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A REVIEW ON LAMIVUDINE & ABACAVIR IN BULK & PHARMACEUTICAL DOSAGE FORM

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ABSTRACT

A simple and rapid high performance liquid chromatographic method was developed and validated for simultaneous estimation of abacavir and lamivudine in their tablet dosage form. Abacavir is an antiretroviral drug used to treat HIV/AIDS. Lamivudine (2′,3′-dideoxy-3′-thiacytidine, commonly called 3TC) is a potent nucleoside analog reverse transcriptase inhibitor (nRTI). In the present study focus is laid on this combination drug, the retention times of Lamivudine and Abacavir were found to be 0.9 min and 4.5 min respectively. Hence, the developed method can be successfully employed for routine quality control of Lamivudine and Abacavir in drug testing laboratories and pharmaceutical industries.

KEYWORDS: Antiretroviral agents, Lamivudine, Abacavir, RP-HPLC, HIV.

1. INTRODUCTION

Abacavir and lamivudine are synthetic nucleoside analogs showing a potent and synergistic effect on inhibition of the human immunodeficiency virus (HIV-1), the causative agent of acquired immunodeficiency Syndrome **(**AIDS). HIV encodes at least three enzymes: protease, reverse transcriptase and endonuclease. The abacavir and lamivudine belong to the class of nucleoside reverse transcriptase inhibitors (NRTI). New therapeutic strategy of AIDS treatment requires the combination of these antiretroviral (ARV) drugs.[2]

1.1 Lamivudine

Lamivudine (2′,3′-dideoxy-3′-thiacytidine, commonly called 3TC) is a potent nucleoside analog reverse transcriptase inhibitor (nRTI). Lamivudine has been used for treatment of chronic hepatitis B at a lower dose than for treatment of HIV/AIDS. It improves the

seroconversion of e-antigen positive hepatitis B and also improves histology staging of the liver.[3]

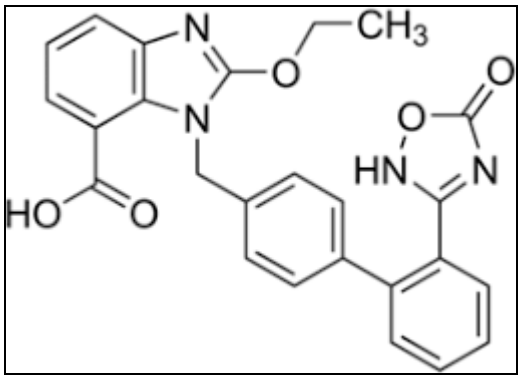

Fig. 1: Structure of Lamivudine.

Table 1: General profile of Lamivudine.

Category	Treatment of HIV infection and chronic hepatitis B (HBV).
Chemical Name	4-amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3-oxathiolan-5-yl]-1,2-dihydropyrimidin-2-one
Molecular Formula	C8H11N3O3S
Molecular Weight	229.254 g/mol
Description	White crystalline powder.
Solubility	Freely soluble in ethanol, DMSO, and dimethyl formamide (DMF),
PKa	13.83
Melting point	175-177° C

1.1.1. Mechanism of action

Lamivudine is an analogue of cytidine. It can inhibit both types (1 and 2) of HIV reverse transcriptase and also the reverse transcriptase of hepatitis B virus. It is phosphorylated to active metabolites that compete for incorporation into viral DNA. They inhibit the HIV reverse transcriptase enzyme competitively and act as a chain terminator of DNA synthesis. The lack of a 3'-OH group in the incorporated nucleoside analogue prevents the formation of the 5' to 3' phosphodiester linkage essential for DNA chain elongation, and therefore, the viral DNA growth is terminated.

1.1.2. Pharmacokinetics

After oral administration of lamivudine, it is well absorbed. And about 0.1 g of adult oral about 1hr reached peak plasma concentration Cmax 1.1-1.5 u g/ml, bioavailability is 80-85%. and at the same time of food taking, the Tmax delayed 0.25-2.5 HR and lower 10-40% of Cmax, but the bioavailability is unchanged. Intravenous administration research results table

Ming lamivudine average distribution capacity is 1.3 L/Kg, system average clearance rate of 0.3 L/h/kg, seventy percent by organic cation transport system and renal clearance and elimination half-life is 5-7hr. within the therapeutic dose range and lamivudine pharmacokinetics showed a linear relationship, the plasma protein binding rate is low. In vitro studies have shown that with serum albumin binding rate is <16-36%. It can pass through the blood brain barrier into the cerebrospinal fluid.

