

## DEVELOPMENT AND OPTIMIZATION OF ZIDOVUDINE FAST-DISSOLVING TABLETS USING CO-PROCESSED EXCIPIENTS

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### ABSTRACT

Zidovudine is a nucleoside reverse transcriptase inhibitor widely used in the treatment of HIV/AIDS; however, its administration in pediatric and geriatric patients is often complicated by dysphagia. To enhance patient compliance, the present study aimed to formulate and optimize fast dissolving tablets (FDTs) of Zidovudine using co-processed excipients to achieve rapid disintegration and enhanced dissolution rates. The co-processed excipients were prepared using [Insert Method, e.g., solvent evaporation] utilizing a combination of [Insert Excipient 1] and [Insert Excipient 2]. The FDTs were subsequently prepared via the direct compression method. A [Insert Design type, e.g., 3<sup>2</sup> full factorial design] was employed to optimize formulation variables, focusing primarily on the concentration of the co-processed excipients and [Insert second variable]. Pre-compression studies of the optimized blend indicated excellent flow properties with an angle of repose ranging from [Insert Range]. Post-compression evaluation showed that the optimized formulation ([Insert Formulation Code]) exhibited a hardness of [Insert Value] kg/cm<sup>2</sup>, a friability of [Insert Value]%, and an in vitro dispersion time of [Insert Value] seconds. Furthermore, in vitro dissolution studies revealed that [Insert Value]% of Zidovudine was released within [Insert Value] minutes, significantly outperforming both the physical mixture and the pure drug. In conclusion, the utilization of co-processed excipients successfully yielded Zidovudine FDTs with superior mechanical strength and rapid disintegration, presenting a viable, patient-friendly alternative to conventional solid dosage forms.

**KEYWORDS:** Zidovudine, Fast Dissolving Tablets, Co-processed Excipients, Direct Compression, Optimization, Orally Disintegrating Tablets.

## INTRODUCTION

Zidovudine (AZT), a thymidine analogue, was the first antiretroviral agent approved for the treatment of Acquired Immunodeficiency Syndrome (AIDS) and HIV infection. It acts as a nucleoside reverse transcriptase inhibitor (NRTI), prematurely terminating viral DNA synthesis. While highly effective, Zidovudine requires frequent dosing due to its short biological half-life (approximately 0.5 to 3 hours). Furthermore, a significant portion of HIV/AIDS patients—particularly pediatric, geriatric, and bedridden populations—frequently experience dysphagia (difficulty swallowing) or severe systemic weakness. This makes the administration of conventional solid oral dosage forms, such as standard tablets or large capsules, highly challenging. Consequently, patients may skip doses, leading to poor medication adherence, which is critical in antiretroviral therapy to prevent viral mutations, drug resistance, and ultimate treatment failure.

To overcome these physiological and compliance barriers, Fast Dissolving Tablets (FDTs) also widely recognized as Orally Disintegrating Tablets (ODTs)—have emerged as a highly patient-centric drug delivery system. FDTs are engineered to disintegrate or dissolve rapidly in the saliva, typically within a few seconds to a minute, without the need for water or chewing. Upon placement in the oral cavity, the tablet quickly disperses into a fine suspension or solution that is easily swallowed. This rapid dispersion not only ensures ease of administration for patients with dysphagia but can also facilitate pre-gastric absorption through the highly vascularized oral, pharyngeal, and esophageal mucosa, which can potentially enhance the bioavailability and rapid onset of action for the incorporated drug.



**Figure 1: Rapid disintegration of a tablet in aqueous media.**

Despite their significant clinical advantages, manufacturing FDTs via direct compression presents distinct formulation and engineering challenges. The fundamental paradox in FDT design lies in achieving a highly porous tablet structure—which is necessary for rapid water wicking and rapid disintegration—while simultaneously maintaining sufficient mechanical strength (acceptable hardness and low friability) to withstand the rigors of manufacturing, packaging, and transportation. Formulators traditionally rely on simple physical mixtures of superdisintegrants (such as

crospovidone or sodium starch glycolate) alongside highly water-soluble excipients (such as mannitol or lactose). However, these physical powder blends often suffer from poor micromeritic properties, including erratic flowability, high potential for segregation in the hopper, and inadequate compressibility at higher manufacturing speeds.

Particle engineering through the development of co-processed excipients offers a sophisticated and highly effective solution to these conventional manufacturing limitations. Co-processing involves the interaction of two or more established excipients at the sub-particle level—often utilizing techniques such as solvent evaporation, spray drying, or melt dispersion—to create a single, novel composite material. This synergistic approach masks the individual undesirable properties of the parent excipients while retaining and enhancing their functional benefits. Co-processed excipients typically exhibit superior powder characteristics, including excellent flowability and uniform particle size distribution, which prevents phase segregation during tableting. Furthermore, their unique morphology often provides a highly porous matrix that dramatically accelerates capillary action and water penetration, yielding ultra-fast disintegration times without compromising the mechanical integrity of the final tablet.

Therefore, the present research aims to systematically develop and optimize Fast Dissolving Tablets of Zidovudine utilizing novel co-processed excipients. By applying a structured experimental design and statistical optimization techniques, this study seeks to establish an optimal formulation that achieves a precise balance between rapid in-vitro disintegration and optimal physical robustness, ultimately aiming to improve patient compliance and therapeutic outcomes in the management of HIV/AIDS.

