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ORIGINAL ARTICLE

Micellar HPLC method for the simultaneous determination of three anticonvulsant drugs in dosage forms and biological fluids. Application to dissolution-rate testing

Méthode HPLC micellaire de détermination simultanée de trois médicaments anticonvulsivants dans les formes médicamenteuses et les liquides biologiques. Application aux tests de dissolution

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Dissolution testing and human urine and plasma

Summary This work describes a micellar liquid chromatographic method which was developed and validated to determine simultaneously three structurally-related antiepileptic drugs; namely carbamazepine (CMZ), oxcarbazepine (OCZ) and eslicarbazepine acetate (ECZ). The analysis was achieved using a phenyl column (250 mm × 4.6 mm i.d., 5 μm particle size), a mobile phase consisting of a mixture of 0.3% triethylamine and 10% n-butanol in a solution of 0.05 M sodium dodecyl sulphate adjusted to pH 7.0 using 0.02 M orthophosphoric acid. The mobile phase was pumped at a flow rate of 1.5 mL min^{-1} and detection was adjusted at 215 nm. The method showed good linearity ($r^2 > 0.998$) over the concentration ranges of 0.1—10 for CMZ and OCZ and 0.2—20 μg mL^{-1} for ECZ. The suggested method was successfully applied for the analysis of the studied drugs in their dosage forms and for the determination of CMZ and OCZ in spiked human urine and plasma without prior extraction. The proposed method was further extended to the analysis of real samples of plasma and urine of volunteers receiving therapy of CMZ and OCZ. Furthermore, the method was successfully applied to tablets dissolution-rate testing, and the results were satisfactory.

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MOTS CLÉS
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Carbamazépine ;
Oxcarbazépine ;
Acétate d'eslicarbazépine ;
Test de dissolution ;
Dosages urinaires et plasmatiques

Résumé Ce travail décrit une méthode de chromatographie liquide micellaire qui a été développée et validée pour déterminer simultanément trois anticonvulsivants structurellement liés, à savoir la carbamazépine (CMZ), l'oxcarbazépine (OCZ) et l'acétate d'eslicarbazépine (ECZ). L'analyse a été réalisée à l'aide d'une colonne à groupements phényle (250 mm × 4,6 mm i.d., taille des particules 5 μm), une phase mobile composée d'un mélange de 0,3 % de triéthylamine et 10 % de n-butanol dans une solution de 0,05 M de sodium dodécyl sulfate, ajusté à pH 7,0 à l'aide d'acide orthophosphorique 0,02 M. La phase mobile était pompée à un débit de 1,5 mL/min^{-1} et la détection a été ajustée à 215 nm. La méthode a montré une bonne linéarité (r^2 > 0,998) sur les plages de concentration de 0,1—10 pour la CMZ et OCZ et 0,2—20 μg mL^{-1} pour l'ECZ. La méthode proposée a été appliquée avec succès pour l'analyse de ces substances dans leurs formes pharmaceutiques et pour la détermination de la CMZ et de l'OCZ dans des échantillons enrichies d'urine humaine et de plasma sans extraction préalable. La méthode proposée a été étendue à l'analyse d'échantillons réels de plasma et d'urine de bénévoles recevant un traitement de la CMZ et OCZ. En outre, la méthode a été appliquée avec succès à des tests de dissolution de comprimés, et les résultats ont été satisfaisants.

Introduction

Epilepsy is one of the most common serious neurological disorders [1]. Different forms of epilepsy are treated by a wide variety of pharmacological treatments so as to provide a better life for most patients. Several new antiepileptic drugs (AEDs) were introduced into clinical practice, considering the therapeutic options beyond the traditional first-line medications, such as carbamazepine (CMZ), which is the first generation of AEDs (Fig. 1). CMZ is one of the choices for partial seizures and hemifacial spasm treatment [1]. New AEDs, such as oxcarbazepine (OCZ), which is the second generation of AEDs, decreased epilepsy treatment side effects and is used as monotherapy or adjunctive therapy in the treatment of partial seizures (Fig. 1) [1,2]. Because the epileptic patients are still suffering from seizures, extensive research has been conducted for ideal AEDs such as eslicarbazepine acetate (ECZ), which is the third generation of AEDs (Fig. 1) [3]. ECZ was approved for use in Europe, the United States and Canada as an adjunctive therapy for partial-onset seizures [4]. CMZ is official in both the British Pharmacopoeia (BP) [5] and the United States Pharmacopoeia (USP) [6] while OCZ is the subject of a monograph in BP [5].

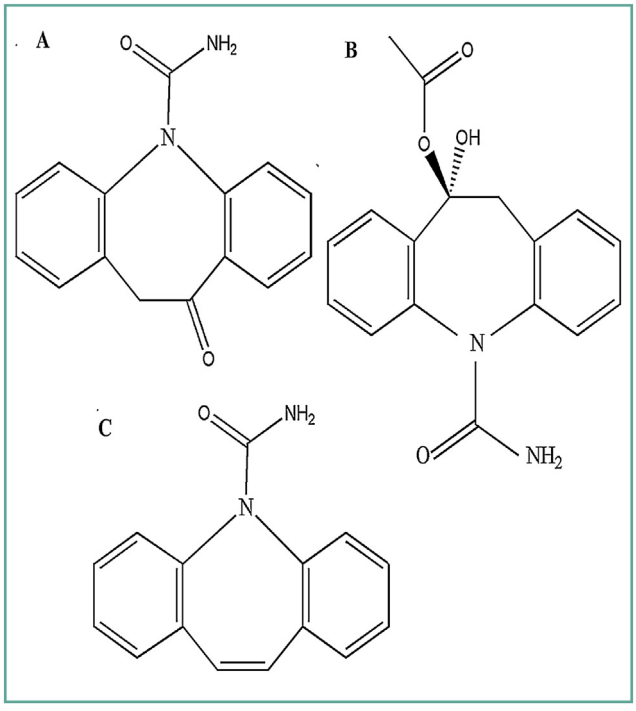

Figure 1. Structural formulae of (A) OCZ, (B) ECZ and (C) CMZ.
Formules développées des (A) OCZ, (B) ECZ et (C) CMZ.

For the estimation of CMZ in dosage forms and biological fluids, several analytical methods were developed; including spectrophotometry [7—9], high performance liquid chromatography (HPLC) [10—15] and gas chromatography [16]. For the determination of OCZ, spectrophotometry [17,18], HPLC [15,19—24] and HPTLC [25] were used. Similarly for ECZ; the reported methods include spectrophotometry [26] and HPLC [4,27—31]. A very few methods have been reported in literature for the simultaneous analysis of OCZ and ECZ, viz HPLC [32,33] and for CMZ, OCZ and ECZ HPLC methods [34,35] were also reported. The previously reported methods require tedious extraction procedures for clean-up from the endogenous compounds of plasma or urine samples, and this requires the use of toxic organic solvents; in addition to risk of the loss of the drugs during the extraction process [32,35].

Dissolution testing is an essential in-vitro test in pharmaceutical industry to characterize solid dosage forms. It appears as a useful tool that can give important information about similarity of a product; so, it is one of the most significant quality control tests of solid dosage forms. Poorly soluble drugs in recent years are increasing the need for finding suitable conditions for their routine quality control [36], such as dissolution-rate testing.

Micellar HPLC has been frequently reported for the separation of a number of drugs [37—40]. The field of the

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