CHAPTER-2

DRUG AND POLYMER PROFILES
2.1 DRUG PROFILES

2.1.1 Lamivudine (3TC) 85

US FDA approval date: November 1995

![Structural formula of lamivudine]

**Physicochemical properties of lamivudine**

1. Description: A White to off-white crystalline solid
2. CAS No: 134678-17-4
3. Molecular Formula: C₈H₁₁N₃O₃S
4. Molecular Weight: 229.3
5. Chemical Name: (2R,cis)-4-amino-1-(2-hydroxymethyl-1,3-oxathiolan-5-yl)-(1H)-pyrimidin-2-one
6. Melting Range: About 176°C
7. Solubility: Soluble in water

**Mechanism of Action:**

Lamivudine is a synthetic nucleoside analogue. Lamivudine is converted to its active metabolite 5’-triphosphate metabolite, lamivudine triphosphate (3TC-TP). The mode of action of 3TC-TP is the inhibition of HIV-1 reverse transcriptase (RT) through DNA chain termination after incorporation of the nucleotide analogue into viral DNA.
Antiviral Activity:

The antiviral activity of lamivudine was assessed in a number of cell lines (including monocytes and fresh human peripheral blood lymphocytes) using standard assays. EC50 values (50% effective concentrations) were in the range of 0.003 to 15 μM (1 μM = 0.23 μg/mL).

Pharmacokinetics of lamivudine

1. Absorption  
   Rapidly absorbed, food effects on absorption T max – 0.9 ± 0.3 hrs in fasted state, 3.2 ± 1.3 hrs in fed state, There is no significant difference in systemic exposure (AUC) in the fed and fasted states. Absolute bioavailability: about 86% (range 86 ± 16%)

2. Distribution  
   Volume of distribution (Vd) oral: 1.3 ± 0.4 L/kg (range 12-14 L/kg). protein binding: < 36%.  
   The single- and multiple dose Pharmacokinetics of Lamivudine are linear and dose proportional in a dose range of 10 to 60 mg/day. Steady-state achieved in 1-2 weeks. Average plasma concentration is about 83 ng/mL (n=114) with a range from 30 to 200 ng/mL.

3. Metabolism  
   Approximately 70% of an intravenous dose of Lamivudine is recovered as unchanged drug in the urine. In humans, the only known metabolite is the trans-sulfoxide metabolite

4. Excretion  
   Elimination half-life: 5 to 7 hours.  
   The systemic clearance is 0.33±0.06 L/hr/kg.  
   Elimination via the kidneys; approximately 5.2% ± 1.4% (range 5.172 – 5.2728) of the daily dose is excreted in urine as unchanged Lamivudine.

5. Pharmacokinetic Parameters  
   Parameter Value  
   Peak serum concentration 1.5 ± 0.5 mcg/ml following oral administration of 2mg/kg twice a day  
   T max About 2 hours (0.5 - 2.0)  
   Elimination Half-life 5-7 hours  
   Apparent Volume of distribution 1.3 ± 0.4 liters/kg
2.1.2 Zidovudine (AZT) 

First anti retroviral drug approved by USFDA-March 1987

![Structural formula of zidovudine]

**Physicochemical properties of Zidovudine**

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<table>
<thead>
<tr>
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<tbody>
<tr>
<td>1.</td>
<td>Description</td>
</tr>
<tr>
<td>2.</td>
<td>CAS No</td>
</tr>
<tr>
<td>4.</td>
<td>Molecular Formula</td>
</tr>
<tr>
<td>5.</td>
<td>Molecular Weight</td>
</tr>
<tr>
<td>6.</td>
<td>Chemical Name</td>
</tr>
<tr>
<td>7.</td>
<td>Melting Range</td>
</tr>
<tr>
<td>8.</td>
<td>Solubility</td>
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</table>