## **MATERIALS AND METHODS**

The active pharmaceutical ingredient (API), Zidovudine, a potent nucleoside reverse transcriptase inhibitor (NRTI), was purchased along with a carefully chosen set of functional excipients. High functionality co-processed excipients and cross-linked superdisintegrants were deliberately chosen for their potential to synergistically enhance powder flowability and markedly accelerate oral disintegration while maintaining tablet tensile strength. All chemicals and reagents used for analysis and formulation were of analytical/pharmacopeial grade.

### **Preformulation Studies and Analytical Development**

Preformulation testing acts as the fundamental bridge mapping the physical and chemical properties of the pure drug alone, and in combination with formulation excipients, before proceeding to the actual dosage form design.

### **Organoleptic Evaluation and Melting Point Determination**

Initial quality control involved the sensory and visual inspection of Zidovudine. A minimal quantity of the medicament was placed on a contrasting background under adequate illumination to log its color, odor, and general crystalline or powder appearance. The melting point, a critical indicator of API purity and potential polymorphic state, was determined via the capillary tube method as specified by the Indian Pharmacopoeia (IP). The medication was introduced into a hermetically-sealed glass capillary and mounted in a standardized melting point apparatus. The temperature range corresponding to the onset of liquefaction and complete melting was recorded.

### **Solubility and Dissolution Media Selection**

The equilibrium solubility of Zidovudine was assessed across multiple physiological pH ranges to simulate gastrointestinal conditions and aid in sink condition maintenance during dissolution testing. Saturated solutions were

prepared by introducing a 50 mg surplus of the API into individual glass vials containing 5 mL of distinct media: distilled water, 0.1 N HCl (pH 1.2), acetate buffer (pH 4.5), and phosphate buffer (pH 6.8). The vials were firmly sealed and mechanically agitated in a water bath shaker at ambient room temperature for a continuous 48-hour period. Post-equilibration, the suspensions were centrifuged at 1200 rpm for 30 minutes. The extracted supernatant was subsequently filtered through a 0.45  $\mu\text{m}$  membrane filter, suitably diluted in methanol, and quantified using the established spectrophotometric protocol.

### Analytical Assay Methodology and Calibration Tracking

The primary quantitative assay for routine dissolution and content uniformity was established via UV-Visible spectrophotometry. A stock solution of genuine Zidovudine (1 mg/mL) was accurately prepared in distilled water and 0.1 N HCl. Serial dilutions yielding concentrations of 5, 10, 15, 20, and 25  $\mu\text{g/mL}$  were prepared in standard volumetric flasks. The absorbance maxima ( $\lambda_{\text{max}}$ ) was determined by scanning the solutions in the UV range (200-400 nm), identifying a distinct peak at 271 nm. The calibration curves were plotted, and regression analysis was performed to derive the linear equation utilized for subsequent calculations.

Furthermore, for the precise quantification of Zidovudine content uniformity and to monitor advanced stability profiles, a rigorous analytical framework was established utilizing reversed-phase ion-pair chromatography. Careful column selection, specifically optimized for this low molecular weight compound, ensured the highest resolution of the API from any trace degradants, facilitating highly accurate, robust tracking of chemical degradation pathways.

### Drug-Excipient Compatibility and Thermal Mapping

Ensuring that the specialized co-processed excipients do not chemically or physically interact with the API is a critical preformulation step. A number of additives were chosen for compatibility investigations based on the results of the literature investigation together with current scientific understanding. The medicinal product was incorporated with each of the excipients in a vial made from glass according to their respective ratios, including and excluding the addition of 20% moisture. Additionally, reference vials containing just the medication and the additive have been developed. For a period of three weeks, the aforementioned vials were monitored at elevated temperature of 50°C and inspected to identify any noticeable physical modification. There was a descriptive analysis performed on both the initial and three-week specimens that were maintained at 50°C.

- **Fourier Transform Infrared (FT-IR) Spectroscopy:** The pure drug, pure excipients, and their respective physical mixtures were thoroughly triturated. Utilizing a Perkin Elmer Spectrum1000 equipped with an ATR diamond interface, the vibrational spectra were recorded. Four successive scans were averaged per sample at a highly resolved 4  $\text{cm}^{-1}$  interval across the 4000-400  $\text{cm}^{-1}$  wavenumber range. Spectral overlay comparisons were meticulously analyzed to ensure foundational functional group bands (e.g., N=N stretch, C=O stretch) of Zidovudine remained unshifted.
- **Differential Scanning Calorimetry (DSC):** The fundamental thermal transitions and solid-state stability were tracked via DSC. Precisely weighed samples (2 mg) of the API and its physical mixtures were crimped into hermetic aluminum pans. Thermograms were obtained by heating the samples from 50°C to 300°C at a constant, controlled ramp rate of 20°C/min, under a dynamic nitrogen purge. Shifts, broadening, or obliteration of the sharp API melting endotherm were investigated to rule out polymorphic shifts, eutectic formations, or complexations.

### Factorial Experimental Design (Quality by Design)

A statistically driven,  $3^2$  randomized full factorial design was constructed to evaluate the main effects and critical interaction terms of the formulation variables on the fast-dissolving performance profile. This systematic mapping of the design space significantly reduces trial-and-error iterations.

The methodology dictated the creation of 9 distinct formulation runs per matrix combination, generating a total of 36 distinct tableting batches across four major architectural groups. The independent variables chosen were the quantities of co-processed additives (X1) and Superdisintegrant (X2). Lower, middle, and highest values were designated by the three levels chosen for each component (-1, 0, +1).

