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Introduction and Overview

1.1 Demands in chiral bioanalysis

It is well-established that in most cases of chiral drugs the pharmacological activity is restricted to one of the enantiomers (eutomer), whereas the other enantiomer (distomer) has either no effect or may show side effects - even being toxic [Ward T.J. & Ward K.D., 2010; Gilpin R.K. & Gilpin C.S., 2009; Bartos & Gorog, 2009; Gübitz & Schmid, 2008; Tzanavaras, 2010; Christodoulou, 2010; Zeng A.G. et al., 2010]. Information on the qualitative and quantitative composition of biologically active chiral compounds (enantiomers, diastereoisomers) in various real matrices, such as biological, pharmaceutical, environmental, food, beverage, etc., is required by control authorities and it is relevant in particular research areas, [see e.g., Hashim, 2010]. Enantioselective drug absorption, distribution, metabolism, elimination or liberation studies are included among the most advanced analytical problems being solved in pharmaceutical and biomedical research. This is due to (i) the multicomponent character of biological matrices (many potentially interfering compounds per sample), (ii) a very low concentration of the analyte(s) (pg-ng/mL) among the matrix constituents present in the sample in a wide concentration scale (pg-mg/mL), (iii) identical physicochemical properties of enantiomers in an achiral environment and in many cases (iv) limited/minute amounts of the sample [Maier et al., 2001; Camilleri, 1991; Bonato, 2003; Lin C.C. et al., 2003; Scriba, 2003, 2011; Van Eeckhaut & Michotte, 2006; Hernández et al., 2008, 2010; Caslavská & Thormann, 2011].

1.2 Possibilities of capillary electrophoresis in chiral bioanalysis

Among high performance separation techniques, high performance liquid chromatography (HPLC) is the most matured, universal, robust, sensitive, selective, and therefore, the most frequently used technique (also) for the analysis of biomarkers, drugs and their metabolites in biological samples, as it can be seen from many application examples, [see e.g., Maier et al., 2001; Camilleri, 1991; Bonato, 2003; Lin C.C. et al., 2003; Scriba, 2003; Van Eeckhaut & Michotte, 2006; Hernández et al., 2008; Konieczna et al., 2010; Gatti & Gioia, 2008; El-Enany et al., 2007]. On the other hand, among the benefits of capillary electrophoresis (CE), pronounced especially in the chiral field, we can count its high separation efficiency, versatility and simplicity in the creation of (chiral) separation systems, short analysis time, good compatibility with aqueous samples and low consumption of chiral selector (low cost of enantioselective analyses) [Chankvetadze, 2007; Altria K. et al., 2006; Ward T.J. & Baker, 2008; Suntornsuk, 2010; Preinerstorfer et al., 2009; Bartos & Gorog, 2009; Ward T.J. & Ward K.D., 2010; Frost et al., 2010; Scriba, 2011]. Moreover, an analysis of recent trends indicates that CE can show real advantages over chromatographic methods, especially when a high resolution power, high sensitivity and low limit of detection/quantitation is ensured. CE meeting these criteria is directly applicable in the area of (chiral) analysis of low molecular ionic (and in some cases also neutral) compounds, such as drugs, their metabolites,

biomarkers, etc., present in complex matrices such as biological samples [Mikuš & Maráková, 2009; Bonato, 2003; Lin C.C. et al., 2003; Scriba, 2003, 2011; Van Eeckhaut & Michotte, 2006; Hernández et al., 2008, 2010; Kraly et al., 2006; Caslavská & Thormann, 2011; Kitagawa & Otsuka, 2011].

The high resolution power and low limit of detection/quantitation are provided in CE itself by (i) an extremely high peak efficiency and (ii) wide range of various applicable electromigration effects and electrophoretic experimental modes enhancing selectivity and/or decreasing limit of detection (LOD) [Mikuš & Maráková, 2009]. Among such effects/modes, the (countercurrent) movement of analytes/selectors via electroosmotic flow (EOF), countercurrent migration of charged analyte and oppositely charged selector, in-capillary stacking effects for the analyte preconcentration, removing of undesired compounds by electrokinetic injection of the sample and/or by electronic switching in on-line coupled electrophoretic systems are of the highest importance [Lin C.H. & Kaneta, 2004; Hernández et al., 2008, 2010; Chankvetadze, 1997; Chankvetadze et al., 2001; Scriba 2002; Simpson et al., 2008; Kaniansky & Marák, 1990; Danková et al., 1999; Fanali et al., 2000; Breadmore et al., 2009; Malá et al., 2009; Mikuš & Maráková, 2010].