1.2. Abacavir

Abacavir is chemically {(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9-yl] cyclopent-2- en-1-yl} methanol. It has molecular formula C14H18N6O and Molecular weight of 286.332 g/mol. It is a white to off-white solid freely soluble in water.[23]

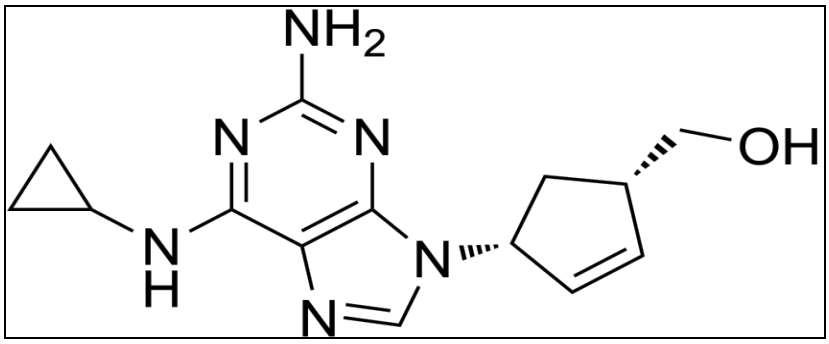

Fig. 2: Structure of Abacavir.

Table 2: General profile of Abacavir.

Category	Anti-Retroviral agents.
Chemical Name	[(1S,4R)-4-[2-amino-6-(cyclopropylamino)-9H-purin-9- yl]cyclopent-2-en-1-yl]methanol
Molecular Formula	C14H18N6O
Molecular Weight	286.3323 g/mol
Description	white to off-white solid
Solubility	soluble in Water, chloroform, Methanol
PKa	15.41 (Acidic) 2.19(Basic)
Melting point	165 °C to 170 °C
Storage	Keep container tightly closed in a dry and well-ventilated place.

1.2.1. Mechanism of action

Abacavir is a carbocyclic synthetic nucleoside analogue and an antiviral agent. Intracellularly, abacavir is converted by cellular enzymes to the active metabolite carbovir triphosphate, an analogue of deoxyguanosine-5'-triphosphate (dGTP). Carbovir triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) both by competing with the natural substrate dGTP and by its incorporation into viral DNA. Viral DNA growth is terminated

because the incorporated nucleotide lacks a 3'-OH group, which is needed to form the 5′ to 3′ phosphodiester linkage essential for DNA chain elongation.

1.2.2. Pharmacokinetics

Rapid and extensive after oral administration (83% bioavailability, tablet). When a 300 mg tablet is given twice daily to subjects, the peak plasma concentration (Cmax) was 3.0 ± 0.89 mcg/mL and the area under the curve (AUC 0-12 hours) was 6.02 ±1.73 mcg•hr/mL Moderate (approximately 50%). Binding of abacavir to plasma protein was independent of concentration. Hepatic, by alcohol dehydrogenase and glucuronosyltransferase to a 5′-carboxylic acid metabolite and 5′-glucuronide metabolite, respectively. These metabolites have no antiviral activity. Abacavir is not significantly metabolized by cytochrome P450 enzymes. Elimination of abacavir was quantified in a mass balance study following administration of a 600-mg dose of 14C- abacavir: 99% of the radioactivity was recovered, 1.2% was excreted in the urine as abacavir, 30% as the 5′-carboxylic acid metabolite, 36% as the 5′-glucuronide metabolite, and 15% as unidentified minor metabolites in the urine. Fecal elimination accounted for 16% of the dose. Renal excretion of unchanged abacavir is a minor route of elimination in humans.

1.2.3. Adverse reaction

Adverse reactions of a more intense character including epigastric, discomfort, nausea, and vomiting followed by diarrhoea, drowsiness, weakness, dizziness, malaise and headache might be seen.

2. REPORTED METHOD IS CATEGORIZED DEPENDING ON THE FOLLOWING CONSIDERATIONS

Sr. no	Drug	Method	Description	Details	Ref.no.
1	Lamivudine and Abacavir in pharmaceutical Dosage form.	RP-HPLC	**Column**	non polar column-Kromasil 250 mm × 4.5mm, 5 µm,	[1]
			Mobile phase	buffer:acetonitrile (65:35)	
			Flow rate	1 mL/min	
			Wavelength	257 nm	
			Retention time	2.250 min and 2.734 min	
2	Lamivudine and Abacavir in pharmaceutical Dosage form.	RP-HPLC	**Column**	Inertsil ODS (150×4.6, 5µm)	[2]
			Mobile phase	phosphate buffer:Acetonitrile (pH 4.0)	
			Flow rate	1ml/min	
			Wavelength	254 nm	
			Retention time	4.107 min and 2.487 min	
3	Lamivudine and	RP-HPLC	**Column**	Inertsil ODS 250 x 4.6 mm, 5mm	[3]