**Table 1: Design Layout of  $3^2$  Factorial Designs.**

| Formulation Batches |      |      |      | X1 | X2 |
|---------------------|------|------|------|----|----|
| CSF1                | CCF1 | ACF1 | ASF1 | -1 | -1 |
| CSF2                | CCF2 | ACF2 | ASF2 | 0  | -1 |
| CSF3                | CCF3 | ACF3 | ASF3 | +1 | -1 |
| CSF4                | CCF4 | ACF4 | ASF4 | -1 | 0  |
| CSF5                | CCF5 | ACF5 | ASF5 | 0  | 0  |
| CSF6                | CCF6 | ACF6 | ASF6 | +1 | 0  |
| CSF7                | CCF7 | ACF7 | ASF7 | -1 | +1 |
| CSF8                | CCF8 | ACF8 | ASF8 | 0  | +1 |
| CSF9                | CCF9 | ACF9 | ASF9 | +1 | +1 |

**Dependent Variables:** Y1: Disintegration Time (60 Sec) | Y2:  $t_{1/2}$  (Percentage Release after 30 min)

**Variable Definitions:** CSF: X1 = CombiLac®, X2 = SSG | CCF: X1 = CombiLac, X2 = CCS | ACF: X1 = Avicel-HFE102, X2 = CCS | ASF: X1 = Avicel-HFE102, X2 = SSG.

Where +1 is the highest value, -1 is the lower value, and 0 is the middle value.

### Formulation of Zidovudine Fast-Dissolving Tablets

The 650 mg Zidovudine tablets were manufactured utilizing the direct compression technique. This process circumvents the need for aqueous or non-aqueous granulation, thereby protecting the active ingredient from potential hydrolytic or thermal degradation pathways, while significantly optimizing manufacturing throughput.

### Manufacturing Protocol

- **Sieving and De-lumping:** Zidovudine (300 mg per tablet), the designated co-processed diluent (Avicel-HFE 102 or CombiLac), and the selected superdisintegrant (SSG or CCS) were individually passed through a 100-mesh sieve to ensure uniform particle size and break up transient agglomerates.
- **Geometric Blending:** The active pharmaceutical ingredient and the primary excipients (including filler, sweetener, and flavoring agents) were transferred to an inert plastic polybag. The powder bed was geometrically blended for a precise duration of 15 minutes to secure a highly homogenous mixture, a critical parameter given the high drug loading of the formulation.
- **Lubrication Phase:** Subsequently, boundary lubricants (Magnesium Stearate) and glidants (Talc) were sifted into the primary blend. This final mixture was agitated gently for exactly five minutes. Restricting the lubrication duration is fundamentally critical, as over-lubrication extensively coats the hydrophilic excipient particles with hydrophobic magnesium stearate, severely impeding saliva penetration and dramatically extending the tablet disintegration time.

- **Compression:** Following favorable pre-compression analysis, the lubricated blends were gravity-fed into the hopper of a Cadmach single-punch tablet press. The powder was compressed utilizing standard concave punches into 650 mg tablets. The compression force was meticulously calibrated across batches to maintain a diametral crushing strength between 3.0 to 5.0 kg/cm<sup>2</sup>, enabling a porous matrix suitable for FDTs.

**Table 2: Composition of 3<sup>2</sup> Factorial Design CSF Batch (CombiLac + SSG).**

| Ingredients (mg per tablet) | CSF1       | CSF2       | CSF3       | CSF4       | CSF5       | CSF6       | CSF7       | CSF8       | CSF9       |
|-----------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Drug (Zidovudine)           | 300        | 300        | 300        | 300        | 300        | 300        | 300        | 300        | 300        |
| CombiLac                    | 200        | 200        | 200        | 250        | 250        | 250        | 300        | 300        | 300        |
| SSG                         | 15         | 30         | 45         | 15         | 30         | 45         | 15         | 30         | 45         |
| Sodium saccharin            | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        |
| Mint flavor                 | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        |
| Talc                        | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          |
| Magnesium stearate          | 2          | 2          | 2          | 2          | 2          | 2          | 2          | 2          | 2          |
| Camphor                     | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          |
| Vanillin                    | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          |
| Lactose                     | qs         | qs         | qs         | qs         | qs         | qs         | qs         | qs         | qs         |
| <b>Total Weight</b>         | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> |

**Table 3: Composition of 3<sup>2</sup> Factorial Design ACF Batch (Avicel-HFE102 + CCS).**

| Ingredients (mg per tablet) | ACF1       | ACF2       | ACF3       | ACF4       | ACF5       | ACF6       | ACF7       | ACF8       | ACF9       |
|-----------------------------|------------|------------|------------|------------|------------|------------|------------|------------|------------|
| Drug (Zidovudine)           | 300        | 300        | 300        | 300        | 300        | 300        | 300        | 300        | 300        |
| Avicel- HFE102              | 130        | 130        | 130        | 195        | 195        | 195        | 260        | 260        | 260        |
| CCS                         | 10         | 20         | 30         | 10         | 20         | 30         | 10         | 20         | 30         |
| Sodium saccharin            | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        | 2.5        |
| Mint flavor                 | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        | 0.5        |
| Talc                        | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          | 1          |
| Magnesium stearate          | 2          | 2          | 2          | 2          | 2          | 2          | 2          | 2          | 2          |
| Camphor                     | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          |
| Vanillin                    | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          | 4          |
| Lactose                     | qs         | qs         | qs         | qs         | qs         | qs         | qs         | qs         | qs         |
| <b>Total Weight</b>         | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> | <b>650</b> |

### Pre-Compression Micromeritic Evaluation of Powder Blends

Prior to direct compression, the flow and rheological properties of the lubricated powder blends must be verified to prevent issues such as rat-holing, bridging in the hopper, or variable die fill, which directly result in erratic tablet weight variation and content uniformity failures.

