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Stability indicating spectrophotometric method for determination of brivudine

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ABSTRACT

A stability indicating spectrophotometric method was developed for the determination of brivudine in presence of its degradation products. Hence an attempt was made to develop stress degradation and stability indicating studies of Brivudine. UV Spectrophotometric method was reported for the estimation of Brivudine in formulation. Characterization of degradation products of Brivudine photometric method by demonstration of different degradation behavior has been performed as per the current ICH guidelines. The UV spectrophotometric method is found to be simple, specific, sensitive, reproducible and precise because of good recovery and low standard deviation values. Since the developed method shown no interference from the excipients like talc, magnesium stearate etc. these method can be used for the routine analysis of Brivudine from its dosage form. Brivudine absorbance was slightly increased by oxidation degradation study. Stress degradation studies on Brivudine as per ICH guidelines were illustrated. From the studies we can conclude, that the drug is stable under all stress degradation conditions because the λ_{max} should not change. But slight changes occur in thermal degradation due to the variation of % RSD. Hence the proposed method is suitable for the analysis of Brivudine.

Keywords: Brivudine, Stability indicating, Spectrophotometric method

INTRODUCTION

This compound belongs to the class of organic compounds known as pyrimidine 2'-deoxyribonucleosides. These are compounds consisting of a pyrimidine linked to a ribose which lacks a hydroxyl. Brivudine is a synthetic nucleoside analogue and is phosphorylated intracellularly to its active 5'-triphosphate metabolite, lamivudine triphosphate (L-TP). This nucleoside analogue is incorporated into viral DNA by HIV reverse transcriptase and HBV polymerase, resulting in DNA chain termination. Brivudine is well absorbed after oral administration and absorption is not affected by food. There is high first-pass metabolism in the liver to bromovinyluracil, which lacks antiviral activity. At steady state (brivudine 125 mg daily for 5 days),

the *C*max and *C*min are 1.7 µg/mL (at 1 hour) and 0.06 µg/mL, respectively. The plasma terminal elimination half-life is approximately 16 hours; metabolites are excreted in urine (65%) and plasma (21%). Brivudine is highly protein-bound (>95%).

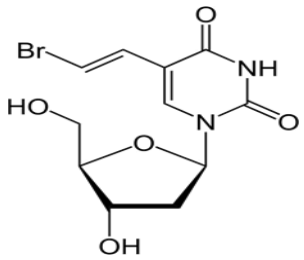

Figure 1. Structure of Brivudine

Brivudine is available as a 125 mg tablet and as a 0.1% ointment for ophthalmologic use. The standard dose for herpes zoster is 125 mg orally once daily for 7days. Plasma half-life is approximately 16 hours. Brivudine is available as a 125 mg tablet and as a 0.1% ointment for ophthalmologic use. The standard dose for herpes zoster is 125 mg orally once daily for 7 days. As this drug is not taken as combination no potentially dangerous interactions are reported so far. In clinical trials with brivudine, the most commonly observed adverse effects were nausea (2.1%), abdominal pain (0.8%), vomiting (0.5%) and headache (1%) and did not differ significantly from adverse effects reported with aciclovir or famciclovir. Rare cases of brivudine-as acute hepatitis and delirium have been reported. Brivudine has a critically important drug interaction that has been an obstacle to its regulatory approval in some countries. Literature survey revealed that, hardly very few UV Spectrophotometric methods was reported for the estimation of Brivudine in formulation [1]. Hence an attempt was made to develop stress degradation and stability indicating studies of Brivudine.

MATERIALS AND METHODS

Selection of solvent

Solubility of the drug was done by trial and error method Brivudine has been diluted in methanol and showed a better distribution spectrum at the wavelength of 250nm so was selected as the solvent of choice.

Preparation of standard stock solution

Stock solution of 10mg in 100ml was prepared from this 1 ml was taken in a 10ml standard flask and made up to the volume with methanol to get concentration of 100µg/ml.

Selection of wavelength

From the stock solution 4µg/ml of Brivudine was prepared separately using methanol. The solution was scanned between 200-400nm and spectra was recorded. Brivudine exhibited maximum absorbance at 250nm [2]. Hence 250nm was selected as wavelength (λ_{max}) for the proposed study.

Preparation of standard curves

A dilution was prepared from standard stock solution to get a concentration ranging from 2-10µg/ml using ethanol. Absorbance of these solutions was measured at 250nm the measured absorbance was plotted against concentration [3]. From the graph it was found that the Brivudine showed the linearity range between the 2-10 µg/ml

METHOD VALIDATION

The method developed UV / visible spectrophotometric method as per ICH guidelines was validated in terms of linearity, accuracy, precision.