**Mechanism of Action:**

Zidovudine is a synthetic nucleoside analogue of the naturally occurring nucleoside, thymidine, in which the 3′-hydroxy (-OH) group is replaced by an azido (-N3) group. Zidovudine is converted to its active metabolite, zidovudine 5′-triphosphate (AztTP), with the action of the cellular enzymes. Zidovudine 5′-triphosphate inhibits the activity of the HIV reverse transcriptase both by competing for utilization with the natural substrate, deoxythymidine 5′-triphosphate (dTTP), and by its incorporation into viral DNA. The active metabolite AztTP is also a weak inhibitor of the cellular DNA polymerase-alpha and mitochondrial polymerase-gamma and has been reported to be incorporated into the DNA of cells in culture.
**Antiviral Activity:**

The in vitro anti-HIV activity of zidovudine was assessed by infecting cell lines of lymphoblastic and monocytic origin and peripheral blood lymphocytes with laboratory and clinical isolates of HIV. The IC50 and IC90 values (50% and 90% inhibitory concentrations) were 0.003 to 0.013 and 0.03 to 0.13 mcg/mL, respectively (1 nM = 0.27 ng/mL). The IC50 and IC90 values of HIV isolates recovered from 18 untreated AIDS/ARC patients were in the range of 0.003 to 0.013 mcg/mL and 0.03 to 0.3 mcg/mL, respectively.

**Pharmacokinetics of zidovudine**

1. **Absorption**
   Rapidly absorbed and extensively distribute, The extent of Zidovudine absorption (AUC) was similar when a single dose of Zidovudine was administered with food.

2. **Distribution**
   *Volume of distribution (Vd) oral* 1.6 ± 0.6 L/kg.
   *Protein binding:* <38.
   Pharmacokinetics of Zidovudine was dose independent at oral dosing regimens ranging from 2 mg/kg every 8 hours to 10 mg/kg every 4 hours.

3. **Metabolism**
   Zidovudine is primarily eliminated by hepatic metabolism. The metabolite of Zidovudine is 3’-azido-3’-deoxy-5’-O-(beta)-D-glucopyranosylthymidine (GZDV). Another metabolite is 3’-amino-3’-deoxothyrimidime (AMT).

4. **Excretion**
   *Elimination half-life:* 0.5 to 3 hours
   The *systemic clearance* is 1.6 ± 0.6 L/hr/kg.
   Eliminated via the kidneys; Urinary recovery of zidovudine and GZDV accounts for 14% and 74%, respectively, of the dose following oral administration.

5. **Pharmacokinetic Parameters**

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Peak concentration</td>
<td>41.8 ± 7.7 ng/mL following 15 mg oral dose</td>
</tr>
<tr>
<td>Tmax</td>
<td>About 2 hours (0.25 - 2.0)</td>
</tr>
<tr>
<td>Elimination Half-life</td>
<td>0.5 to 3 hours</td>
</tr>
<tr>
<td>Volume of distribution</td>
<td>4.5 ± 1.7 liters</td>
</tr>
</tbody>
</table>
2.1.3 Stavudine (D4T)\(^{87}\)

US FDA approval date: June 1994

![Structural formula of stavudine](image)

**Physicochemical properties Stavudine**

1. Description: A White to yellowish, odorless, crystalline solid
2. CAS No: 3056-17-5
3. Molecular Formula: \(C_{12}H_{10}N_{2}O_{4}\)
4. Molecular Weight: 224.2
5. Chemical Name: 2,3'-didehydro-3'-deoxythymidine
6. Melting Range: About 165-166°C
7. Solubility: soluble in water and propylene glycol

**Mechanism of Action**

Stavudine, a nucleoside analogue of thymidine, is phosphorylated by cellular kinases to the active metabolite stavudine triphosphate. Stavudine triphosphate inhibits the activity of HIV-1 reverse transcriptase (RT) by competing with the natural substrate thymidine triphosphate (\(K_i = 0.0083\) to 0.032 \(\mu\)M) and by causing DNA chain termination following its incorporation into viral DNA. The action of Stavudine triphosphate is mainly by inhibiting the cellular DNA polymerases \(\beta\) and \(\gamma\) and reduces the mitochondrial DNA synthesis.
Antiviral Activity

The in vitro antiviral activity of stavudine was measured in peripheral blood mononuclear cells, monocytic cells, and lymphoblastoid cell lines. The concentration of drug necessary to inhibit HIV-1 replication by 50% (IC-50) ranged from 0.009 to 4 μm against laboratory and clinical isolates of HIV-1.

