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Applicability of LC–MS/MS to optimize derivatization of topiramate with FMOC-Cl using reacted/intact drug ratio

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Highlights

- To analysis of topiramate using HPLC the drug reacted with FMOC-CL as labeling agent.
- Different factors involved in this reaction were monitored using LC–MS/MS.
- In spectra obtained from LC–MS/MS method both free and reacted topiramate are visible.
- Reacted/free topiramate ratio was used in this study as new and more accurate index.
- LC–MS/MS showed organic/aqueous phase ratio has most important role in the reaction.

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Abstract

Topiramate is an antiepileptic agent, which is structurally different from the other anticonvulsants. The drug has no UV–Vis absorption or emits fluorescence. Thus for its analysis using high performance liquid chromatography (HPLC) with conventional UV or fluorescence detectors, the drug should be derivatized with a suitable reagent. In previous study using fluorenylmethyl chloroformate (FMOC-Cl) and HPLC coupled with fluorescence detector, we reported an analytical method for derivatization and analysis of the drug in human serum. In this method, several factors including time and temperature of the reaction, pH and concentration of the used buffer, ratio of organic phase in the medium and removal of the reagent excess by glycine should be optimized to obtain maximum yield of the product. In HPLC coupled with fluorescence detector, there is not any signal from intact topiramate and only the final product (FMOC-topiramate) is appeared. Thus to optimize the reaction conditions for obtaining the highest derived yield, intensity of the final product peak is considered as a criteria for progression of the reaction. In LC–MS/MS system however, both free and reacted topiramate are visible in observed spectra. In the present study reaction of the drug with FMOC-Cl was re-optimized using LC–MS/MS technique on the basis of reacted/free topiramate ratio as the new and more accurate index. The results showed that, ratio of organic/aqueous phase has a dominant effect

on the reaction, the most efficient temperature is 70°C and the reaction is reversed following addition of the glycine.

Keywords

Topiramate; Derivatization; FMOC-Cl; LC–MS/MS; Optimization

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Introduction

Topiramate (2,3:4,5-bis-*O*-(-1-methyl)-[beta]-d-fructopyranose sulfamate), is an antiepileptic drug, which is administrated to control partial seizure with or without secondary generalization. Although the role of its therapeutic drug monitoring in management of epileptic patients and drug toxicity is not established yet [1], a reliable and simple method of analysis is needed to support clinical and pharmacokinetic studies of the drug. Current methods for assay of topiramate in biological fluids consisted of gas chromatography (GC) [2], [3], [4], fluorescence polarization immunoassay [5], [6] and LC–MS [7], [8], [9], [10], [11]. The drug, is a sulfamate-substituted monosaccharide which structurally different from other anticonvulsants and has no UV–Vis absorption or emits fluorescence. Thus for analysis of topiramate using high performance liquid chromatography (HPLC) with conventional UV–Vis or fluorescence detectors, the drug should be derivatized using a labeling agent. Derivatization of the drug by either 9-fluorenylmethyl chloroformate (FMOC-Cl) or 4-chloro-7-nitrobenzofurazan (NBD-Cl) and its analysis using HPLC coupled with fluorescence or UV detections [12], [13], [14] have been reported in our laboratory. In these methods derivatization reaction was found to be affected by different parameters including time and temperature of the reaction, pH and concentration of the used buffer, ratio of organic phase in the medium and removal of the reagent excess by glycine. These parameters should be optimized to provide the highest yield of the product. In conventional HPLC-fluorescence methods only derivatized drug is chromatographed and free topiramate is not visible. Thus, the parameters involved in the reaction are optimized to provide maximum signal intensity of the reacted drug. In LC–MS/MS system however, both reacted and un-reacted topiramate are chromatographed and can be considered to obtain the best reaction conditions. In the present study reaction of the drug with FMOC-Cl was re-optimized using LC–MS/MS technique on the basis of reacted/free topiramate ratio as the new and more accurate index.

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Chemicals

Topiramate (purity 99.5%) and FMOC-Cl were from Sigma (St. Louis, MO, USA). HPLC grade acetonitrile and methanol as well as dichloromethane, boric acid, potassium chloride, potassium hydroxide, potassium dihydrogen phosphate, triethylamine, phosphoric acid and glycine were purchased from Merck (Darmstand, Germany). Methanol and acetonitrle were of HPLC grade and all reagents were maximum available purity and used without further purification. Water was glass-double distilled and further …

LC–MS/MS study of the reaction

Reaction of topiramate with FMOC-Cl was studied by LC–MS/MS technique in both positive and negative electrospray ionization. The negative mode produces stronger mass response hence, acquisition of mass spectrometry data were made in the negative ESI. The mass parameters were optimized to obtain the highest molecular ion abundance of the analytes. The maximum ion intensity were achieved when the source temperature, ion spray current and fragmentor voltage were set at 300°C, 4000V, and 135V, …

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Chapter

Topiramate: Comprehensive profile

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> ...The present procedure, omitting extraction and drying steps, seems to be faster and simpler than the previously reported analytical methods for topiramate and was demonstrated to possess adequate sensitivity for routine therapeutic drug monitoring in plasma from patients with epilepsy. In a different study Mohammadi et al. investigated the applicability of LC-MS/MS to optimize derivatization of topiramate with FMOC-Cl using reacted/intact drug ratio [38]. The authors re-optimized the method conditions using LC-MS/MS technique on the basis of reacted/free topiramate ratio as the new and more accurate index....

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