World Journal of Pharmaceutical Sciences
ISSN (Print): 2321-3310; ISSN (Online): 2321-3086
Available online at: http://www.wjpsonline.org/
Review Article

Analytical and Bio-analytical Methods of Telbivudine: A Review

M. Gnana Chandrika, M. Vamsi Krishna and K. Padmalatha

Department of Pharmaceutical Analysis, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada-521108, Andhra Pradesh, India

Received: 01-06-2020 / Revised Accepted: 19-06-2020 / Published: 01-07-2020

ABSTRACT

Telbivudine is a synthetic thymidine nucleoside analog with specific activity against the hepatitis B virus. Telbivudine acts by inhibiting HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'–triphosphate. This leads to the chain termination of DNA synthesis, thereby inhibiting viral replication. HPLC and LC-MS/MS methods have been reported for the estimation of telbivudine in bulk drugs, pharmaceutical formulations and biological fluids. In this review we have presented the different analytical and bio-analytical methods reported for the telbivudine.

Keywords: Telbivudine, Hepatitis B virus, Analytical and bio-analytical methods

Address for Correspondence: M. Gnana Chandrika, Department of Pharmaceutical Analysis, Vijaya Institute of Pharmaceutical Sciences for Women, Enikepadu, Vijayawada-521108, Andhra Pradesh, India; **E-mail:** chandrika.bharathi@gmail.com

How to Cite this Article: M. GnanaChandrika, M. Vamsi Krishna and K. Padmalatha. Analytical and Bio-analytical Methods of Telbivudine: A Review. World J Pharm Sci 2020; 8(7): 12-15.

This is an open access article distributed under the terms of the Creative Commons Attribution-NonCommercial-ShareAlike 4.0 International License, which allows adapt, share and build upon the work non-commercially, as long as the author is credited and the new creations are licensed under the identical terms.

© 2020 World J Pharm Sci

INTRODUCTION

Telbivudine is a synthetic thymidine nucleoside analog with specific activity against the hepatitis B virus. Telbivudine is orally administered, with good tolerance, lack of toxicity and no dose-limiting side effects. The chemical name for telbivudine is 1-((2S,4R,5S)-4-hydroxy-5hydroxymethyltetrahydrofuran-2-y1)-5-methyl-1H-pyrimidine-2,4-dione, or 1-(2-deoxy-β-L-ribofuranosyl)-5methyluracil. Telbivudine is the unmodified β-L enantiomer of the naturally occurring nucleoside, thymidine. Its molecular formula is $C_{10}H_{14}N_2O_5$, which corresponds to a molecular weight of 242.23. Structure of telbivudine is given in figure 1.

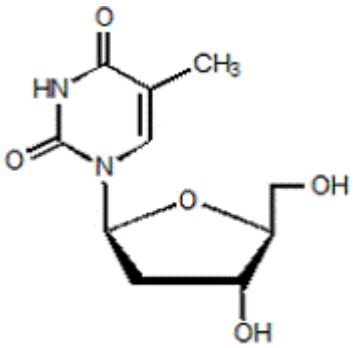

Figure 1: Structure of telbivudine

Telbivudine is a white to slightly yellowish powder. Telbivudine is sparingly soluble in water (greater than 20 mg per mL), and very slightly soluble in absolute ethanol (0.7 mg per mL) and n-octanol (0.1 mg per mL).

Telbivudine inhibits HBV DNA polymerase (reverse transcriptase) by competing with the natural substrate, thymidine 5'–triphosphate. This leads to the chain termination of DNA synthesis, thereby inhibiting viral replication. Incorporation of telbivudine into viral DNA also causes DNA chain termination, resulting in inhibition of HBV replication. Telbivudine inhibits anticompliment or second-strand DNA. In this article we are presenting different analytical and bio-analytical methods available for the Telbivudine.

Analytical and Bio-analytical Methods:

Raj kumar and subramanyam [1] developed a novel, stability-indicating reversed-phase high performance liquid chromatography (RP-HPLC) method for the quantitative determination of telbivudine in active pharmaceutical ingredients and in its Pharmaceutical dosage form by using develosil C18, 5µm, 150 x 4.6 mm i.d. column with a mobile phase containing a mixture of acetonitrile: phosphate buffer (pH 3.0) (40:60v/v) and conditions optimized were flow rate (1.0 ml/minute), wavelength (273 nm), run time was 10 min and a peak eluted at 3.52 min and column oven temperature was maintained ambient. Calibration curve was plotted with a range from 0-40µg/ml. Stress degradation conditions were established for telbivudine by subjecting it to acid, base, oxidation and thermal stress. The stress samples were assayed against a qualified reference standard and found that 5, 10 and 8% was degraded in acid, base and peroxide conditions respectively.

