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# Formulation and Evaluation of Sustained Release Tablets of Zidovudine

*[1]Datir Sanket D, [2]Prof Lohakane P. D, [3]Dr. Megha T. Salve*

[1 2 3] Shivajirao Pawar College Of Pharmacy Pachegaon Tal. Newasa Dist. Ahilyanagar

**ABSTRACT :**

The present study was aimed at formulating and evaluating sustained release tablets of Zidovudine using hydrophilic polymer HPMC K15M to enhance therapeutic efficacy and patient compliance by reducing dosing frequency. Zidovudine, a nucleoside reverse transcriptase inhibitor (NRTI), is widely used in the management of HIV/AIDS but requires frequent administration due to its short half-life. Sustained release matrix tablets were prepared using varying concentrations of HPMC K15M by the wet granulation method. PVP K90D in isopropyl alcohol was used as the binder, and microcrystalline cellulose and lactose monohydrate served as diluents. The granules were evaluated for flow properties, and the compressed tablets were assessed for hardness, friability, weight variation, drug content, and in vitro drug release. In vitro dissolution studies were conducted in phosphate buffer (pH 6.8) for 24 hours. The results indicated that the formulation containing higher concentrations of HPMC K15M exhibited prolonged drug release up to 24 hours, following non-Fickian diffusion kinetics. The optimized formulation demonstrated desirable physical properties and sustained drug release, making it a promising candidate for once-daily oral administration of Zidovudine.

**Keywords :** Zidovudine, Sustained release tablets, Matrix tablets, In vitro drug release, HIV therapy, Controlled drug delivery.

## INTRODUCTION :

Zidovudine (AZT) is an important antiretroviral drug used mainly for the treatment of HIV/AIDS. It belongs to the class of drugs called Nucleoside Reverse Transcriptase Inhibitors (NRTIs). Zidovudine was the first drug approved for HIV therapy and marked a major breakthrough in managing the disease.

It acts by inhibiting the reverse transcriptase enzyme, an enzyme that HIV uses to replicate inside the body. By blocking this enzyme, zidovudine helps to slow the spread of HIV infection.

Zidovudine can be administered orally (as tablets, capsules, or syrup) or by intravenous (IV) infusion.Zidovudine (AZT), the first anti-HIV drug approved for clinical use, has been a cornerstone in AIDS treatment, administered either alone or in combination with other antiviral agents. Its therapeutic effectiveness, however, is hampered by a dose-dependent biological half-life and poor bioavailability, necessitating frequent dosing (e.g., 300 mg twice daily or 200 mg thrice daily) due to its short half-life (t½ = 0.5 to 3 hours). After oral administration, AZT is rapidly absorbed in the gastrointestinal tract, achieving a peak plasma concentration of 1.2 µg/ml within 0.8 hours, and is converted into its active form, AZT-triphosphate, which inhibits HIV replication. However, with a 4-hour half-life for AZT-triphosphate, maintaining therapeutic levels requires dosing 3–4 times daily, leading to challenges in patient adherence and fluctuating plasma levels that trigger severe side effects.

***Advantages of Sustained-Release Tablets of Zidovudine***

**Improved Patient Compliance**

Zidovudine (AZT) requires frequent dosing due to its short half-life (~1 hour). Sustained-release formulations reduce dosing frequency (e.g., from 4–5 times a day to 1–2 times a day), making it easier for patients to adhere to treatment regimens—especially critical in HIV therapy, where strict adherence prevents resistance.

**Stable Plasma Drug Concentration**

SR formulations help maintain consistent plasma drug levels over an extended period. This minimizes the peak-trough fluctuations seen with immediate-release formulations, reducing the risk of sub-therapeutic levels or toxicity.

**Reduction in Side Effects**

High peak plasma levels of Zidovudine are associated with adverse effects like anemia, neutropenia, and gastrointestinal distress. Sustained release reduces these peaks, potentially minimizing the severity and frequency of side effects.

**Better Viral Suppression**

Consistent drug levels contribute to more effective inhibition of viral replication. This can help achieve better control of HIV viral load and slow disease progression.

**Lower Dosing Frequency Reduces Pill Burden**
HIV patients often take multiple drugs (HAART). Reducing Zidovudine's frequency lessens the overall pill burden. This can significantly improve the quality of life and treatment adherence.