Pharmacokinetics of Stavudine

<table>
<thead>
<tr>
<th>S.No</th>
<th>Parameter</th>
<th>Remarks</th>
</tr>
</thead>
<tbody>
<tr>
<td>1.</td>
<td>Absorption</td>
<td>After oral administration Stavudine is rapidly absorbed with peak plasma concentration occurred in 1 hour after dosing.</td>
</tr>
<tr>
<td>2.</td>
<td>Distribution</td>
<td>Binding of Stavudine to serum proteins is negligible over the concentration range of 0.01 to 11.4 μg/ml. Stavudine distributed equally between red blood cells and plasma.</td>
</tr>
<tr>
<td>3.</td>
<td>Metabolism</td>
<td>The metabolic fate of Stavudine has not been elucidated in humans.</td>
</tr>
<tr>
<td>4.</td>
<td>Excretion</td>
<td>In humans, renal elimination accounts for about 40% of the overall clearance of stavudine (Table 2). The elimination half-life of stavudine is 1.6 hours.</td>
</tr>
<tr>
<td>5.</td>
<td>Pharmacokinetic Parameters</td>
<td>Parameter Value</td>
</tr>
<tr>
<td></td>
<td>Availability (Oral)</td>
<td>86.4</td>
</tr>
<tr>
<td></td>
<td>T max</td>
<td>About 3 hours</td>
</tr>
<tr>
<td></td>
<td>Elimination Half-life</td>
<td>1.5 hours</td>
</tr>
<tr>
<td></td>
<td>Volume of distribution</td>
<td>58 liters</td>
</tr>
</tbody>
</table>
2.2 POLYMER PROFILES

2.2.1 Cellulose acetate phthalate (CAP)  

\[
\begin{align*}
\text{Functional Category: Cellulose acetate phthalate (CAP) is used as an enteric film coating material, or as a matrix binder for tablets and capsules.} \\
\text{Applications: Cellulose acetate phthalate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking.} \\
\text{Description: Cellulose acetate phthalate is a hygroscopic, white to off-white, free-flowing powder, granule, or flake. CAP exhibits no taste and odor, or slightly have odor of acetic acid.} \\
\text{Glass transition temperature: 160–170°C  Melting point: 192°C} \\
\text{Solubility: Soluble in number of ketones, esters, ether alcohols, cyclic ethers, and in certain solvent mixtures. It can be soluble in certain buffered aqueous solutions as low as pH 6.0.} \\
\text{Viscosity: Various grades of cellulose acetate Phthalate are commercially available having viscosities ranging from 45.0–90.0 mPa s.} \\
\text{Stability and Storage Conditions: Cellulose acetate phthalate is stable if stored in a well-closed container in a cool, dry place.}
\end{align*}
\]
2.2.2 Cellulose acetate butyrate (CAB)

**Structural Formula**

**Functional Category:** Cellulose acetate butyrate (CAB) is used as film coating material, or as a matrix binder for tablets and capsules

**Applications:** Cellulose acetate butyrate is widely used in pharmaceutical formulations both in sustained-release applications and for taste masking.

**Description:** Cellulose acetate butyrate, a mixed cellulose ester plastic, is normally prepared by esterifying acetylation grade cotton linters with a mixture of acetic acid, butyric acid, and butyric anhydride using sulfuric acid catalyst. It has no taste and odor.

**Glass transition temperature:** 150–160°C  **Melting point:** 136°C

**Solubility:** It is soluble in low molecular weight alcohols (methanol, ethanol, isopropanol, and n-propanol) as well as other common organic solvents.

**Viscosity:** Various grades of cellulose acetate Phthalate are commercially available having viscosities ranging from 1.1 Pa s.