Sangeetha D et al., [2] developed and validated stability indicating method for telbivudine by RP-HPLC in bulk drug. The chromatographic separation was performed by using mobile phase consisting of acetonitrile and phosphate buffer in the ratio of 70:30 % v/v. The column used was ODS-HG-5 (150×4.6 mm, 5µ) with flow rate of 0.8 ml/min using PDA detection at 274nm. The described method was found to be linear over the range of 70-120µg/ml and correlation coefficient was found to be 0.993. The results of the study showed that the proposed RP-HPLC method is simple, rapid, precise, reliable, accurate and economical which is useful for the routine determination of telbivudine in bulk drugs.

Bicui Chen et al. [3] determined telbivudine in the plasma of chronic hepatitis B patients by high-performance liquid chromatographic-tandem mass spectrometry. In this study, a sensitive, rapid and safe quantitative bioanalytical method has been established by using LC-MS/MS for the determination of telbivudine in a clinical study of chronic hepatitis B (CHB) patients. The assay was linear in a dynamic 10-10,000 ng/mL range (r2> 0.999) and total analysis time was 6 min in this method. The validated method was applied to quantitatively determine plasma concentration in CHB patients during long-term telbivudine treatment. The results revealed that telbivudine concentration in creatinekinase (CK)-elevated group (707.92- 2788.78 ng/mL) was significantly higher than those of normal CK (412.63- 1108.32 ng/mL). This method was adapted for therapeutic drug monitoring.

Chromatographic separation was performed on an Inertsil Sustain C18 Column (3 µm, 3.0 mm I.D. ×100 mm L., Shimadzu.). Mobile phase A is 0.1 % formic acid in Purified Water [v/v] and mobile phase B is acetonitrile were operated with a gradient elution program at a flow rate of 0.4 mL/min. The auto-sampler temperature was maintained at 10 °C. The amount of injected sample was 1 µL. Mass spectrometry was operated in positive electrospray ionization (ESI) and multiple reaction monitoring (MRM) mode.

Zhou et al. [4] evaluated pharmacokinetics of telbivudine in adult patients with chronic hepatitis

B virus (HBV) infection following once-daily oral administration at escalating doses of 25, 50, 100, 200, 400, and 800 mg/day for 4 weeks. Plasma concentrations of telbivudine were assessed by a validated high performance liquid chromatographic (HPLC) method with UV detection. Mobile phase used was 20 mM phosphate buffer containing 2% [v/v] acetonitrile. Reverse-phase chromatography was performed with 50 µl aliquots on a NovapakC18 column. Elution was carried out isocratically at 1 ml/min. The retention time of telbivudine was approximately 4.9 min. Telbivudine was monitored at 267 nm. This assay was characterized by a lower limit of quantitation of 0.1 µg/ml, intra- and interday precisions (coefficients of variation [CVs]) from 1.1 to 10.6%, and accuracies (percent deviation) from -3.3 to 6.1%.

Zhou et al [5] studied the influence of food on the pharmacokinetics of telbivudine, following 600 mg oral dose administration with and without a high fat/ high-calorie meal. Plasma samples were analyzed for telbivudine concentration using a validated high-performance liquid chromatography (HPLC) method with massspectrometric (MS/MS) detection. Reverse-phase chromatography was performed on a TSK-GEL Amide- 80 column (4.6 × 150 mm, 5 µ; Tosoh Bioscience). Elution was carried out isocraticallyat 1 mL/min with a mobile phase of 90:10 (v/v) methanol:25 mM ammonium formate (pH 3.5). Under these conditions, the retention time was approximately 1.68 min for telbivudine. Telbivudine was monitored using mass analyzer at mass transition of 243.0 to 127.1m/z. This assay has a lower limit of quantitation (LOQ) of 10 ng/mL, with a calibration curve range from 10 to 5000 ng/mL. Intra- and interday precision (percentage coefficient of variation) and accuracy (percentage deviation) ranged from 2.3% to 5.6% and –4.2% to 1.4%, respectively. Results of study indicated that absorption of telbivudine was not affected by a high-fat/high-calorie meal.