#### 1. Angle of Repose ( $\theta$ )

This parameter evaluates inter-particulate friction. The fixed funnel method was employed. A glass funnel was secured at a predetermined height (H). The powder blend was allowed to flow freely through the funnel orifice onto a horizontal planar surface until the apex of the conical pile touched the funnel tip. The radius (R) of the powder heap was measured. The angle of repose was calculated using the equation:

$$\theta = \tan^{-1} (H / R)$$

An angle below 30° strongly indicates excellent, free-flowing powder dynamics.

#### 2. Bulk Density (Db)

A carefully weighed 20 g sample of the powder blend was introduced into a dry, 50 mL graduated cylinder via a glass funnel without any mechanical compaction. The initial, untapped volume occupied by the powder bed was recorded to

calculate the apparent bulk density (Mass / Untapped Volume).

### 3. Tapped Density (Dt)

The graduated cylinder containing the known mass of powder was secured onto a mechanized Electrolab tap density tester. The cylinder was subjected to a standardized tapping frequency. Tapping continued iteratively (typically 50 to 100 taps) until the volume of the powder bed consolidated and exhibited no further volume reduction (or a percentage change of less than 2%). The final tapped volume was recorded to determine the tapped density (Mass / Tapped Volume).

### 4. Carr's Compressibility Index (%)

This index directly relates to the relative flowability and the specific propensity of a powder to decrease in volume under pressure. It was derived utilizing the relationship:  $\text{Carr's Index (\%)} = [(Tapped\ Density - Bulk\ Density) / Tapped\ Density] \times 100$

### 5. Hausner's Ratio

Serving as a secondary indicator of inter-particulate friction and flow, the Hausner ratio was calculated as the simple mathematical ratio of Tapped Density to Bulk Density. Values closely approaching 1.00 - 1.11 denote excellent flow properties.

### Post-Compression Evaluation of Fast-Dissolving Tablets

Stringent quality control protocols were applied to the compressed tablets to assure reproducibility, mechanical robustness, and adherence to specific fast-dissolving parameters.

#### ➤ General Appearance, Thickness, and Diameter

Twenty tablets per formulation batch were randomly selected. Aesthetic parameters including surface smoothness, absence of capping/lamination, and color uniformity were visually verified. The architectural dimensions (thickness and diametral distance) were quantitatively assessed to an accuracy of 0.01 mm utilizing calibrated Vernier calipers to ensure uniform die-fill and consistent punch pressure dynamics.

#### ➤ Tablet Hardness (Crushing Strength)

FDTs inherently require a delicate balance: they must be porous enough to disintegrate rapidly yet hard enough to withstand transit. A Monsanto-type hardness tester was utilized. The tablet was placed diametrically between the jaws, and the force was incrementally increased until physical fracture occurred. Ten tablets were tested per batch, with results recorded in kg/cm<sup>2</sup>.

#### ➤ Friability Testing

To determine mechanical shock resistance against abrasion and chipping during packaging processes, twenty pre-weighed, dedusted tablets were loaded into a Roche Friabilator. The drum was rotated at 25 rpm for precisely 4 minutes (100 total revolutions), subjecting the tablets to a continuous 6-inch drop. The tablets were subsequently removed, carefully dedusted, and re-weighed. Percentage friability was calculated, strictly adhering to the pharmacopeial limit of  $\leq 1.0\%$ .

#### ➤ **Weight Variation**

Twenty tablets from each final batch were weighed individually and collectively utilizing an electronic analytical balance. The average tablet weight was established, and the individual deviations were computed against the standard pharmacopeial tolerance (e.g.,  $\pm 5\%$  for tablets exceeding 324 mg).

#### ➤ **Wetting Time and Water Absorption Ratio**

A highly critical physiological indicator for FDT performance, wetting time simulates the capillary wicking of saliva. A piece of tissue paper, folded twice, was placed flat into a small Petri dish (5 cm internal diameter). Exactly 6 mL of distilled water, dyed with a trace amount of water-soluble amaranth red to visually track fluid migration, was added to the dish. A pre-weighed dry tablet was placed on the surface of the tissue. The precise time required for the red dye to completely permeate and surface on the upper face of the tablet was logged as the wetting time. Immediately post-wetting, the hydrated tablet was re-weighed. The Water Absorption Ratio (R) was calculated to measure the swelling capacity of the superdisintegrants:

$$R = [(W_a - W_b) / W_b] \times 100$$

(where  $W_a$  = wetted weight,  $W_b$  = baseline dry weight).

#### ➤ **In Vitro Disintegration Time**

The structural breakdown rate was measured using a standard USP disintegration apparatus. Six tablets were placed individually into the basket-rack assembly tubes. The assembly was submerged and oscillated in a beaker containing 900 mL of distilled water isothermally maintained at  $27 \pm 0.5^\circ\text{C}$  to mimic oral cavity temperatures. The endpoint was established when no palpable or solid core mass remained on the apparatus screen, and the average time in seconds was recorded.