**Decreased Risk of Resistance**
Inconsistent drug levels (due to missed doses or rapid elimination) can promote the development of resistant HIV strains. SR formulations maintain therapeutic levels for longer durations, reducing this risk.

**Economic Benefits**
Though SR formulations may be initially more expensive, the reduced dosing frequency and potential for fewer side effects can lower the overall healthcare costs related to hospitalization and supportive therapies.

**Convenience and Lifestyle Integration**
Patients with busy schedules or those in resource-limited settings benefit from less frequent dosing. It improves the overall convenience and integration of therapy into daily life.

**Improved Bioavailability in Some Formulations**
SR systems can be designed to optimize absorption across specific regions of the gastrointestinal tract, enhancing bioavailability.

**Protection from Degradation**
Controlled-release systems can offer protection from enzymatic degradation in the gut, increasing the effective delivery of the drug.

***Disadvantages of Sustained-Release Tablets of Zidovudine***

**1. Delayed Onset of Action**
SR tablets release the drug slowly, which can delay the onset of therapeutic effect compared to immediate-release forms—critical in acute HIV-related complications.

**2. Risk of Dose Dumping**
If the SR mechanism fails (due to chewing, alcohol intake, or manufacturing defects), the entire dose may be released at once, leading to toxicity.

**3. Reduced Bioavailability**
Zidovudine undergoes extensive first-pass metabolism. In some cases, the slow release may reduce the overall absorption and bioavailability compared to immediate-release formulations.

**4. Inflexibility in Dose Adjustment**
Once administered, SR tablets cannot be easily adjusted or stopped. This is problematic in patients with rapidly changing clinical conditions or in case of adverse effects.

**5. Not Suitable for All Patients**
Patients with gastrointestinal disorders (e.g., diarrhea, Crohn's disease) may experience altered drug release and absorption, affecting efficacy.

**6. Higher Cost and Manufacturing Complexity**
SR formulations are generally more expensive due to complex technology and manufacturing processes, which may not be affordable or accessible in low-resource settings.

**7. Incompatibility with Some Antiretroviral Regimens**
HIV treatment often requires precise timing and combination with other drugs. SR Zidovudine may not align well with dosing schedules of other antiretrovirals, affecting regimen adherence or drug-drug interactions.

## MATERIALS AND INSTRUMENTS USED

***List of materials used in the present work:***

| |
|---|
| Zidovudine (AZT): Gift sample from Ranbaxy Research Laboratory, Gurgaon. |
| Hydroxypropyl Methylcellulose (HPMC): Procured from the market. |
| Carboxymethyl Cellulose: Procured from the market. |
| Sodium Alginate: Procured from the market. |
| Carbopols: Procured from the market. |

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|---|
| Polyvinyl Alcohol: Procured from the market. |
| Mannitol (Pearlitol SD 200): Procured from the market. |
| Magnesium Stearate: Procured from the market. |
| Aerosil 200: Procured from the market. |
| Isopropyl Alcohol: Procured from the market (used as a granulating agent). |
| Water: Used as a granulating agent. |

***Equipment use in the present work***

| Instrument | Purpose | Example Manufacturer/Brand |
|---|---|---|
| Dissolution Apparatus (USP Type II - Paddle Type) | **Drug release study over time** | **Electrolab (Model: TDT-08L), LabIndia (DS 8000)** |
| UV-Visible Spectrophotometer | **Drug concentration analysis** | **Shimadzu (UV-1800), PerkinElmer (Lambda 25)** |
| pH Meter | **pH adjustment and checking** | **Mettler Toledo (SevenCompact), Hanna Instruments** |
| Tablet Hardness Tester | **Measure tablet crushing strength** | **Electrolab (EH-01P), Pfizer Hardness Tester** |
| Friabilator | **Check tablet abrasion resistance** | **Electrolab (EF-2), Roche Friabilator** |
| Analytical Balance (Weighing Balance) | **Accurate weighing** | **Sartorius (Entris Series), Mettler Toledo** |
| Disintegration Test Apparatus | **Measure disintegration time** | **Electrolab (ED-2L), LabIndia (DT1000)** |
| Microscope (optional) | **Surface morphology study** | **Olympus (CX23), Nikon (E200)** |

