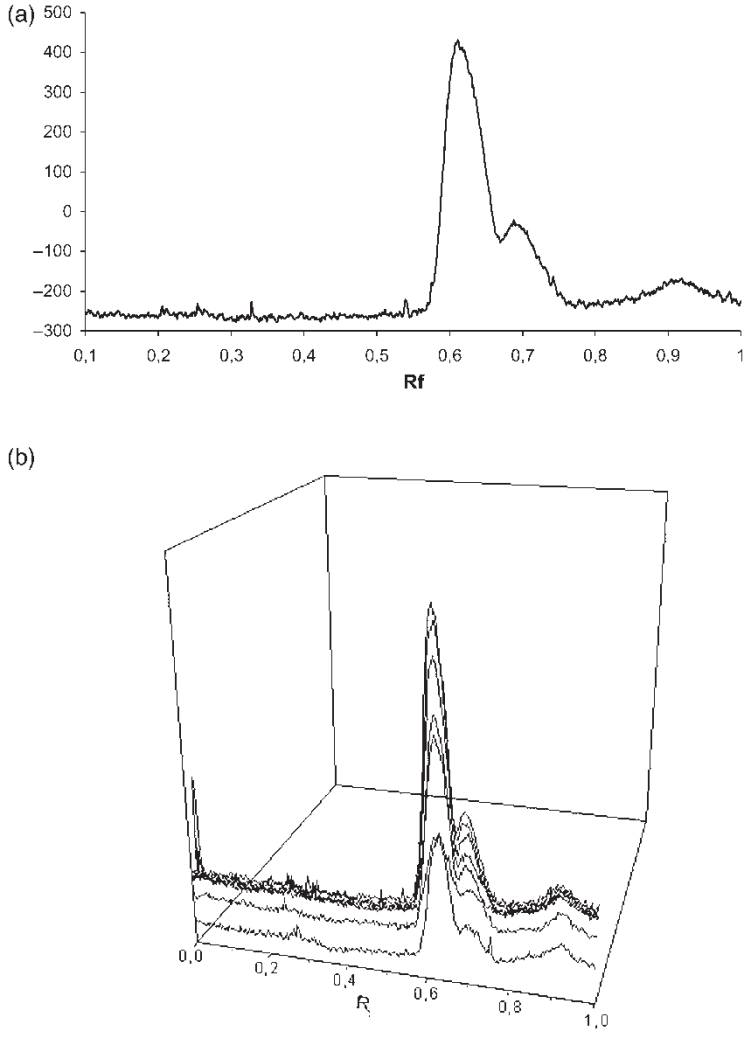

Figure 5. Densitograms of the naproxen sample (for the chromatographic spot shown in Figure 3c) chromatographed on the silica gel 60 F_{254} layer impregnated with L-arginine by means of ethanol (plus several drops of glacial acetic acid) as mobile phase at 22 ± 2°C. (a) Single scan along the vertical axis of symmetry of the spot; (b) 3D densitogram of the whole spot.

noteworthy that the bottom of the V-shaped spot deviates from the vertical by 2 mm to the right.

Mass distribution of naproxen in the "watershed" points valid for the sample developed on the impregnated silica gel layers is given in Figure 7b. Again the two chromatographic spots are clearly visible from this diagram

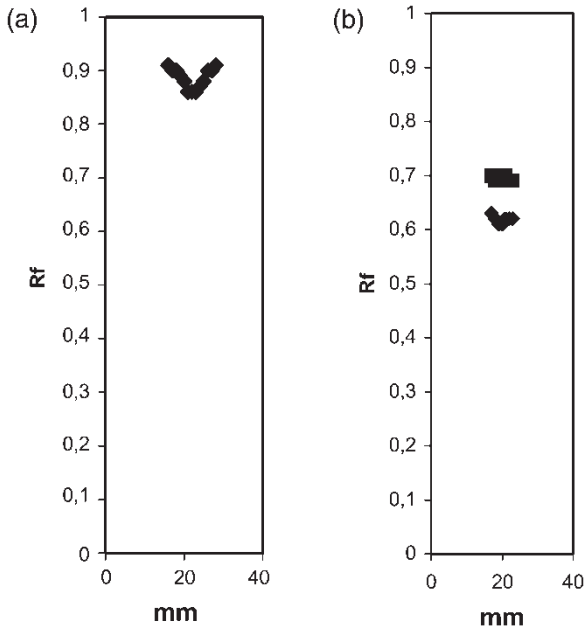

Figure 6. The chromatographic spot 'watersheds' showing the maximum R_F values for each individual densitometric scan recorded in the 1 mm intervals for the tracks 20 mm wide of the naproxen spots obtained (a) on the plain silica gel layer (Figure 2c) and (b) on the silica gel layer impregnated with L-arginine (Figure 3c).

and the predominant amount of naproxen in the more strongly retained (i.e., lower) spot is evident. It can roughly be estimated that the masses of naproxen in the two spots remain in the quantitative ratio of 1 to 3.

The results presented in this paper allow formulating the following–and rather cautious–conclusions. From the densitograms of naproxen obtained on the impregnated silica gel layer and showing two partially separated peaks (Figure 5), it clearly is evident that the analyte sample was the scalemic mixture of *S*-(+)- and *R*-(−)-naproxen. In the case of the plain silica gel layer, no vertical separation of the two naproxen antimers was observed, but the horizontal enantioseparation was most probably achieved, and each of the two skewed arms of the V character contained one antimer of the analyte (Figures 2c, 6a, and 7a). It seems that the chiral microcrystalline silica gel layer can exert horizontal enantioseparation.