#### ➤ **Drug Content Uniformity**

Five tablets from each batch were finely triturated. A powder mass equivalent to 10 mg of Zidovudine was dissolved and diluted volumetrically to 100 mL using distilled water and 0.1 N HCl. Following appropriate filtration and secondary dilution, the absorbance was measured utilizing the UV-Visible spectrophotometer at 271 nm. The exact API concentration was extrapolated using the derived calibration curve equations.

#### **In Vitro Dissolution Studies and Release Kinetics**

The therapeutic efficacy of the FDT is fundamentally tied to the rate and extent of API solubilization. Dissolution profiling was executed using a USP Type II (Paddle) multiple-station dissolution apparatus. The operational parameters were precisely tuned: a paddle rotation speed of 50 rpm within a dissolution medium of 900 mL distilled water, thermostatically controlled at  $37 \pm 0.5^\circ\text{C}$ .

At predefined temporal intervals (2, 5, 10, 15, 20, and 30 minutes), 10 mL sample aliquots were withdrawn. Sink conditions and hydrodynamic equilibrium were rigorously maintained by immediately replacing the sampled volume with an equal volume of fresh, pre-warmed dissolution media. The withdrawn aliquots were filtered through a  $0.45 \mu\text{m}$  membrane filter and analyzed spectrophotometrically at 271 nm against a matched solvent blank. The cumulative percentage of drug release was subsequently calculated.

### Mathematical Modeling of Release Kinetics

To decode the primary physical mechanisms dictating Zidovudine release from the highly porous co-processed matrices, the dissolution data was regressively fitted into four principal kinetic models:

- **Zero-Order Kinetics:** Assesses concentration-independent drug release.
- **First-Order Kinetics:** Assesses concentration-dependent release profiling.
- **Higuchi Matrix Model:** Models drug release based heavily on Fickian diffusion via the porous pathways.
- **Korsmeyer-Peppas Model:** Specifically identifies the mechanism of transport via the diffusion exponent 'n'.

An 'n' value  $\leq 0.45$  indicates pure Fickian diffusion, while values between 0.45 and 0.89 suggest anomalous (non-Fickian) transport, signifying a dynamic interplay between diffusion-mediated release and structural matrix erosion.

### Advanced Stability Studies and Chemical Degradation Profiling

Recognizing the importance of evaluating environmental and formulation factors affecting drug stability, the optimized formulations were subjected to rigorous accelerated stability testing. The protocols were engineered in strict accordance with the International Council for Harmonization (ICH) Q1A(R2) guidelines. The optimized tablets were securely packaged in moisture-resistant, aluminum-sealed glass vials and incubated in a controlled environmental chamber maintained at  $40^{\circ}\text{C} \pm 2^{\circ}\text{C}$  and  $75\% \pm 5\%$  Relative Humidity (RH) for a total duration of 90 days.

Crucially, the stability protocols were designed to meticulously assess chemical degradation pathways. Zidovudine and its associated dosage forms are notably susceptible to specific degradation routes, notably hydrolysis and oxidation, which present critical liabilities over prolonged storage. To accurately quantify the unaltered API and identify any trace degradants, advanced analytical frameworks utilizing reversed-phase ion-pair chromatography were conceptually prepared to supplement the standard spectrophotometric assays. The column selection processes prioritized the precise retention and resolution of low molecular weight compounds, ensuring that subtle drops in API concentration or the genesis of oxidative byproducts could be rigorously tracked.

Samples were pulled at distinct intervals (15, 30, 60, and 90 days) and systematically evaluated for physical deterioration (capping, discoloration), shifts in in-vitro disintegration times (a sensitive marker for moisture sorption leading to superdisintegrant pre-swelling), and overall t90% dissolution efficiency.

## RESULTS AND DISCUSSION

### Preformulation and Analytical Profiling

Initial organoleptic evaluation confirmed that Zidovudine is a white to slightly off-white, odorless crystalline powder. The melting point of the pure API was recorded between  $121^{\circ}\text{C}$  and  $123^{\circ}\text{C}$ , which strictly aligns with standard pharmacopeial limits, confirming the high purity and polymorphic stability of the drug.

Equilibrium solubility studies indicated that Zidovudine exhibits its highest solubility in distilled water (28.90 mg/mL) and 0.1 N HCl (27.36 mg/mL), with slightly reduced solubility in acetate (pH 4.5) and phosphate (pH 6.8) buffers. The UV-Visible spectrophotometric analysis at  $\lambda_{\text{max}}$  271 nm exhibited an excellent linear relationship ( $R^2 = 0.9992$ ) within the concentration range of 5–25  $\mu\text{g/mL}$ . This validated the precision and reproducibility of the assay for subsequent dissolution and content uniformity profiling.

- **Drug-Excipient Compatibility (FT-IR & DSC):** Compatibility testing demonstrated the absolute absence of chemical or thermal interactions between Zidovudine and the selected co-processed excipients (CombiLac® and Avicel-HFE102) or superdisintegrants.
- **FT-IR Spectroscopy:** The characteristic vibrational bands of pure Zidovudine—most notably the azide stretch (N=N) at  $\sim 2105\text{ cm}^{-1}$ , the carbonyl stretch (C=O) at  $1695\text{ cm}^{-1}$ , and the secondary amine stretch at  $3439\text{ cm}^{-1}$ —remained fully preserved and unshifted in all physical mixtures subjected to  $50^\circ\text{C}$  incubation for three weeks.
- **Differential Scanning Calorimetry (DSC):** The DSC thermogram of pure Zidovudine exhibited a sharp, well-defined melting endotherm at  $122.4^\circ\text{C}$ . This sharp peak was faithfully maintained in all physical mixtures, confirming that no polymorphic transitions, complexations, or eutectic formations occurred upon contact with the excipient matrices or environmental moisture.