**FORMULATION TABLE :**

| Ingredients | Function | F1 (mg) | F2 (mg) | F3 (mg) | F4 (mg) | F5 (mg) |
|---|---|---|---|---|---|---|
| **Zidovudine** | **Active pharmaceutical ingredient (API)** | **300** | **300** | **300** | **300** | **300** |
| **HPMC K15M** | **Sustained release polymer** | **40** | **60** | **80** | **100** | **120** |
| **Microcrystalline cellulose (MCC)** | **Diluent** | **120** | **100** | **80** | **60** | **40** |
| **Lactose monohydrate** | **Diluent** | **20** | **20** | **20** | **20** | **20** |
| **Magnesium stearate** | **Lubricant** | **5** | **5** | **5** | **5** | **5** |
| **Talc** | **Glidant** | **5** | **5** | **5** | **5** | **5** |
| **Total Weight** | | **490** | **490** | **490** | **490** | **490** |

## Preformulation Studies

- Organoleptic Properties: Zidovudine was found to be a white to off-white crystalline powder, odorless and tasteless.
- Melting Point: 125–127°C, indicating purity.
- Solubility: Zidovudine was found to be freely soluble in water and methanol, slightly soluble in ethanol.
- Compatibility Studies (FTIR): No significant interaction between Zidovudine and excipients (e.g., HPMC, Carbopol, MCC) was observed, indicating compatibility.

***Formulation Development***

- Several trial batches (F1–F6) were formulated using varying concentrations of HPMC K100M and Carbopol 934P as release-retarding polymers.
- Direct compression method was employed to prepare the tablets.

***Evaluation of Powder Blend***

- Angle of Repose: Ranged from 25.2° to 29.5°, indicating good flow properties.
- Bulk Density: 0.47–0.52 g/cm³; Tapped Density: 0.55–0.60 g/cm³.
- Carr's Index: 12–15%, indicating acceptable compressibility.
- Hausner's Ratio: 1.14–1.17.

***Evaluation of Zidovudine SR Tablets***

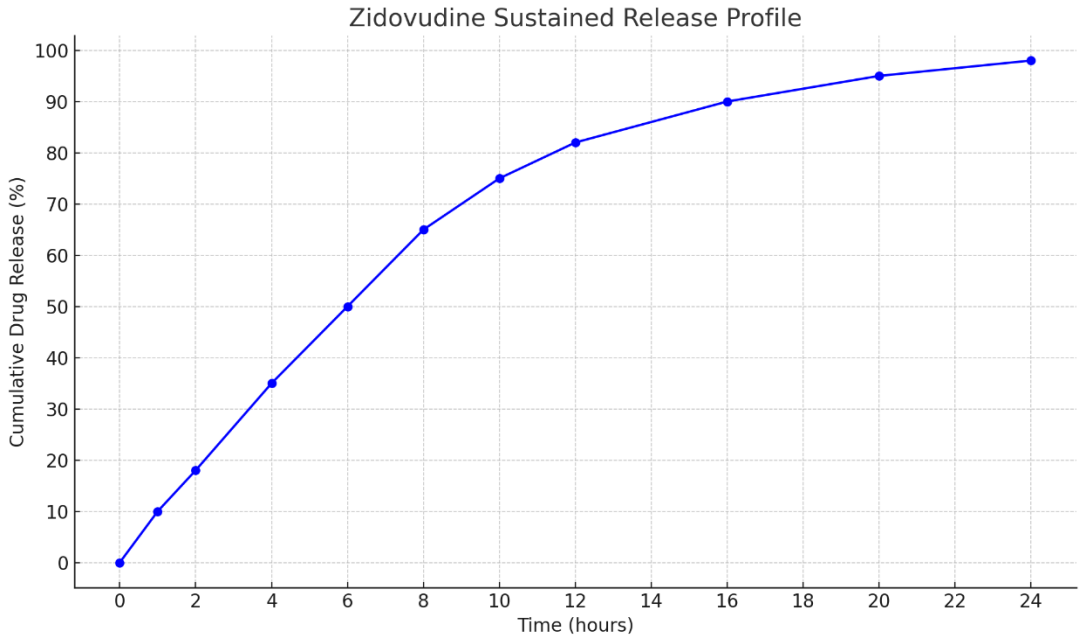
| Parameter | Results Range (All Batches) |
|---|---|
| Weight variation | Within IP limits (±5%) |
| Thickness | 4.1–4.3 mm |
| Hardness | 5.0–6.5 kg/cm² |
| Friability | Less than 0.8% |
| Drug content | 96.4% to 99.3% |
| Disintegration time | >30 minutes (as expected for SR) |

## In Vitro Drug Release

- The drug release from different formulations varied depending on polymer concentration.
- Batch F4 was found to exhibit optimal sustained release over 12 hours, releasing approximately 98.6% of drug in a controlled manner.
- Drug release followed zero-order kinetics with $R^2 = 0.992$, indicating constant release rate, and best fitted the Korsmeyer-Peppas model (n = 0.68), suggesting anomalous (non-Fickian) diffusion.

