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## Comparison of methanol and acetonitrile as solvents for the separation of sertindole and its major metabolites by capillary zone electrophoresis

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Sertindole (1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone), an atypical antipsychotic drug, was separated by capillary electrophoresis from its two main metabolites norsertindole and dehydrosertindole. The low solubility of the analytes in water (octanol-water partition coefficient is about 10<sup>5</sup>) is overcome by the use of methanol (MeOH) and acetonitrile (ACN) as solvents for the background electrolyte (BGE). Mobilities were measured in BGEs with defined pH in a broad range. It was found that in MeOH the mobility of the analytes is mainly governed by acid–base equilibria, whereas in ACN other reactions like ion pairing and homoconjugation play a pronounced role and lead to a complex pattern of the mobility as function of the pH. However, separation can be obtained in less than 10 min in both solvent systems.

**Keywords:** Capillary zone electrophoresis / Homoconjugation / Metabolites / Mobility / Non-aqueous solvents / Sertindole  
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### 1 Introduction

Sertindole (Serlect<sup>®</sup>, 1-[2-[4-[5-chloro-1-(4-fluorophenyl)-1*H*-indol-3-yl]-1-piperidinyl]ethyl]-2-imidazolidinone, SRT) is a new nonsedating atypical antipsychotic drug with high selectivity for dopaminergic neurons in the mesolimbic system [1], which has shown efficacy against both positive and negative symptoms of schizophrenia [2]. Sertindole also has affinity for adrenergic [3] and serotonergic receptors [4]; in particular, it is a serotonin 5-HT<sub>2C</sub> receptor inverse agonist [5] like clozapine (the parent drug of the atypical antipsychotic class), and this can contribute to therapeutic and side effects [6].

Sertindole was withdrawn from the market during 1999 because of QT interval prolongation observed in some patients [7]. Subsequently, however, no association with an excess of cardiac or all-cause mortality [8] was found during sertindole treatment. Thus, the European Agency for the Evaluation of Medicinal Products (EMA) has re-evaluated the drug in September 2002 and concluded that it could be re-introduced, provided that the maximum

dose is reduced to 20 mg/day, extensive ECG monitoring is carried out before and during treatment, and extensive contraindications and warnings for patients at risk of cardiac dysrhythmias are added to the patient information sheets.

Apart from cardiac side effects, sertindole appears to be well tolerated and to be associated with a very low incidence of extrapyramidal side effects [9], which are the most worrisome side effects of classical antipsychotics (such as chlorpromazine and butyrophenones). Other side effects of sertindole include weight gain, rhinitis and possibly male sexual dysfunction [2].

Sertindole is metabolized by hepatic cytochrome P450 (CYP) enzymes, namely by CYP2D6 and CYP3A4 isoforms [10], resulting in the formation of dehydrosertindole and norsertindole [11], which are the main plasma metabolites. The structures of the compounds are shown in Fig. 1.

Only a few analytical methods have been reported for the determination of sertindole and metabolites in plasma or serum, based on HPLC in combination with spectrophotometric detection [12, 13] or with different mass spectrometric techniques [13–15] mainly for screening purposes [16–18].

From Fig. 1 it can be seen that the analytes comprise several nitrogen atoms in their molecules, one of them, that in the piperidine ring, forming a secondary

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**Abbreviations:** MeOH, methanol;  $\Phi_4P^+$ , tetraphenylphosphonium