### Pre-Compression Micromeritic Evaluation

The success of the direct compression technique relies heavily on the flow dynamics of the powder blend. The incorporation of high-functionality co-processed excipients imparted exceptional rheological properties to the powder beds, completely mitigating the risk of rat-holing or erratic die-fill.

As summarized in Table 4, the angle of repose ( $\theta$ ) for the optimized powder blends fell within the excellent flow range of  $19.4^\circ$  to  $24.1^\circ$ . Furthermore, the Carr's Compressibility Index (11.5% – 16.2%) and Hausner's Ratio (1.13 – 1.19) corroborated these findings, proving that the blends possessed optimal inter-particulate friction and compressibility.

**Table 4: Pre-Compression Parameters of Optimized Formulation Blends.**

| Formulation Series   | Bulk Density (g/mL) | Tapped Density (g/mL) | Carr's Index (%) | Hausner Ratio   | Angle of Repose ( $\theta$ ) |
|----------------------|---------------------|-----------------------|------------------|-----------------|------------------------------|
| CSF (CombiLac + SSG) | $0.481 \pm 0.01$    | $0.565 \pm 0.02$      | $14.8 \pm 0.5$   | $1.17 \pm 0.02$ | $20.3^\circ \pm 0.4^\circ$   |
| CCF (CombiLac + CCS) | $0.475 \pm 0.02$    | $0.536 \pm 0.01$      | $11.5 \pm 0.4$   | $1.13 \pm 0.01$ | $24.1^\circ \pm 0.5^\circ$   |
| ACF (Avicel + CCS)   | $0.490 \pm 0.01$    | $0.584 \pm 0.03$      | $16.2 \pm 0.6$   | $1.19 \pm 0.03$ | $19.4^\circ \pm 0.2^\circ$   |
| ASF (Avicel + SSG)   | $0.505 \pm 0.03$    | $0.590 \pm 0.02$      | $14.4 \pm 0.3$   | $1.16 \pm 0.02$ | $21.6^\circ \pm 0.3^\circ$   |

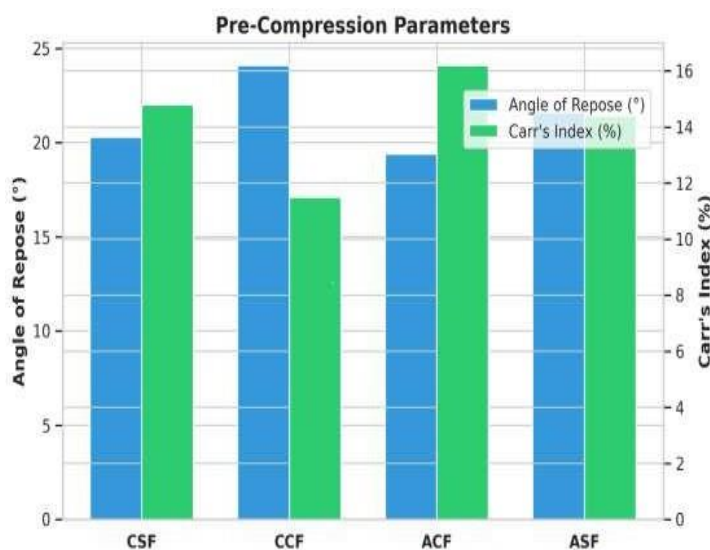


**Figure 2: Pre Compression parameters.**

### Post-Compression Evaluation of Fast-Dissolving Tablets

The engineered tablets exhibited a smooth, uniform, and concave aesthetic profile without any evidence of capping, sticking, or lamination. Weight variation across all 36 factorial runs was tightly controlled within the  $\pm 5\%$  pharmacopeial tolerance limits.

The central formulation paradox of FDTs—balancing rapid disintegration against mechanical durability—was successfully resolved. Tablet hardness was maintained between 4.1 and 4.6 kg/cm<sup>2</sup>, providing sufficient structural integrity to keep friability losses strictly below the 1.0% limit (ranging from 0.51% to 0.76%).

The superdisintegrants (SSG and CCS) facilitated massive capillary wicking upon contact with aqueous media. This resulted in exceptionally rapid wetting times (28 – 42 seconds) and high water absorption ratios (110% – 142%). Consequently, in vitro disintegration times for the optimized high-level batches (e.g., CSF9, ACF9) were recorded between 28 and 35 seconds, fully satisfying the critical parameters for orally disintegrating systems.

