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Separation of (*R*,*S*)-mexiletine by capillary zone electrophoresis and preparative resolution of mexiletine racemate with (*R*)- or (*S*)-mandelic acid

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Mexiletine, an antiarrhythmic substance, used in the long-term treatment of ventricular arrhythmias – due to the presence of one chiral carbon in its structure – exists in two enantiomers which have different pharmacokinetic properties. The distribution rate and the elimination of the both enantiomers are similar, but the urinary excretion of mexiletine conjugates consists predominantly of the (*R*)-enantiomer [1]. The binding of (*R*)-mexiletine to human serum proteins is higher than that of its enantiomer [2]. Maximum tissue concentration was observed at 5 min after dosage but stereoselective uptake was found only in the liver tissue and was higher for (*S*)-mexiletine. The relatively higher brain accumulation of the individual enantiomers may be related to the CNS side-effects commonly associated with mexiletine therapy [3]. The two main steps of mexiletine metabolism are aromatic and aliphatic hydroxylations, however, the hydroxylation in *p*-position of the aromatic nucleus was favored for (*S*)-mexiletine, while the (*R*)-enantiomer was predominantly metabolized by aliphatic hydroxylation [4].

Enantiomers of (*R*,*S*)-mexiletine were separated and determined by HPLC and two modifications of this method were described: separation on chiral columns (Pirkle phenylglycine [5] or Chiralcel OJ modified cellulose column [6]), and pre column preparation of diastereoisomers of (*R*,*S*)-mexiletine with *o*-phthaldialdehyde and *N*-acetyl-L-cysteine followed by separation on a RP-18 column [6].

Stereoisomers of mexiletine in a preparative scale were obtained by resolution of the racemate with L-(-)-dibenzoyltartaric acid and the absolute configuration of individual isolates was determined by X-ray analysis in combination with stereoselective synthesis [7].

Here, the separation of (*R*)- and (*S*)-mexiletine by capillary zone electrophoresis (CZE) in the presence of cyclodextrins and the preparation of both stereoisomers by crystallization of their diastereometric salts with chiral acids is described.

(*R*)- and (*S*)-Mexiletine are separated by CZE only if a chiral selector is added into the BGE. The effect of various cyclodextrins added into a TRIS/phosphate buffer (pH 2.4) was studied, however, a satisfactory separation was observed in the presence of modified cyclodextrins only (HP-BCD, HP-GCD and D-BCD, $R_s = 1.42$, 0.82 and 1.33, respectively in a BGE completed with 20 mM of cyclodextrin). The resolution of enantiomers was dependent on the concentration of the added cyclodextrin and this function for HP-BCD was expressed by the equation: $R_s = 0.029 + 0.126\ c - 0.002\ c^2$ (c in mM; regression coefficient $r^2 = 0.994$). Temperature was an another factor affecting resolution ($R_s = 0.94$ and 1.42 at 25 °C and 15 °C, respectively, in BGE with 20 mM HP-BCD). The highest resolution ($R_s = 1.65$) was observed at 30 kV, 15 °C and 30 mM HP-BCD. The (*S*)-stereoisomer of mexiletine showed a higher affinity to HP-BCD, forming a more stable complex (Fig.).

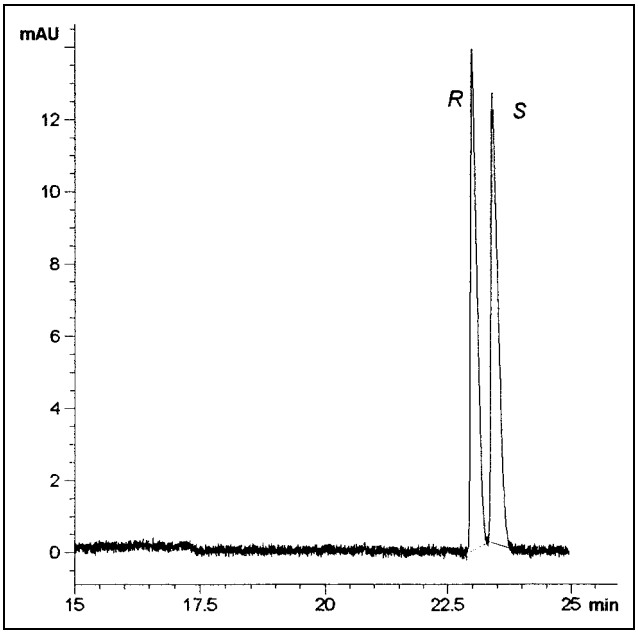
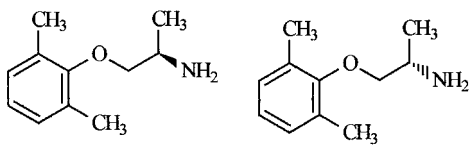


Fig.: Separation of (*R*)- and (*S*)-mexiletine by CZE 72 cm × 0.05 mm, 50 mM TRIS/phosphate, pH 2.4, 30 kV, 15 deg, 30 mM HP-BCD

Enriched enantiomers of mexiletine were prepared in a preparative scale by partial crystallization of its diastereomeric salts with (*R*)- or (*S*)-mandelic acid; after three consecutive crystallizations of a particular salt from methanol – acetone the enantiomeric excess ee was 95%. The absolute configuration of the product obtained by resolution of (*R*,*S*)-mexiletine with (*S*)- or (*R*)-mandelic acid was (*R*)- or (*S*)-mexiletine, respectively, as confirmed by optical rotation and comparison of the obtained with published data [7].