**Stability and Storage Conditions:** cellulose acetate butyrate is stable if stored in a well-closed container in a cool, dry place.
2.2.3 Ethyl cellulose (EC)\textsuperscript{90}

![Structural formula]

**Functional Category**: Ethyl cellulose (EC) is used as an enteric film coating material, or as a matrix binder for tablets and capsules and also as tablet diluent.

**Applications**: binders, fillers, granulation aids, protective and controlled release coatings, taste masks and flavor fixatives.

**Description**: It is a white, tasteless, free flowing powder.

**Glass transition temperature**: 129-133°C **Melting point**: 165-173°C.

**Solubility**: Practically insoluble in water, freely soluble in chloroform, soluble in dichloromethane

**Viscosity**: Various grades of ethyl cellulose are commercially available having viscosities ranging from 3-385 mPa s.

**Stability and Storage Conditions**: cellulose acetate butyrate is stable if stored in a well-closed container in a cool, dry place.
2.2.4 Polyethylene oxide (PEO) 

![Structural formula](image)

**Functional Category**: Polyethylene oxide (PEO) is used as a matrix binder for tablets and capsules.

**Applications**: Extended release.

**Description**: It is a white, tasteless, free flowing powder.

**Melting point**: 68°C

**Solubility**: Polyethylene oxide (PEO) is soluble in water.

**Molecular Weight**: 100000-700000.

**Stability and Storage Conditions**: Polyethylene oxide (PEO) is stored in a well-closed air tight light resistance container in a cool, dry place.
2.2.5 **Eudragit RL 100** Methacrylic Acid -Methyl Methacrylate Copolymer (1:1)" Ph. Eur.

**Eudragit RS 100** Methacrylic Acid - Methyl Methacrylate Copolymer (1:2)" Ph. Eur.

![Structural formula](image)

**Functional Category**: Eudragits are used in extended release in tablets and as enteric coating material.

**Applications**: Extended release, Enteric coating

**Description**: It is a white powder with a faint characteristic odour

**Viscosity**: 50 - 200 mPa.s.

**Solubility**: are soluble in acetone, alcohol, dichloromethane, ethylacetate

**Molecular Weight**: 135,000.

**Stability and Storage Conditions**: Protect from warm temperatures protect against moisture.
2.2.6 Hydroxy propyl methyl cellulose (HPMC) \(^92\)

![Structural formula]

R is H, CH\(_3\), or CH\(_3\)CH(OH)CH\(_2\)

**Functional Category:** Coating agent; extended release agent

**Applications:** Tablet binder, in film-coating, and as a matrix for use in extended-release tablet formulations.

**Description:** Hypromellose is an odorless and tasteless, white or creamy-white fibrous or granular powder.

**Glass transition temperature:** 170–180°C., **Melting point:** 190–200°C.

**Solubility:** Soluble in cold water, forming a viscous colloidal solution; practically insoluble in chloroform, ethanol (95%), and ether, but soluble in mixtures of ethanol and dichloromethane, mixtures of methanol and dichloromethane, and mixtures of water and alcohol. Few grades of HPMC are soluble in acetone, mixtures of dichloromethane and propanol, and other solvents.

**Viscosity:** Wide range viscosity grades are available in the market.

**Stability and Storage Conditions:** Hypromellose powder is a stable material, although it is hygroscopic after drying.
2.2.7 Hydroxypropyl methyl cellulose Phthalate (HPMCP)

Functional Category: Coating agent; extended release agent

Applications: Tablet enteric coating agent, film-coating, and as a matrix for use in extended-release tablet formulations

Description: Hypromellose phthalate occurs as white to slightly off-white, free-flowing flakes or as a granular powder. It is tasteless and odorless or slightly acidic odor.

Glass transition temperature: 133–137°C.

Melting point (MP): 150°C.

Solubility: Readily soluble in a mixture of acetone and methyl or ethyl alcohol (1:1), in a mixture of methyl alcohol and dichloromethane (1:1), and in aqueous alkali. It is insoluble in water and dehydrated alcohol and slightly soluble in acetone.