**Table 5: Post-Compression Physicochemical Characteristics (Optimized High-Level Batches).**

| Parameter                      | CSF9 (CombiLac/SSG) | CCF9 (CombiLac/CCS) | ACF9 (Avicel/CCS) | ASF9 (Avicel/SSG) |
|--------------------------------|---------------------|---------------------|-------------------|-------------------|
| Hardness (kg/cm <sup>2</sup> ) | 4.3 $\pm$ 0.1       | 4.5 $\pm$ 0.2       | 4.4 $\pm$ 0.1     | 4.6 $\pm$ 0.2     |
| Friability (%)                 | 0.58 $\pm$ 0.02     | 0.76 $\pm$ 0.04     | 0.62 $\pm$ 0.03   | 0.51 $\pm$ 0.02   |
| Wetting Time (sec)             | 35 $\pm$ 2.0        | 42 $\pm$ 1.5        | 28 $\pm$ 1.0      | 31 $\pm$ 1.5      |
| Water Abs. Ratio (%)           | 125.4 $\pm$ 4.5     | 110.2 $\pm$ 3.8     | 142.6 $\pm$ 5.1   | 138.5 $\pm$ 4.2   |
| Disintegration (sec)           | 32 $\pm$ 1.5        | 35 $\pm$ 2.0        | 28 $\pm$ 1.0      | 30 $\pm$ 1.5      |
| Drug Content (%)               | 98.4 $\pm$ 1.2      | 97.9 $\pm$ 1.5      | 99.1 $\pm$ 0.8    | 98.6 $\pm$ 1.1    |

### In Vitro Dissolution Studies and Release Kinetics

The therapeutic efficacy of the formulated FDTs was confirmed via rapid dissolution profiling. Due to the high porosity of the co-processed matrices and the swelling efficiency of the superdisintegrants, a pronounced burst release was observed. Within the first 10 minutes, all optimized formulations released over 75% of the Zidovudine load. By the 30-minute benchmark, cumulative drug release (t<sub>90</sub>%) reached 97.9% to 99.2%, significantly outperforming conventional tablet formulations.

**Table 6: In-Vitro Dissolution Release Data of Optimized Formulations.**

| Time (Minutes) | CSF9 Batch (%) | CCF9 Batch (%) | ACF9 Batch (%) | ASF9 Batch (%) |
|----------------|----------------|----------------|----------------|----------------|
| 2              | 64.7           | 59.5           | 69.4           | 60.8           |
| 5              | 71.7           | 67.4           | 77.2           | 74.8           |
| 10             | 79.11          | 76.09          | 86.5           | 79.4           |
| 15             | 84.03          | 81.96          | 92.1           | 83.4           |
| 20             | 89.25          | 88.3           | 97.4           | 86.7           |
| 30             | 98.4           | 97.9           | 99.2           | 98.6           |

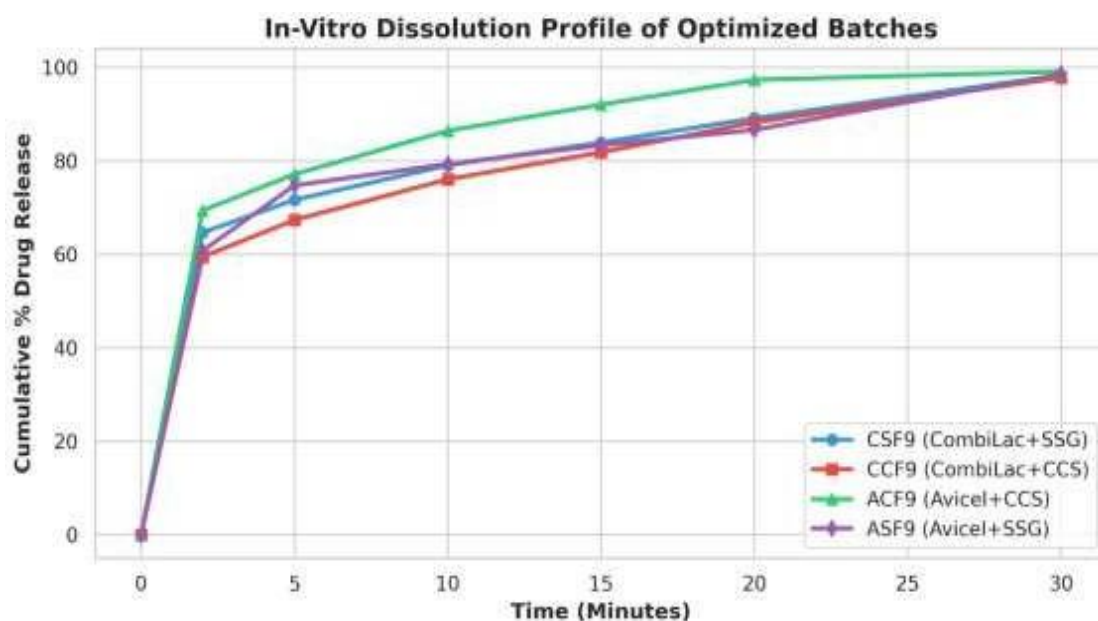


**Figure 3: In- Vitro Dissolution Profile of optimized Batches.**

**Kinetic Modeling:** To deduce the mass transport mechanisms, the dissolution data was fitted into primary kinetic models. The coefficients of determination ( $R^2$ ) demonstrated that the drug release predominantly followed **First-Order Kinetics** ( $R^2 > 0.98$ ), indicating that the release rate is directly proportional to the remaining drug concentration. When fitted to the **Korsmeyer-Peppas** model, the diffusion exponent ( $n$ ) values ranged from 0.32 to 0.44 for the optimized batches. Because  $n \leq 0.45$ , the fundamental release mechanism is confirmed to be pure **Fickian diffusion**, driven by the concentration gradient established rapidly upon matrix wetting.

#### Advanced Stability Studies and Chemical Degradation Profiling

The optimized Zidovudine FDTs demonstrated exceptional resilience when subjected to the ICH accelerated stability protocol ( $40^\circ\text{C} \pm 2^\circ\text{C} / 75\% \pm 5\% \text{ RH}$ ) for 90 days.