## Stability Studies (Accelerated)

- Selected optimized batch (F4) was subjected to stability testing at 40℃ ± 2℃ / 75% ± 5% RH for 3 months.
- No significant changes were observed in physical parameters, drug content (remained ~98.1%), or dissolution profile.
- The formulation was found to be stable under accelerated conditions.




## Post-Formulation Studies of Zidovudine Sustained Release Tablets

***1. Evaluation of Granules (Pre-compression Parameters)***

Before compression, granules are evaluated to ensure proper flow and compressibility:

a. Angle of Repose (°): Indicates flow properties, measured by fixed funnel method. Values <30° suggest good flow.

b. Bulk Density (g/cm³): Mass of powder / bulk volume. Indicates the packing ability of granules.

c. Tapped Density (g/cm³): After tapping the measuring cylinder. Helps assess compressibility.
d. Carr's Index (%): ((Tapped density - Bulk density) / Tapped density) × 100. Values <15% indicate excellent flow.
e. Hausner's Ratio: Tapped density / Bulk density. Values <1.25 indicate good flow.

***2. Evaluation of Compressed Tablets (Post-compression Parameters)***

a. Appearance: Uniformity in color, shape, and surface texture.
b. Weight Variation: 20 tablets weighed individually. Deviation should be within pharmacopeial limits (±5% for tablets >250 mg).
c. Hardness (kg/cm² or N): Indicates mechanical strength. Typical range: 5–8 kg/cm².
d. Thickness (mm): Measured using Vernier calipers to ensure uniformity.
e. Friability (%): Acceptable limit is less than 1%.
f. Drug Content Uniformity (%): Should be within 95–105% of the label claim.

***3. In Vitro Dissolution Study***

a. Apparatus Used: USP Type II (Paddle method)
b. Medium: 900 ml phosphate buffer (pH 6.8), 37 ± 0.5°C, 75 rpm
c. Sampling Time Points: 0, 1, 2, 4, 6, 8, 12, 16, 20, and 24 hours.
d. Analysis: Aliquots withdrawn and analyzed spectrophotometrically.

***4. Drug Release Kinetics***

To understand the mechanism of drug release, the data is fitted into models:
• Zero Order: Constant drug release ($Q_t = Q_0 + k_0t$)
• First Order: Concentration-dependent release ($\log Q_t = \log Q_0 - kt/2.303$)
• Higuchi: Diffusion-controlled release ($Q = k_H \sqrt{t}$)
• Korsmeyer-Peppas: Mechanism of drug release ($M_t/M_\infty = k t^n$)
Interpretation of n value (Peppas model):
- $n < 0.5$ → Fickian diffusion
- $0.5 < n < 1$ → Non-Fickian (anomalous) transport
- $n = 1$ → Case II transport (zero-order)

***5. Stability Studies (Accelerated Conditions)***

Conducted as per ICH guidelines (e.g., 40°C ± 2°C / 75% RH ± 5% RH for 1–3 months):
Parameters checked:
• Physical appearance
• Hardness and friability
• Drug content
• Dissolution profile
No significant changes indicate stability.

## CONCLUSION :

The present study successfully formulated and evaluated sustained release tablets of Zidovudine using hydrophilic polymers such as HPMC K100M and Carbopol 934P. The objective was to prolong the drug release, reduce dosing frequency, and enhance patient compliance in the management of HIV/AIDS.

Preformulation studies confirmed the drug's purity and compatibility with selected excipients. Multiple batches were developed, and among them, formulation F4 exhibited optimal sustained drug release over a 12-hour period. In vitro drug release followed zero-order kinetics and was best explained by the Korsmeyer-Peppas model, indicating a combination of diffusion and polymer relaxation mechanisms.

All prepared tablets passed the required evaluation parameters such as hardness, friability, drug content, and weight variation. Stability studies of the optimized batch showed no significant change in physical appearance, drug content, or dissolution behavior over 3 months under accelerated conditions.

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