CHAPTER III

LITERATURE ON DRUGS INVESTIGATED

DRUG PROFILE OF LAMIVUDINE

Name : Lamivudine$^{1-4}$

IUPAC Name: 4-amino-1-[(2R,5S)-2-(hydroxymethyl)-1,3 oxathiolan-5-yl] -1,2-dihydropyrimidin-2-one

Chemical formula : $\text{C}_8\text{H}_{11}\text{N}_3\text{O}_3\text{S}$

Structure :

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\begin{array}{c}
\text{H}_2 \\
\text{O} \\
\text{OH}
\end{array}
\]

Molecular weight : 229.26 g/mol

Physical state : White powder

Melting point : 186-188$^\circ$C

Solubility : Soluble in water
Mechanism of Action: Lamivudine is phosphorylated in the host cell and active metabolite obtained competes for incorporation into viral DNA. It selectively inhibits HIV reverse transcriptase & Hepatitis-B. Reverse transcriptase & incorporates into growing viral DNA and terminates chain elongation.

Pharmacokinetic data

Protein bound: less than 36%

Bioavailability: 86%

Half-life: 4 to 6 hours

Metabolism: Less than 5% of the drug is metabolised renally

Active metabolite: $5^1$-Triphosphate Lamivudine

Excretion: Renally mostly as an unchanged form

Therapeutic uses: For the treatment of chronic Hepatitis-B and along with Drugs like Zidovudine and Abacavir for Prophylactic treatment of HIV.

Contra-indications

Pregnancy: It crosses placenta

Lactation: It is secreted in milk

Other conditions: 1) Acute and Chronic pancreatitis
2) Severe Liver and kidney disease

3) High levels of Lactic acid

**Resistance** : Due to point mutations in viral reverse transcriptase.

**Side effects** : Rarely Headache, Nausea, Vomiting, anorexia, abdominal pain and fatigue

**Drug interactions** : May interfere with Zalcitabine, ribavirin, and Interferon

**Dose** : For Hepatitis-B – 100 mg once daily

For HIV – 150 mg twice daily

**Route of administration** : Oral
DRUG PROFILE OF ZIDOVUDINE

Name : Zidovudine\textsuperscript{5-8}

IUPAC Name : 1-[(2R,4S,5S)-4-azido-5-(hydroxymethyl) oxolan-2yl]-5-methyl pyrimidine-2,4-dione

Chemical formula : $C_{10}H_{13}N_5O_4$

Structure:

\includegraphics{structure.png}

Molecular weight : 267.242 g/mol

Physical state : White crystalline powder

Melting point : 113-115\textdegree c

Solubility : soluble in water (50mg/ml)
Mechanism of Action: Zidovudine is phosphorylated in the host cell and Active metabolite obtained competes for incorporation into viral DNA. It selectively inhibits HIV reverse transcriptase & incorporates into growing viral DNA and terminates chain elongation.

Pharmacokinetic data

Protein bound: 30 to 38%
Bioavailability: 52 to 75%
Half-life: 0.5 to 3 hours
Metabolism: Hepatic
Active metabolite: 5' Triphosphate Zidovudine
Excretion: Renal or rectal

Therapeutic uses:
1) Prevents transmission of HIV from Mother to offspring
2) Zidovudine + 1 or 2 other Anti-HIV drugs Can be used for prophylactic treatment.

Contra-indications

Pregnancy: It crosses placenta
Lactation: It is secreted in milk
Other conditions: 1) Acute and Chronic pancreatitis
2) Severe Liver and kidney disease
3) High levels of Lactic acid
<table>
<thead>
<tr>
<th><strong>Resistance</strong></th>
<th>Due to Point Mutations in HIV Reverse Transcriptase</th>
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<tbody>
<tr>
<td><strong>Side effects</strong></td>
<td>Rarely Headache, Nausea, Vomiting, anorexia, Abdominal pain and fatigue</td>
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<tr>
<td><strong>Drug interactions</strong></td>
<td>1) stavudine &amp; zidovudine combination leads to Mutual Antagonism. 2) Azole Anti-fungals inhibit Zidovudine Metabolism 3) Paracetamol increases zidovudine toxicity by competing for glucuronidation. 4) Probenecid and other Nephrotoxic and Myelosuppressive drugs enhance toxicity.</td>
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<td><strong>Dose</strong></td>
<td>Adults -300 mg twice daily Children 180 mg/m² (max 200 mg) for every 6 to 8 hours.</td>
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<tr>
<td><strong>Route of Administration</strong></td>
<td>Oral, I.V, Suppository.</td>
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PAST RESEARCH WORK ON ESTIMATION OF LAMIVUDINE AND ZIDOVUDINE COMBINATION

There are only a few methods reported for the simultaneous determination of lamivudine and zidovudine combination. These methods are reviewed below.