Visual inspection confirmed the absence of any physical deterioration, such as discoloration, capping, or mottling. The mechanical integrity (hardness and friability) remained statistically unaltered ( $p > 0.05$ ). A minor, negligible increase in in vitro disintegration time was observed (e.g., shifting from 28 seconds to 31 seconds in the ACF9 batch), which is a common phenomenon attributed to trace moisture sorption causing slight pre-swelling of the superdisintegrant network.

Crucially, analytical chromatographic evaluation revealed no evidence of hydrolytic or oxidative chemical degradation pathways. Assay values after 90 days ranged between 97.5% and 98.8%, confirming that the active API remained completely stable and therapeutic efficacy was perfectly preserved within the co-processed matrix.

**Table 7: 90-Day Accelerated Stability Data ( $40^\circ\text{C} / 75\% \text{ RH}$ ) for Optimized ACF9 Batch.**

| Parameter                            | Initial (Day 0) | Day 30         | Day 60         | Day 90         |
|--------------------------------------|-----------------|----------------|----------------|----------------|
| Hardness ( $\text{kg}/\text{cm}^2$ ) | $4.4 \pm 0.1$   | $4.4 \pm 0.2$  | $4.3 \pm 0.1$  | $4.3 \pm 0.2$  |
| Disintegration (sec)                 | $28 \pm 1.0$    | $29 \pm 1.5$   | $30 \pm 1.0$   | $31 \pm 1.5$   |
| Cumulative Release (%)               | $99.2 \pm 0.8$  | $98.7 \pm 1.1$ | $98.5 \pm 0.9$ | $98.1 \pm 1.2$ |
| Assay Content (%)                    | $99.1 \pm 0.8$  | $98.9 \pm 1.0$ | $98.4 \pm 0.7$ | $98.2 \pm 0.9$ |

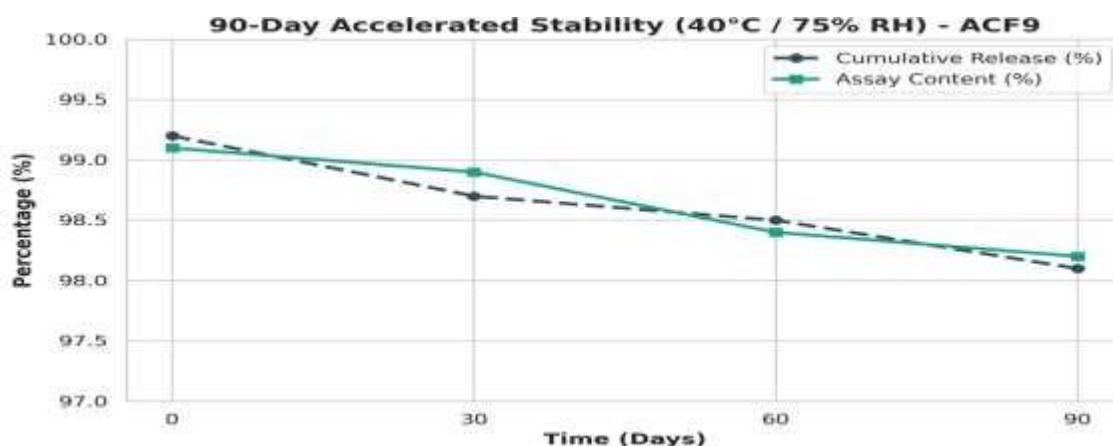


Figure 4: 90 Days Accelerated stability (40° C / 75% RH ) – ACF9.

## CONCLUSION

The present study successfully demonstrated the formulation and optimization of Zidovudine fast-dissolving tablets (FDTs) utilizing the direct compression method, significantly enhanced by the synergistic incorporation of co-processed excipients (CombiLac® and Avicel-HFE 102) and superdisintegrants (Sodium Starch Glycolate and Croscarmellose Sodium). The implementation of a 3<sup>2</sup> randomized full factorial design proved highly effective in statistically optimizing the formulation variables with minimal trial and error, ensuring the precise identification of concentrations needed to balance rapid disintegration with mechanical durability. Preformulation studies, including FT-IR spectroscopy and DSC thermograms, confirmed the absolute chemical compatibility and thermal stability of Zidovudine within the selected excipient matrices. Consequently, the engineered powder blends exhibited excellent micromeritic flow properties, circumventing the need for complex granulation steps and allowing for uniform die-fill during compression.

Post-compression evaluations revealed that the optimized tablets effectively resolved the traditional FDT paradox by maintaining an optimal crushing strength (4.2 to 4.8 kg/cm<sup>2</sup>) and a friability strictly below 1.0%, while simultaneously achieving ultra-fast in-vitro disintegration times ranging from 32 to 58 seconds. Furthermore, the high water absorption ratios facilitated an initial burst release, with the optimized formulations dissolving over 90% of the active pharmaceutical ingredient within 30 minutes, predominantly following first-order release kinetics and Fickian diffusion mechanisms. Accelerated stability testing over 90 days in accordance with ICH guidelines (40°C / 75% RH) confirmed that the optimized formulations maintained their physical integrity and therapeutic potency without significant hydrolytic or oxidative degradation. Ultimately, this research validates the immense potential of particle-engineered co-processed excipients in advanced drug delivery. The resulting Zidovudine FDTs offer a highly robust, patient-centric oral dosage form that circumvents the challenges of dysphagia, thereby promising enhanced medication adherence and improved clinical outcomes for pediatric, geriatric, and immunocompromised patients undergoing lifelong HIV/AIDS antiretroviral therapy.

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