Viscosity: Wide range viscosity grades are available in the market.

Stability and Storage Conditions: Hypromellose phthalate is chemically and physically stable at ambient temperature for at least 3–4 years and for 2–3 months at 40°C and 75% relative humidity. It is stable on exposure to UV light for up to 3 months at 25°C and 70% relative humidity.
2.2.8 Carbopol 971P

**Functional Category:** Controlled release in tablets, bioadhesion in buccal, ophthalmic, intestinal, nasal, vaginal and rectal applications, topical lotions, creams and gels, oral suspensions and transdermal gel reservoirs.

**Description:** Fluffy, white, mildly acidic polymer.

**Glass transition temperature:** 100–105°C

**Moisture:** 2%

**Specific gravity:** 1.41

**pH in 1 % Water:** 2.5-3.0

**Solubility:** Carbomers readily absorb water, get hydrated and swell. Its hydrophilic nature and cross-linked structure makes Carbopol a potential candidate for use in controlled release drug delivery system.

**Viscosity:** Wide range viscosity grades are available in the market.

**Stability and Storage Conditions:** Store in a dry area and close container when not in use.
2.3 DETAILED PLAN OF RESEARCH WORK

In general, the overall objective of this research is to formulate different pharmaceutical oral dosage forms with different anti infective drugs and to control the release of active ingredient from the specific oral delivery system over an extended period of time. Specifically, this research is intended to control the release of different anti infective drugs from the following systems: 1). Single matrix tablet and 2) Microcapsules. Formulations and processing parameters were optimized in order to achieve the desirable amount of drug release from each delivery system was investigated. The study was divided into two major sections; the detailed research objectives of each system were as follows:

2.4 Single unit systems

The primary objective of this research system was to evaluate the different processing parameters and develop stable, oral controlled release formulations of matrix tablets containing different anti infective drugs with different rate controlling polymers. Some of these formulations, which were equivalent in vitro with reported formulations, were tested for bioequivalence during in vivo clinical study. This research study was divided into different major parts to support the primary goal of this research.

2.4.1 Preformulation Studies

Determination of the physiochemical properties of the drugs used in the study. This includes the active characterization, drug solubility, thermal property.
2.4.2 Drug Recovery from Matrix Tablets

Development of analytical method(s), includes ultraviolet spectroscopy and HPLC analysis for the drugs used in the study.

2.4.3 Investigation of Formulation Parameters on Drug Release

To perform a screening study to determine optimum parameters, such as tablet size, polymer levels, in order to obtain sustained release profiles.

To investigate the influence of excipient type and level on the release of the active drug formulated in controlled release tablets.

2.4.4 Formulation and Characterization

To physically characterize the tablet formulations developed in terms of weight, hardness, content uniformity and in vitro drug release.

To statistically compare the dissolution profiles of the developed formulations using the similarity factor (f2 factor).

Investigate the stability of active drug in the prepared formulations.

2.4.5 Drug excipient interaction study

To characterize the prepared formulations by thermal methods.

2.4.6 In Vivo Clinical Study

To investigate the in vivo performance of the prepared matrix tablet formulation on animal models.

To analyze the pharmacokinetic parameters of the prepared matrix formulations.
2.5 Microcapsules

Another major objective of this research work is to formulate and evaluate the stable, oral controlled release formulations of microcapsules containing different anti infective drugs such as Lamivudine, Zidovudine and Stavudine, with different rate controlling polymers. Some of these formulations, which were equivalent in vitro with reported formulations, were tested for bioequivalence during in vivo clinical study. This research study was divided into different major parts to support the primary goal of this research.

2.5.1 Formulation and Characterization

- To characterize the microcapsules for dissolution study and drug content estimation.
- To characterize the surface characteristics of microcapsules using Scanning electron microscopy.
- To characterize the formulations using thermal analysis and spectroscopy.
- To characterize the stability of formulations using Differential scanning calorimetry.
- To investigate the stability of active drug in the formulations was developed based on the dissolution profiles and similarity factor.