In the case of the silica gel layer impregnated with L-arginine the situation was more complex. Namely, we obtained the vertical separation of the scalemic mixture of the two naproxen antimers, as shown in Figures 5, 6b, and 7b. The R_F value of the upper spot was equal to 0.69 and the lower spot again resembled the V character (R_F of its lowest part was equal to 0.61). This result can most probably be interpreted in the following way: In

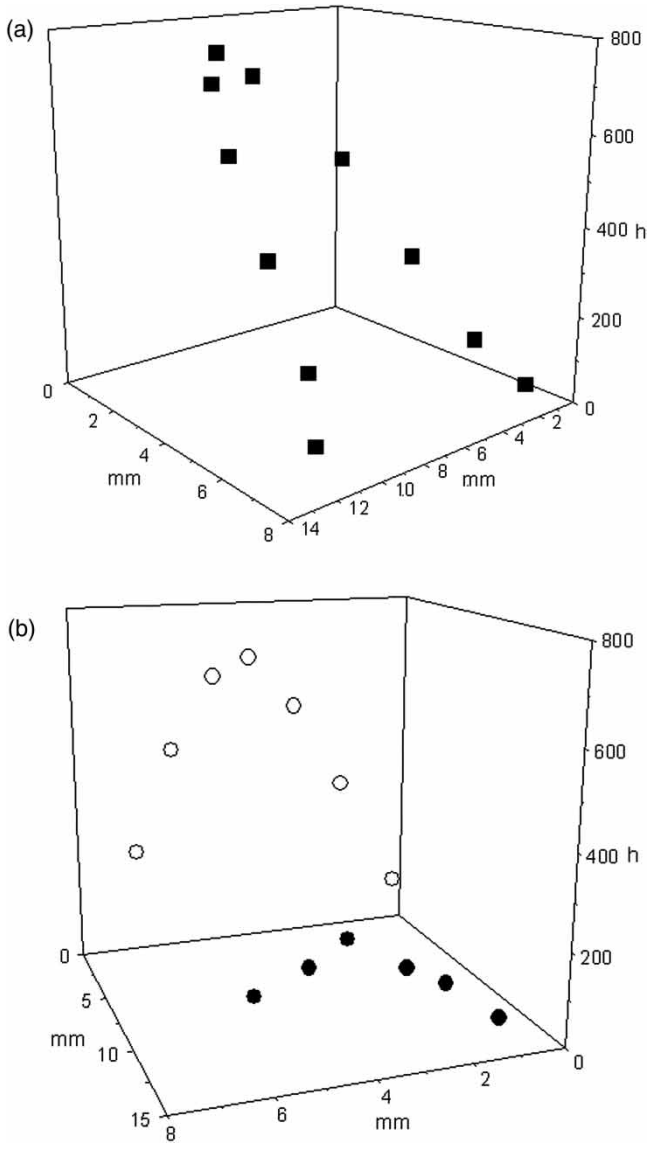

Figure 7. Diagrams showing the spot heights for the 'watershed' lines (see Figure 6) with the chromatographic spots of naproxen obtained (a) on the plain silica gel layer (Figure 2c) and (b) on the silica gel layer impregnated with L-arginine (Figure 3c).

the examined scalemic mixture of *S*-(+)-naproxen one antimer–most probably the *S*-(+) species–quantitatively predominates. As naproxen–like any other profen–is 2-arylpropionic acid, it can appear in the form of the cyclic dimers H-bonded through the two carboxylic groups. Thus, in the

scalemic mixture one can expect the presence of the two dimer types: those involving exclusively the antimer that appears in the higher amount (in our case these most probably are the *S*···*S* naproxen dimers) and of the mixed dimers (the *S*···*R* type). This is highly probable, particularly in view of the results given in paper,[9] although an ultimate confirmation could only by provided by the in situ polarimetric measurements. Thus, the upper spot in Figures 5, 6b, and 7b can probably be attributed to the optically active *S*···*S* naproxen dimer and the lower spot can be attributed to the optically inactive *S*···*R* dimer. The V shape of the lower spot (resembling that obtained on the plain silica gel layer) can be indicative of the real presence of the *S*···*R* dimer and the two arms of the V character can represent the two horizontally separated naproxen antimers. Thus, the molecular chirality of L-arginine seems apt to separate the *S*···*S* naproxen dimers from the *S*···*R* ones, and the crystalline chirality of silica gel seems apt to separate the *S*···*R* dimers to the two optically pure antimers. The results obtained for ibuprofen remain in full conformity with those valid for naproxen and, therefore, they were not introduced in this paper.

CONCLUSION

In this study, we confirmed our earlier findings regarding the diverse impact of the two different types of chirality on the 2D enantioseparation of the ibuprofen and naproxen antimers in the 1D development mode. For this purpose we used the flatbed video densitometry to record the pictures of the whole chromatograms and of the individual chromatographic spots. We also used the classical scanning densitometry to monitor the discussed enantioseparations by means of the concentration profiles of the respective antimers. It was demonstrated that the crystalline chirality of the silica gel adsorbent is most probably responsible for the horizontal enantioseparation of the scalemic (or racemic) mixtures of ibuprofen and naproxen into the two fractions of the optically pure antimers *S*-(+) and *R*-(−), whereas the molecular chirality of L-arginine deposited on the silica gel layer is responsible for the vertical enantioseparation of the scalemic mixtures into the two fractions of the H-bonded *S*···*S* and *S*···*R* dimers.

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