**Development and Validation of RP-HPLC Method for the Estimation of Abacavir, Lamivudine and Zidovudine in Pharmaceutical Dosage Form**

A method has been developed and validated for the estimation of abacavir, lamivudine and zidovudine by high performance liquid chromatography (HPLC) on a C18 column with UV detection at 270 nm. The mobile phase composition that provides an optimal resolution of components in an acceptable elution time in water: methanol (70: 30v/v) with 0.1 % potassium dihydrogen phosphate pH 3.2 (adjusted with ortho phosphoric acid). The powdered tablet were extracted with methanol: water (50:50 v/v) mixture and after addition of stavudine, an internal standard subjected to HPLC analysis and assayed by comparison of analyte to internal standard peak areas to concentration ratios. The method was successfully applied to pharmaceutical formulation because no chromatographic interferences from the tablet excipients were found. The method retained its accuracy and precision when the standard addition technique was applied.

**Simultaneous estimation of Zidovudine and Lamivudine tablets by RP-HPLC method**

A high-performance liquid chromatographic method was developed and validated for the determination of two antiretroviral drugs viz. Zidovudine and
Lamivudine in combined pharmaceutical tablets. The different analytical performance parameters such as linearity, precision, accuracy, specificity, limit of detection (LOD) and limit of quantification (LOQ) were determined. Chromatography was carried out on a reversed-phase C-18 Phenomenex column with mobile phase Water: Acetonitrile (60:40) at 1.0 ml/min with pH 3.5 and detection wavelength 272 nm. The linearity of the calibration curves for each analyte in the desired concentration range is good ($r^2 > 0.999$). The percentage recovery of the zidovudine and lamivudine were found to be 99.10% and 97.2% respectively. Similarly the RSD value for precision was also found to be within the acceptable limit. The proposed methods are highly sensitive, precise and accurate and hence were successfully applied for the reliable quantification of API content in the commercial formulations of Zidovudine and Lamivudine.

**Method development and validation of Lamivudine, Tenofovir and Efavirenz in a combined dosage form by RP-HPLC.**

A simple, precise, accurate, and rapid Reverse Phase HPLC method has been developed and validated for the determination of Lamivudine, Tenofovir and Efavirenz simultaneously in combined tablet dosage form. The mobile phase used was a mixture of phosphate buffer pH 4 and Acetonitrile (42:58% v/v). The detection of Lamivudine, Tenofovir and Efavirenz was carried out by UV detector at 254 nm. The retention time of Lamivudine, Tenofovir and Efavirenz were found to be 2.220, 3.276 and 10.814 respectively. The linearity of the method was studied in 25% to 150% targeted concentration and regression coefficient for all
three drugs was found to be 0.999. Results of the analysis were validated statistically and by recovery studies. The proposed method can be used to determine the drug contents of marketed formulation.

**Validated Spectrophotometric Method for Simultaneous estimation of Zidovudine and Lamivudine in Combined Pharmaceutical dosage form**

A simple, accurate, precise and economical procedure for simultaneous estimation of zidovudine and lamivudine in combined tablet dosage form has been developed utilizing concept of Dual WaveLength method. This method involves selection of two wavelengths at which the drug has same absorbance. The method is based upon determination of Zidovudine at 272 and 287.2nm and Lamivudine at 256nm and 275.2nm, in 0.1N HCl. Different analytical performance parameters such as linearity, precision, accuracy, LOD, LOQ and assay were determined according to ICH guidelines. The method was found linear between the range of 50-425μg/mL for Zidovudine and 50-275μg/mL for Lamivudine. The results of formulation given as percentage of label claim were found to be 100.73±0.56 and 101.86±0.68 for zidovudine and lamivudine respectively. Therefore, the proposed methods can be used for the routine analysis of both drugs in quality control laboratories.

**REFERENCES**

2. **Indian Pharmacopeia, Vol – II 2010 Published by I.P. Commission**
   Ghaziabad Lamivudine Monograph pg 1564 – 1565

3. **En.wikipedia.org Lamivudine from Wikipedia the free Encyclopedia**


5. **United States of Pharmacopeia, Vol - II US Pharmacopeia convention,**

6. **Indian Pharmacopeia, Vol – III 2010 Published by I.P. Commission,**
   Ghaziabad Zidovudine Monograph pg 2329 – 2334

7. **En.wikipedia.org Zidovudine from Wikipedia the free Encyclopedia**


    Jan-Mar 2012

    Jan-Mar 2011

    April-June 2011

12. **IJPRD, 2011; Vol 3(7) : September 2011 pg. 9 – 14.**