CE matured to a highly flexible and compatible technique also enables (iii) on-line combinations of CE with nonelectrophoretic techniques (e.g., extraction, membrane filtration, microdialysis, flow injection, etc.) offering additional approaches for the highly effective sample preparation (especially sample clean-up, but also preconcentration) and separation [Breadmore et al., 2009; Chen Y. et al., 2008; Wu X.Z., 2003; Kataoka, 2003; Lü W.J. et al., 2009; de Jong et al., 2006; Mikuš & Maráková, 2010].

The utilization of unique methodological effects and modes mentioned in (ii) and (iii) can significantly enhance analytical potential and the practical use of conventional (single-column) CE, solving its weakest points, such as a poor sensitivity and high concentration LOD, high risk of capillary overloading by major sample matrix constituents and peak overlapping, by numerous matrix constituents. In this way, the need for off-line sample preparation (isolation and concentration of analytes), especially when complex matrices are used (such as proteinic blood derived samples, ionic urine samples, tissue homogenates etc.), can be overcome.

Possibilities to combine CE with various detection techniques are comparable with chromatographic techniques. The high flexibility and compatibility of CE can be demonstrated by on-column and end-column coupling (hyphenation) with powerful detection systems covering demands on extremely sensitive detection (e.g., laser induced fluorescence, LIF), as well as structural characterization of analytes (e.g., mass spectrometry, MS) [Hernández et al., 2008, 2010; Swinney & Bornhop, 2000; Hempel G., 2000; Kok et al., 1998]. Such hyphenation is an essential part of advanced CE methods applied in modern highly demanding analytical research [Mikuš & Maráková, 2009].

1.3 Aim and scope

This scientific monograph deals with the theory and practice of the advanced chiral analysis of biologically active substances, beginning with the chiral separation, continuing with sample preparation and finishing with detection. The knowledge and findings from the review and research papers (involving also the author's works) included here give an integral and comprehensive view on the progressive performance of the chiral separations, analyses in complex matrices, pharmacokinetic and metabolic studies of drugs and analysis of biomarkers in various models and real matrices. The cited papers cover mainly the period from the year 2000 until now, although several former illustrative works are also included [see extensive reviews, e.g., Mikuš & Maráková, 2009; Scriba, 2003, 2011; Bonato, 2003; Lin C.C. et al., 2003; Hernández et al., 2008, 2010; Ward T.J. & Hamburg, 2004; Natishan, 2005; Van Eeckhaut & Michotte, 2006; Ha P.T. et al., 2006; Gübitz & Schmid, 2006, 2007; Caslavská & Thormann, 2011]. Mikuš and Maráková [Mikuš & Maráková, 2009] recently provided a review on the advanced capillary electrophoresis for the chiral analysis of drugs, metabolites and biomarkers in biological samples discussing chiral, sample preparation and detection aspects supported by the application examples. Other extensive review papers by Bonato [Bonato, 2003], Caslavská and Thormann [Caslavská & Thormann, 2011] and Scriba [Scriba, 2011] cover recent advances in the determination of enantiomeric drugs and their metabolites in biological matrices (e.g., biological fluids, tissues, microsomal preparations), as well as pharmaceuticals by CE mediated microanalysis and provide, besides many examples, also a detailed background on this topic. Other beneficial review papers in this area include refs. by Lin et al. [Lin C.C. et al., 2003] discussing recent progress in pharmacokinetic applications of CE, Scriba [Scriba, 2003] giving a view on pharmaceutical and biomedical applications of chiral CE and capillary electrochromatography (CEC), Hernández et al. [Hernández et al., 2008, 2010] giving an update on sensitive chiral analysis by CE in a variety of real samples including complex biological matrices. Several other review papers dealing with pharmaceutical and biomedical applications of chiral electromigration methods have also appeared in recent years [Van Eeckhaut & Michotte, 2006; Ward T.J. & Hamburg, 2004; Natishan, 2005; Ha et al., 2006; Gübitz & Schmid, 2006, 2007].

The aim of this scientific monograph is to demonstrate comprehensively the current position of CE in the area of advanced chiral analysis of biologically active substances in samples with complex matrices (mainly biological). Therefore, the aim is not only to illustrate this by various practical applications, but, especially, to highlight and critically evaluate the progressive of the analytical approaches employed/applied in such examples. These, included in the present book, cover new findings in (i) chiral CE separation approaches (progressive arrangements of separation systems, new chiral selectors), (ii) preconcentration, purification and derivatization pretreatment of complex samples (on-line combinations of various sample preparation techniques with chiral CE) and (iii) detection monitoring of qualitative and quantitative composition of separated electrophoretic zones in complex samples (sensitive detection and/or structural evaluation of analytes). Such advanced approaches, playing a key role in the automatization and miniaturization of analytical procedures along with providing maximum analytical information, are comprehensively described in terms of basic theory, advantages and limitations, and documented by representative application examples.

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