(*R*)-mexiletine (*S*)-mexiletine

Experimental

1. Apparatus and chemicals

A HP ^{3D}Capillary Electrophoresis apparatus (Hewlett Packard, Waldbronn) with a diode array detector (190–600 nm) was used for analysis. Untreated fused silica capillary tubes 72 cm (effective length 64.5 cm) with 0.05 mm ID were applied. The background electrolyte (BGE) consisted of 50 mM TRIS/phosphate buffer pH 2.4**.** The sample solutions were prepared by dissolving 2–5 mg of the compound in 0.1 M aqueous HCl. Before pressure injection (50 mbar · s^{-1}) the solutions were filtered through a 0.20 μm nylon membrane filter.

(*R*,*S*)-Mexiletine (Slovakofarma a.s., Hlohovec), (*R*)- and (*S*)-mandelic acid (Merck, Darmstadt), β-cyclodextrin (BCD), (2-hydroxy-propyl)-β-cyclodextrin (HP-BCD), (2-hydroxypropyl)-γ-cyclodextrin (HP-GCD), γ-cyclodextrin (GCD), heptakis(2,6-di-O-methyl)-b-cyclodextrin (D-BCD) (Cyclolab Ltd. Budapest); all other chemicals were of p.a. purity (Fluka AG, Buchs).

2. Resolution of (R,S)-mexiletine with (R)- or (S)-mandelic acid

(*R*,*S*)-Mexiletine (5.37 g) and (*S*)-mandelic acid (4.57 g) were dissolved in MeOH (10 ml); Me_2CO (70 ml) was added; after 3 h standing at ambient temperature crystalls were filtered off (1st crop, 1.06 g, ee = 85.6%); the filtrate was concentrated; fresh Me_2CO (50 ml) was added to the residue; after 3h the 2nd crop was filtered off (2.35 g, ee = 65.6%), similarly the 3rd crop (6.51g, ee = 45.8%) was obtained.

The 1st crop was recrystallized according to the same procedure and yielded 0.6 g, ee = 95% of (*R*)-mexiletine. The same procedure was done with (*R*)-mandelic acid.

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Mathematical evaluation of the dissolution of metronidazole from tablets

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Metronidazole is frequently used in the treatment of various anaerobic infections. It is well absorbed following oral administration. The drug is useful in prophylaxis in obstetric and gynaecological interventions, colorectal surgery and appendectomy [1]. The single oral dose is generally 250 mg, and the tablets have a high active agent content. Its use has been discussed in various papers [2–4].
The preparation of tablets with a high active agent content is particularly difficult. The aim is not to increase the weight of the tablets during tablet making. The smallest possible amounts of excipients must be applied.
The flow properties of metronidazole crystals are unsuitable, and wet granulation was therefore, selected as tablet manufacturing method. Different cellulose derivatives were chosen as binders. They exhibit surface activity and can promote the dissolution of the drug from the tablet [5]. The compositions of the tablets are listed in Table 1. Granulation was performed with a fluid bed apparatus, and tableting with an excentric tablet machine. The metronidazole dissolution rate was studied with a rotary basket method.

Table 1: Composition of the tablets

Components	Preparation 1 (mg)	Preparation 2 (mg)	Preparation 3 (mg)	Preparation 4 (mg)
Metronidazole	250.00	250.00	250.00	250.00
Avicel PH 101	33.00	33.00	33.00	33.00
Kollidon CL	10.00	10.00	10.00	10.00
Cellosize				
WP 4400 L	4.35	–	–	–
Klucel LF	–	13.2	–	–
Pharmacoat 603	–	–	3.24	–
Tylose				
MH 1000P	–	–	–	3.34
Magnesium				
stearate	2.65	1.8	1.76	1.66
Average mass	300.00	308.00	298.00	298.00

The aim of this work was to study the rate of dissolution of the drug from the tablets and to evaluate the results mathematically. Mathematical evaluation of the dissolution process is known from the literature [6, 7].
The results for metronidazole were evaluated according to the Rosin-Rammler-Sperling-Bennett-Weibull (RRSBW) distribution, and the characteristic dissolution time ($t_{63.2\%}$) was determined after linearized regression and transformation by Langenbucher according to the following equation [8]:

$$M = M_0 \left\{ 1 - \exp\left[-\frac{(t - T)^{\beta}}{a} \right] \right\} \qquad (1)$$

where M is the amount of material dissolved after time t, M_0 is the amount of initial material (maximum), T is the delay time, β is a shape parameter and a is a time parameter.
$\beta = 1$ means first-order kinetics in the dissolution process.
$\beta < 1$ means that fast liberation can be observed at the