Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy 194 (2018) 141–151

Contents lists available at ScienceDirect

Spectrochimica Acta Part A: Molecular and Biomolecular Spectroscopy

journal homepage: www.elsevier.com/locate/saa

Chemometric simultaneous determination of Sofosbuvir and Ledipasvir in pharmaceutical dosage form

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ARTICLE INFO

Article history:
Received 18 August 2017
Received in revised form 29 November 2017
Accepted 3 January 2018
Available online 6 January 2018

Keywords:
Sofosbuvir
Ledipasvir
Simultaneous determination
Partial least squares
Continues wavelet transform
Derivative spectrophotometry

ABSTRACT

Partial least squares (PLS), different families of continuous wavelet transform (CWT), and first derivative spectrophotometry (DS) techniques were studied for quantification of Sofosbuvir (SFB) and Ledipasvir (LDV) simultaneously without separation step. The components were dissolved in Acetonitrile and the spectral behaviors were evaluated in the range of 200 to 400 nm. The ultraviolet (UV) absorbance of LDV exhibits no interferences between 300 and 400 nm and it was decided to predict the LDV amount through the classic spectrophotometry (CS) method in this spectral region as well. Data matrix of concentrations and calibrated models were developed, and then by applying a validation set the accuracy and precision of each model were studied. Actual concentrations versus predicted concentrations plotted and good correlation coefficients by each method resulted. Pharmaceutical dosage form was quantified by developed methods and the results were compared with the High Performance Liquid Chromatography (HPLC) reference method. Analysis Of Variance (ANOVA) in 95% confidence level showed no significant differences among methods.

1. Introduction

Hepatitis C is an infection that caused by hepatitis C virus (HCV) and affects the liver [1]. This virus transmits through blood from intravenous drug use, unsterile medical equipment, and blood transfusions to people [2]. HCV infects 170 to 200 million people all over the world, has been labeled the 'silent epidemic' as result of its concealed attack on the liver [3]. Between 8000 and 10,000 deaths result annually from the disease in the United States alone [4]. There is severe risk of life threatening complications like liver disease and hepatocellular carcinoma in people with cirrhosis resulting from chronic infection with the HCV [5]. To date, no vaccines can be used to prevent HCV infection in human [6]. Although toxicities, poor tolerability, and adverse reactions of different combinations of interferon, pegylated alpha interferon, ribavirin, telaprevir, and boceprevir as prior treatment of six major genotypes of HCV are clear, they were prescribed before recent developed pharmaceutics to treat the disease [7]. Recently combination of sofosbuvir (SFB) and ledipasvir (LDV) as a novel agent to cure chronic hepatitis C genotype 1 infection is introduced [8]. The drug received regulatory approval in the United States in October 2014 and contains 400 mg of SFB and 90 mg of LDV (in the form of ledipasvir acetone (LDV-AS)) [9]. SFB and LDV are nucleotide NS5B and NS5A inhibitors respectively. These two inhibitors attack special HCV proteins and inhibit viral replication [10].

SFB is a white to off-white, non-hygroscopic crystalline solid, slightly soluble in water (pH 1.2–7.7), freely soluble in Ethanol, Acetonitrile and Acetone, soluble in 2-propanol, and insoluble in heptane and its chemical name is (*S*)-isopropyl-2-((*S*)-(((2*R*,3*R*,4*R*,5*R*)-5-(2,4-dioxo-3,4-dihydropyrimidin-1(2H)-yl)-4-fluoro-3-hydroxy-4-methyltetrahydrofuran-2-yl)methoxy) (phenoxy) phosphorylamino) propanoate. LDV is a white to tinted (off-white, tan, yellow, orange, or pink), slightly hygroscopic crystalline solid. It is pH depended to solvate in aqueous media. Its solubility in pH 2.3 buffer is slightly, but in pH 4–7.5 buffer is practically insoluble. It dissolves in Ethanol, Acetonitrile, and Dimethyl sulfoxide freely and slightly in Acetone. The chemical name of LDV- AS is methyl [(2*S*)-1-{(6*S*)-6-[5-(9,9-difluoro-7-{2-[(1*R*,3*S*,4*S*)-2-{(2*S*)-2-[(methoxycarbonyl)amino]-3-methylbutanoyl}-2azabicyclo[2.2.1]hept-3-yl]-1*H*-benzimidazol-6-yl}-9*H*-fluoren-2-yl)-1*H*-imidazol-2-yl]-5-aza spiro[2.4]hept-5-yl}-3-methyl-1-oxobutan-2-yl] carbamate propan-2-one (1:1) [11]. Structures of compounds have shown in Fig. 1A and B, respectively.