	Abacavir in pharmaceutical Dosage form.		**Mobile phase**	buffer: acetonitrile:methanol(50:20:30%v/v/v)	
			Flow rate	1.0 ml/min	
			Wavelength	225nm	
			Retention time	2.2 min and 2.9 min	
4	Lamivudine and Abacavir in pharmaceutical Dosage form.	RP-HPLC	**Column**	Symmetry Premsil C18 (250 mm × 4.6 mm, 5 µm) column	[4]
			Mobile phase	methanol: water (0.05% orthophosphoric acid with pH3) 83:17 v/v	
			Flow rate	1ml/min.	
			Wavelength	245 nm	
			Retention time	7.4 min and 3.5 min	
5	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	RP-HPLC	**Column**	Phenomenex C18 (250 x 4.6 mm, 5 µm particle size) column	[5]
			Mobile phase	phosphate buffer (pH 7.8) and methanol in the ratio of 50:50 % v/v.	
			Flow rate	1.0 mL/min	
			Wavelength	216 nm	
			Retention time	3.147 min and 6.367 min	
6	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	RP-HPLC	**Column**	Inertsil ODS column (4.6×150mm) 5µm	[6]
			Mobile phase	phosphate buffer pH 3.5: acetonitrile: water in the ratio 60:30:10	
			Flow rate	1.0 ml/min	
			Wavelength	245 nm	
			Retention time	1.692 min and 2.210 min	
7	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	RP-HPLC	**Column**	Zorbax C18 (4.6 nm×150 mm), 3.5 µm)	[7]
			Mobile phase	water:methanol (50:50 v/v)	
			Flow rate	1.5 ml/min	
			Wavelength	270 nm	
			Retention time	10.71 min and 3.66 min	
8	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	UPLC	**Column**	zodiac sil RP C18 (4.6 mm × 250 mm, 3.0 µm) column	[8]
			Mobile phase	phosphate buffer (pH 3.0) and methanol in the ratio of 30:70 %v/v	
			Flow rate	0.25 ml/min	
			Wavelength	260 nm	
			Retention time	1.763 min and 2.247 min	
9	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	UPLC	**Column**	Symmetry C18 (2.1 × 100mm, 1.7mm, Make: BEH) or equivalent in an Isocratic Mode	[9]
			Mobile phase	Phosphate Buffer (60%) [pH 3.0] & Methanol (40%) [UPLC Grade]	
			Flow rate	0.25 ml per min	
			Wavelength	280 nm	
			Retention time	1.019 min and 1.271 min	
10	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	HPLC	**Column**	HiQ Sil C 18 V column	[10]
			Mobile phase	0.01 M potassium dihydrogen ortho-phosphate (pH 3.0)	

				and methanol (55:45 v/v)	
			Flow rate	0.8 mL/min	
			Wavelength	272 nm	
			Retention time	3.8 min and 6.3 min	
11	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	HPLC	**Column**	C18 column	[11]
			Mobile phase	water: methanol (70: 30 v/v) with 0.1 % potassium dihydrogen phosphate pH 3.2	
			Wavelength	270 nm	
12	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	HPLC	**Column**	5µm C18 column having dimensions (150X4.6mmid)	[12]
			Mobile phase	methanol: water (70:30, v/v/)	
			Flow rate	1.4 ml/min	
			Wavelength	275nm	
			Retention time	2.259 min and 3.499 min	
13	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	HPLC	**Column**	column C18 150 X 5.0 cm	[13]
			Mobile phase	38:62(v/v) methanol and 1% ortho phosphoric acid	
			Flow rate	0.9 ml/min	
			Wavelength	255nm	
			Retention time	6.8 ± 0.3 and 2.6 ±0.3	
14	Lamivudine and Abacavir in pharmaceutical Tablets Dosage form.	RP-HPLC	**Column**	HiQ Sil C 18 V column	[14]
			Mobile phase	0.01 M potassium dihydrogen ortho-phosphate (pH 3.0) and methanol (55:45 v/v)	
			Flow rate	0.8 mL/min	
			Wavelength	272 nm	
			Retention time	3.8 min and 6.3 min	
15	Lamivudine and Abacavir in human plasma	LC	**Column**	Hypurity Advance C18	[15]
			Mobile phase	acetonitrile:0.1% formic acid (76:24, v/v)	
			Flow rate	0.8 mL/min	
			Retention time	1.13 min & 1.49 min	

3. CONCLUSION

Many methods for determination of Lamivudine and Abacavir have been reported. Some HPLC assay methods were used to monitor Lamivudine and Abacavir. Methods for the analysis of active and inactive metabolites of Lamivudine and Abacavir in Rat and Human plasma have also been reported. Some articles related to the determination of Lamivudine and Abacavir alone or in combination pharmaceutical dosage forms have been mentioned. Lamivudine and Abacavir are antiviral drug used to restrict the replication of virus. A sensitive UPLC -UV, method was developed for the estimation of Lamivudine and Abacavir in bulk and pharmaceutical dosage form and also from single one. Along with the above

technique HPTLC, RP –UPLC has been also studied for the analysis. Validation of the developed method was done as per the ICH guidelines.

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