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ORIGINAL ARTICLE

QuEChERS extraction of benzodiazepines in biological matrices

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Abstract Two common analytical chemical problems often encountered when using chromatographic techniques in drug analysis are matrix interferences and ion suppression. Common sample preparation often involves the dilution of the sample prior to injection onto an instrument, especially for liquid chromatography–mass spectrometry (LC–MS) analyses. This practice frequently does not minimize or eliminate conditions that may cause ion-suppression and therefore, suffer more from reduced method robustness. In order to achieve higher quality results and minimize possible interferences, various sample preparation techniques may be considered. Through the use of QuEChERS ("catchers"), a novel sample preparation technique used for high aqueous content samples, benzodiazepines can be extracted from biological fluids, such as blood and urine. This approach has shown increased recoveries of target compounds when using quantification by both external and internal standard. This increase in the recoveries has been attributed to a matrix enhancement and was determined through the use of the method of standard addition. While improving the overall analytical method for gas chromatography–mass spectrometry (GC–MS) analysis, it is not clear if this approach represents an overall benefit for laboratories that have both GC–MS and high performance liquid chromatography tandem mass spectrometry (HPLC–MS/MS) capability. Demonstrating evidence of variable ionization (enhancement, ion source inertness, etc.), the method of quantification should be focused on in future studies.

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1. Introduction

Benzodiazepines constitute a large and important class of pharmaceuticals displaying antiepileptic, hypnotic, tranquillizing, anticonvulsant, sedative, muscle relaxant, and amnesic properties [1]. They have been shown to be useful in treating a variety of neurological problems such as anxiety, insomnia, agitation, seizures and muscle spasms, as well as alcohol withdrawal [2].

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Due to their beneficial effects, benzodiazepines have become one of the most frequently prescribed anxiolytic drugs worldwide [3]. The benzodiazepine parent structure consists of a 1,4-diazepine fused with a benzene ring, which is termed as a 1,4-benzodiazepine, Fig. 1 [4]. As a synthetic drug having pharmacological properties, benzodiazepines are listed as a schedule IV drug in the United States.

All benzodiazepines share the same mechanism of action, which is the modulation of γ-aminobutyric acid (GABA) uptake; the principle inhibitory neurotransmitter in the brain [2,5–7]. Once bound, the benzodiazepine locks the GABA receptor into a conformation with much higher affinity for the neurotransmitter and enhances ion conduction, resulting in the reduction of neural excitability [2].

There are two main concerns associated with benzodiazepine detection: their elimination half-lives and their metabolism. While the original drug's duration in the system may not be long, their metabolites may remain in the system for an extended period of time. Benzodiazepines are mainly metabolized in the liver by cytochrome P450 isoenzymes which produce dealkylated and hydroxylated analogs of the parent compound; several of which still retain strong pharmacological properties, Fig. 2 [8]. Most of these resultant metabolites tend to exist as other commonly used and prescribed benzodiazepines.

Benzodiazepines are one of the most widely prescribed medications in the United States and are becoming more frequently encountered on the illicit market [9]. When used alone, benzodiazepines carry an extremely low risk of acute toxicity; however, they are often used with other drugs of abuse, which can enhance the toxic effects of benzodiazepines [10]. Due to their excessive utilization and their implication in many cases of multi-drug abuse, benzodiazepines are often found in fatal cases of drug intoxication. Their abuse is also on the increase with young illicit drug users. These young abusers are taking large doses which cause profound behavioral effects and can lead to dependence. Some benzodiazepines, such as flunitrazepam, are deliberately misused in case of chemical submission during sexual assault. The misuse and abuse of these drugs may increase the potential for experiencing negative drug interactions as well as the possibility of drug overdose. Given that benzodiazepines are widely used in clinical and forensic cases, the availability of rapid, sensitive, and selective analytical methods for their determination in biological fluids and pharmaceutical formulations is imperative [11–13].

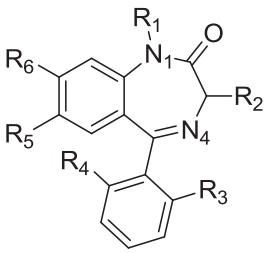

Fig. 1 Parent structure of 1,4-benzodiazepine.

Drug analysis of biological fluids (serum, plasma, urine) usually requires considerable preparation of the samples before they are injected into a chromatographic system for analysis [14]. The identification and confirmation of drugs of abuse requires an analytical technique that is highly sensitive and subjective of the different drugs.

The extraction of analytes from complex media is important because it isolates the analyte(s) of interest. Most of analytical methods attempt to minimize sample preparation steps to minimize costs and the time spent on the sample workup. Previous extraction methods for benzodiazepines include solid–phase extraction (SPE) and liquid–liquid extraction (LLE).

Current laboratory methods employ SPE sample preparation followed by liquid chromatography mass spectrometry (LC–MS). The use of SPE to isolate benzodiazepines from biological samples appears to be efficient, but this methodology carries along with it many disadvantages including irreversible adsorption of analytes on the packing, more complex method development, and batch-to-batch variability [15]. The utilization of LC–MS methods is also associated with various limitations, such as significant time and effort involved in sample preparation, low screening capacity for target contaminants, and insufficient capabilities for structural identification of non-target contaminants [16]. In addition to its limitations, one common concern with LC–MS analysis is ion suppression. Ion suppression is a matrix effect that negatively affects detection capability, and therefore precision and accuracy

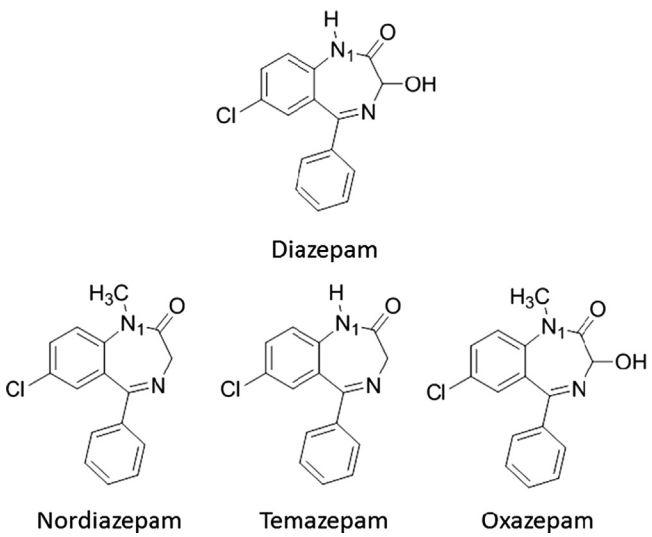

Fig. 2 Diazepam and its three main pharmacological metabolites [8].

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