To date several methods have been reported in the literature using various analytical techniques for analysis of SFB and LDV for clinical purposes, such as ultra-performance liquid chromatography-mass/mass (UPLC–MS/MS) method for the quantification of direct antiviral agents like SFB and LDV in human plasma [12] Simultaneous determination of SFB and LDV in rat plasma by UPLC–MS/MS [5], quantification of SFB and LDV in human plasma by UPLC–MS/MS [13], UPLC-MS/MS for

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https://doi.org/10.1016/j.saa.2018.01.011
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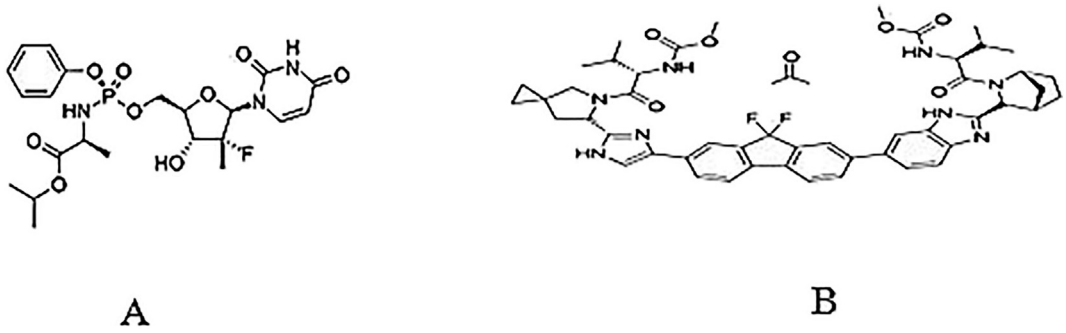

Fig. 1. Chemical Structures of (A) SFB and (B) LDV.

SFB in human plasma [14], Reversed Phase-High Performance Liquid Chromatography (RP-HPLC) method for simultaneous determination of SFB and LDV in tablet dosage form [15].

According to the cost and time consumption quiddity of chromatographic methods, applying some faster and more economical techniques like spectrophotometric methods to determine the proposed analytes seems more profitable. These methods popularity caused by instrumental accessibility, procedures simplicity, satisfying speed, adequate precision, and copasetic accuracy turn them to fully functional techniques. Despite the fact that these techniques are more profitable, classic spectrophotometry (CS) in case of facing with analyte mixture spectrum overlapping is not suitable, and in this way, simultaneous analysis of analytes deal with the obstacles. Thanks to the growing trend of chemometrics in addition to signal processing techniques, it is possible to overcome this shortcoming.

Chemometrics is the science of relating measurements made on a chemical process to get more information from the huge amount of data via the application of mathematical or statistical methods and signal processing techniques can explain as application of kinds of operations on the sequence of measurements with the goal of information quality enhancement. These approaches are used in the qualitative and quantitative analysis. To limit the text to quantitative scope, it would be focused on a multivariate calibration method, which involves the use of multiple variables (e.g. the response at a range of wavelengths). In point of fact, Partial Least Squares (PLS) is one of the best examples of chemometrics methods applied in order to quantify targets frequently [15,16] due to its ability to tackle some problems like interactions, band overlaps and co-linearity [17]. In this technique, spectral and the concentration data were used for data decomposition.

As a strong signal processing approach, combination of wavelet transfer (WT) method with calibration techniques such as PLS has been used to determine active ingredients in analytical chemistry issues [18,19]. Here a signal function or vector decomposition like simpler, fixed building blocks at different scales and positions derived from a spectrum is included [20]. The reason why WT has applied in a vast range of analytical analysis in an efficient way is its efficiency and a

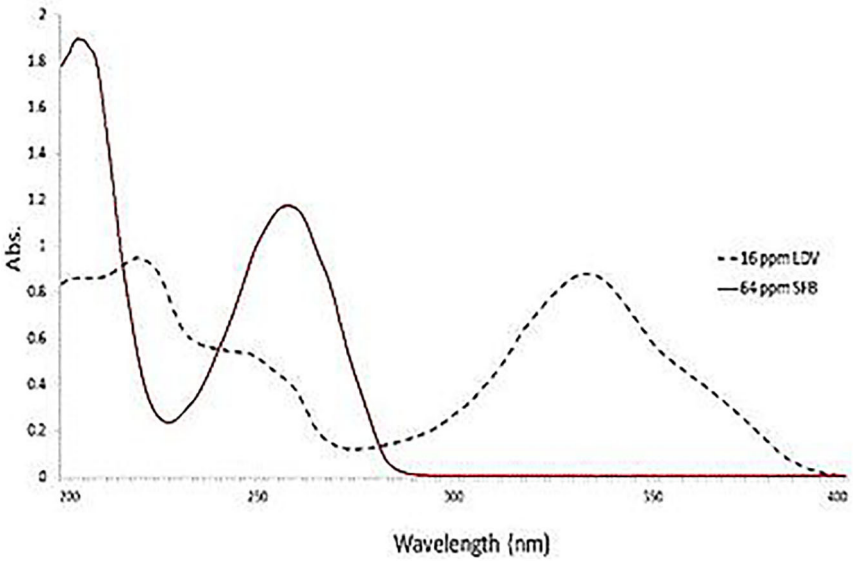

Fig. 2. UV absorption spectra of SFB and LDV.