LINEARITY

Brivudine was found to be linear in a range of 2-10µg/ml. The absorbance of the solution was measured at 250nm, and calibration graph was plotted using concentration Vs absorbance. The

slope, intercept and correlation coefficient value of formulation were found to be 0.9982 and for pure drug were found to be 0.999

ACCURACY

The accuracy, specificity, suitability and validity of the present method were studied by conducting percentage recovery studies. A known quantity of the pure drug was added to the pre-analyzed sample formulation at 50%, 100% levels [4, 5]. The percentage drug recovery was calculated.

PRECISION

Intra-day assay

Intra-day precision was studied by measuring the absorbance of the standard drug solution repeatedly on same day. Solution of 4µg/ml was used for the study. Inter-day precision was studied by measuring the absorbance of the standard drug solution repeatedly on different days [6]. Solution of 4µg/ml was used for the study.

STRESS DEGRADATION STUDIES OF BRIVUDINE

Acidic hydrolysis

To 6mg of drug dissolved in 20ml of Methanol and make up to 100ml by using 2M HCl and the solution was treated for 6 hour at 80ºC on water bath. After the reaction the resultant degradation sample was diluted into 6µg/ml&8µg/ml by using 2M HCl. The forced degradation in acid media was performed in the dark in order to exclude possible photo-degradation. The degraded sample was cooled at room temperature and neutralized with NaOH.

