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ORIGINAL ARTICLE

Validated stability-indicating HPLC-DAD method for determination of the recently approved hepatitis C antiviral agent daclatasvir

Méthode de détermination stabilité-indicative par CLHP-barrette de diodes de l'agent antiviral de l'hépatite C récemment approuvé, le daclatasvir

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HPLC;
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Forced degradation

Summary A comprehensive stability indicating HPLC with diode array detection method was developed for the determination of the recently approved antiviral drug daclatasvir dihydrochloride (DCV) which is used for the treatment of chronic Hepatitis C Virus (HCV) genotype 3 infection. Effective chromatographic separation was achieved using Waters C8 column (4.6 × 250 mm, 5 μm particle size) with isocratic elution of the mobile phase composed of mixed phosphate buffer pH 2.5 and acetonitrile in the ratio of 75:25 (by volume). The mobile phase was pumped at a flow rate of 1.2 mL/min, and quantification of DCV was based on measuring its peak areas at 306 nm. DCV eluted at retention time 5.4 min. Analytical performance of the proposed HPLC procedure was thoroughly validated with respect to system suitability, linearity, range, precision, accuracy, specificity, robustness, detection and quantification limits. The linearity range was 0.6—60 μg/mL with correlation coefficient > 0.99999. The drug was subjected to forced degradation conditions of neutral, acidic and alkaline hydrolysis, oxidation and thermal degradation. The proposed method proved to be stability-indicating by resolution

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of the drug from its forced-degradation products. The validated HPLC method was successfully applied to analysis of the cited drug in its tablets.

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MOTS CLÉS
CLHP ;
Détection barette de diode ;
Daclatasvir ;
HCV ;
Methode indicatrice de stabilité ;
Dégradation forcée

Résumé Une méthode de détermination par CLHP à barrette de diode du médicament antiviral récemment approuvé, le daclatasvir dichlorhydrate (DCV) utilisé pour le traitement de l'infection par le génotype 3 du virus de l'hépatite C (HCV), est proposée. Une séparation chromatographique efficace a été obtenue en utilisant une colonne Waters C8 (4,6 × 250 mm, taille de particule 5 μm) avec élution isocratique avec une phase mobile composée de tampon phosphate à pH 2,5 et d'acétonitrile dans un rapport de 75:25 (en volume). La phase mobile a été pompée à un débit de 1,2 mL/min et la quantification du DCV était basée sur la détection à 306 nm. Le DCV élue à un temps de rétention de 5,4 min. La performance analytique de la méthode CLHP a été validée de façon approfondie en ce qui concerne la pertinence du système, la linéarité, le range, la précision, la spécificité, la robustesse, les limites de détection et de quantification. La plage de linéarité était de 0,6—60 μg/mL avec un coefficient de corrélation > 0,99999. Le médicament a été soumis à des conditions de dégradation forcée d'hydrolyse neutre, acide et alcaline, d'oxydation et de dégradation thermique. La méthode proposée s'est avérée être une indicatrice de stabilité par la résolution du médicament et de ses produits de dégradation forcée. La méthode CLHP validée a été appliquée avec succès à l'analyse du médicament dans des comprimés.
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Introduction

Hepatitis C is a chronic infection associated with considerable morbidity and mortality. In recent years, there has been a shift in treatment methods with the discovery and approval of agents that target specific proteins vital for hepatitis C virus (HCV) replication. Daclatasvir (DCV) (Fig. 1) is an inhibitor of HCV nonstructural protein NS5A. DCV is an oral, direct-acting antiviral with potent activity that has been recently approved in many countries worldwide. In vitro data show that DCV exerts a very potent antiviral effect against several HCV genotypes. Clinical trials proved that oral regimen comprising DCV plus sofosbuvir with or without ribavirin is an important option for use in patients with chronic HCV genotype 1, 3 or 4 infection, including patients with advanced liver disease, post-transplant recurrence and HIV-1 co-infection [1—4].

Few methods of analysis for DCV can be found in the scientific literature. Determination of DCV in human plasma has been carried out using liquid chromatography-tandem mass spectrometry (LC-MS/MS) [5,6] and UPLC-MS/MS [7]. Recently, a chiral HPLC method has been described for separation of DCV enantiomers [8]. On the other hand, a RP-HPLC with UV detection method has been proposed for assay of DCV tablet dosage form and for dissolution study [9]. To the best of our knowledge, no comprehensive forced degradation and stability-indicating report could be found for the estimation of DCV.

The objective of this work is to develop a simple, rapid, selective and reliable HPLC with diode array detection method for the quantitative analysis of DCV in pure and in tablets dosage form. The method was thoroughly validated and tested for its specificity and stability-indicating properties by resolution of DCV from its forced hydrolytic, oxidative and dry heat degradation products.

Experimental

Instrumentation

The HPLC system with diode array detector (DAD) consisted of Waters 2695 Alliance (quaternary pump, vacuum degasser heater, diode array and multiple wavelength detector Waters 2996) connected to a computer loaded with MILLENNIUM32 Login Version 4.00 Software. An automated injector model SM7 with loop capacity 100 μL was used. The column used was Waters C8 (4.6 × 250 mm, 5 μm particle size). Filtration of solutions prior injection to the column was done using cellulose nitrate membrane filters (0.45 μm pore size) (Sartorius Stedim Biotech GmbH, Goettingen, Germany).

Materials and chemicals

Daclatasvir dihydrochloride was kindly donated by Pharco Pharmaceuticals Co., Alexandria, Egypt. HPLC-grade acetonitrile (Carbon Group Ringaskiddy, Cork, Ireland), HPLC-grade methanol (Lab-scan, Gliwice, Poland), reagent-grade potassium dihydrogen phosphate, dipotassium hydrogen phosphate and phosphoric acid (Scharlau Chemie S.A., Sentmenat, Spain), analytical grade of hydrochloric acid (BDH

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