De Nicolò et al. [6] developed UPLC–MS/MS method for the simultaneous quantification of Entecavir, lamivudine, telbivudine and tenofovir in plasma of HBV infected patients. Chro-matographic separation was performed through an Acquity UPLC®HSS T3 1.8 µm (2.1 × 150 mm) column, protected by a frit [0.2 µm, 2.1 mm] (Waters, Milan, Italy) precoloumn, at 40^0C using a column thermostat. Mass spectrometer was settled in the positive ion mode (ES+), with a capillary voltage of 1.0 kV, a source temperature of 150^0C and a desolvation temperature of 400^0C. The nitrogen gas flow was 800 L/h and 50 L/h for desolvation and cone, respectively. Cone voltages were: 40 V, 20 V, 15 V and 30 V for tenofovir, lamivudine, telbivudine and entecavir, respectively. Mobile phase used was water and acetonitrile both containing 0.05% formic acid and run in a gradient mode.

Pei Hu et al. [7] studied single-dose and multiple-dose pharmacokinetics and safety of telbivudine after oral administration in healthy chinese subjects by using LC-MS/MS. Plasma and urine concentrations of telbivudine were quantitated using validated high-performance liquid chromatographic (HPLC) methodologies with tandem mass spectrometric (MS/MS) detection. Liquid chromatography was performed on a TSK-GEL Amide-80 column (4.6 × 150 mm, 5 µm; Tosoh Bioscience). For plasma extracts, elution was performed isocratically at 1 mL/min with a mobile phase of 90:10 (volume/volume [v/v]) methanol:25mM ammonium formate (pH 3.5). Under these conditions, the retention time was approximately 1.69 minutes for telbivudine. For urine extracts, elution was performed isocratically at 1 mL/min with a mobile phase of 98:2 (v/v) methanol:formic acid (1%, v/v). Under these conditions, the retention time was approximately 3.80 minutes for telbivudine.

Zhou et al. [8] conducted pharmacokinetics of telbivudine in healthy subjects and drug-drug interactions between telbivudine and lamivudine or adefovirdipivoxil. Plasma samples were analyzed for telbivudine, lamivudine, and adefovir by using validated high-performance liquid chromatography and tandem mass spectrometry (MS/MS) methodologies. Chromatography was performed on a TSK-GEL Amide-80 column (4.6 by150 mm, 5 µm; Tosoh Bioscience). Elution was carried out isocratically at 1 ml/min with a mobile phase of 90:10 (v/v) methanol–25 mM ammonium formate (pH 3.5). Under these conditions, the retention times were approximately 1.68 and 1.73 min for telbivudine and lamivudine, respectively. The steady-state plasma pharmacokinetics of lamivudine or adefovir were not markedly affected by the co-administration of telbivudine.

CONCLUSIONS

HPLC and LC-MS/MS methods have been reported for the estimation of telbivudine in bulk drugs, pharmaceutical formulations and biological fluids. HPLC methods have been used for the stability studies and LC-MS/MS methods have been reported for the pharmacokinetic studies.

REFERENCES

1. Raj Kumar B, Subrahmanyam KV, A new validated stability-indicating RP-HPLC method for the determination of telbivudine. Journal of Global Trends in Pharmaceutical Sciences2014;5(3):1827- 32.
2. Sangeetha D et al. Stability indicating method development and validation of telbivudine by RP HPLC in bulk drug, Asian Journal of Pharmaceutical Science & Technology 2015; 5 (2): 70-3.
3. Chen B et al. Determination of Telbivudine in the Plasma of Chronic Hepatitis B Patients in Long-Term Treatment by High-Performance Liquid Chromatographic-Tandem Mass Spectrometry, Biomed Chromatogr., 2018; 32(4):doi: 10.1002/bmc.4140.
4. Zhou X J et al. Pharmacokinetics of telbivudine following oral administration of escalating single and multiple doses in patients with chronic hepatitis B virus infection: pharmacodynamic implications. Antimicrob. Agents Chemother2006;50: 874- 9.
5. Zhou X J et al. Brown. Absence of food effect on the pharmacokinetics of telbivudine following oral administration in healthy subjects. J. Clin. Pharmacol 2006; 46: 275- 81.
6. De Nicolò A et al.UPLC–MS/MS method for the simultaneous quantification of anti-HBVnucleos(t)ides analogs: Entecavir, lamivudine, telbivudineandtenofovir in plasma of HBV infected patients. J. Pharm. Biomed. Anal. 2015; 114: 127–32.
7. Hu P et al. Single-dose and multiple-dose pharmacokinetics and safety of telbivudine after oral administration in healthy Chinese subjects. J. Clin. Pharmacol. 2006;46: 999- 1007.
8. Zhou X J et al. Pharmacokinetics of telbivudine in healthy subjects and absence of drug interaction with lamivudine or adefovirdipivoxil. Antimicrob. Agents Chemother.2006;50: 2309- 15.