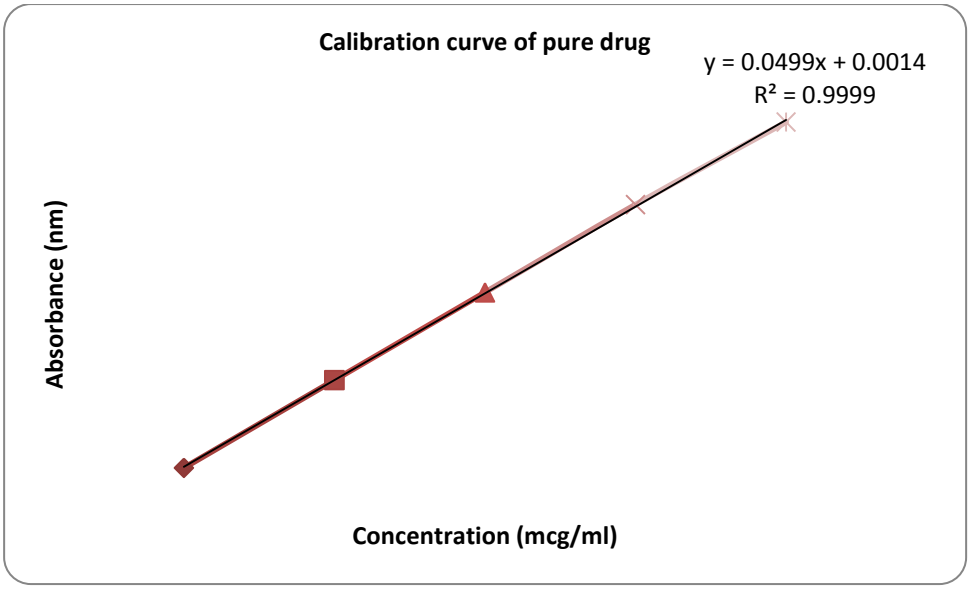

Figure 2. Calibration curve of pure drug

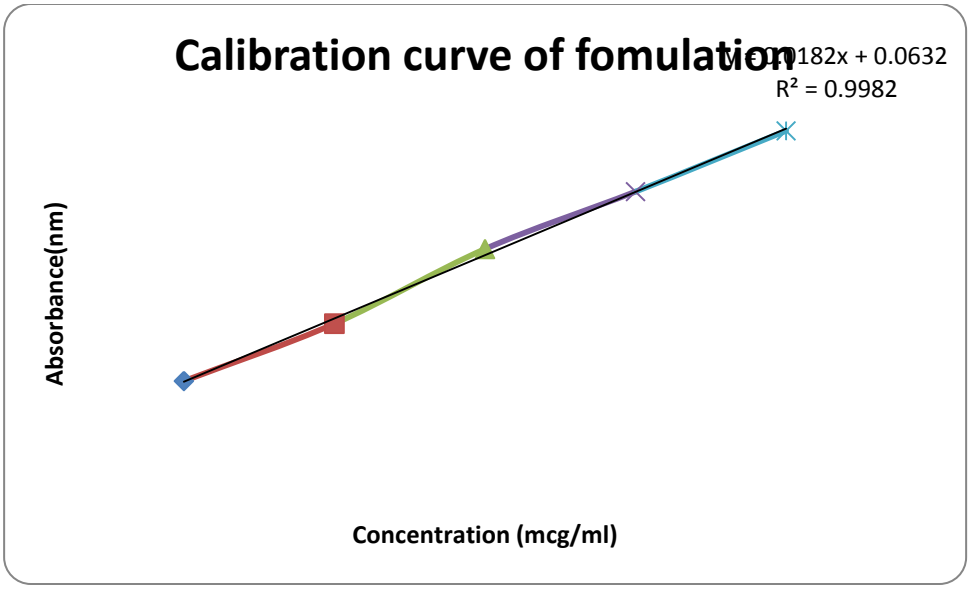

Figure 3. Calibration curve of formulation

RESULTS AND DISCUSSION

Table 1: Results of forced degradation study

S. No	Degradation Condition		RSD
1	Acid Hydrolysis	6	0.327
		8	0.4830
2	Alkaline Hydrolysis	6	0.5649
		8	0.48076
3	Oxidative	6	0.8617
		8	0.3558
4	Thermal Stability	6	0.98039
		8	0.2877
5	Photochemical Stability	UV Chamber at 254 nm	0.3268
			0.2780
		UV Chamber at 365 nm	0.5649
			0.4830
		Sunlight	0.3274
			0.2766

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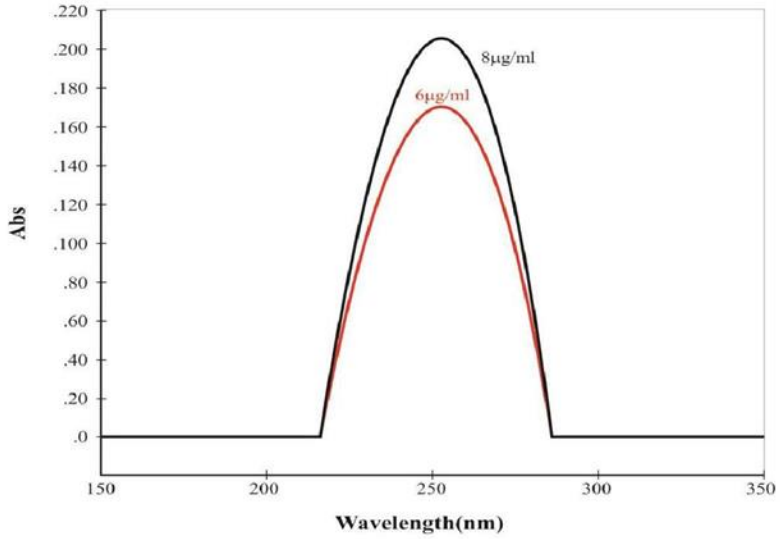

Figure 4. Acid Hydrolysis

Oxidative hydrolysis

To 6mg of drug dissolved in 20ml of Methanol and make upto100ml by using 3%v/v H2O2 and the solution was treated for 6 hour at 80ºC on water bath. After the reaction the resultant degradation sample make concentration 6&8µg/ml by using 3%v/v H2O2. The forced degradation in oxidative media was performed in the dark in order to exclude possible photo-degradation. The degraded sample was cooled at room temperature and neutralized with buffer.

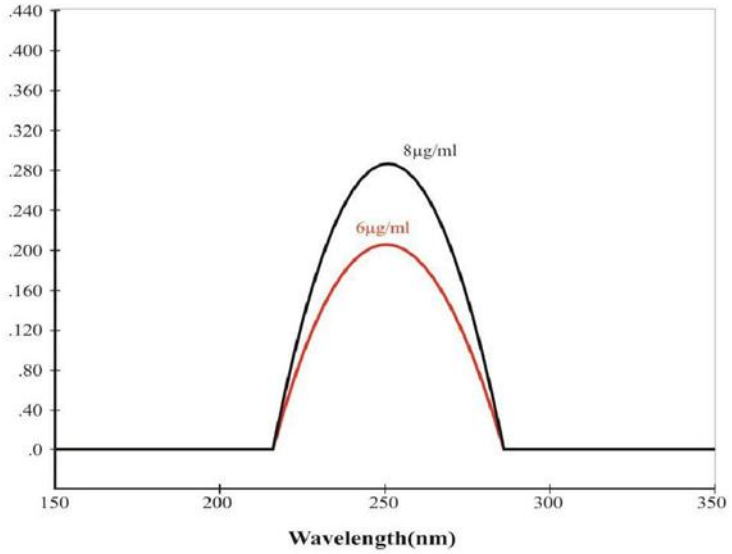

Figure 5. Oxidative Degradation

CONCLUSION

The UV visible-spectrophotometric method is found to be simple, specific, sensitive, reproducible and precise because of good recovery and low standard deviation values. Since the developed method shown no interference from the excipients like talc, magnesium stearate etc. these method can be used for the routine analysis of Brivudine from its dosage form. Brivudine absorbance was slightly increased by oxidation degradation study. Stress degradation studies on Brivudine as per ICH guidelines were illustrated. From the studies we can conclude, that the drug is stable under all stress

degradation conditions because the λ_{max} should not change. But slight changes occur in thermal degradation due to the variation of % RSD.

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