# FORMULATION, IN-VITRO EVALUATION, STUDY OF EFFECT OF HARDNESS ON BUOYANCY TIME OF GASTRO RETENTIVE FILM AND FLOATING TABLETS

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Zidovudine an antiretroviral drug has a short half life of 1-1.5 hours, which requires multiple dosing to achieve desired therapeutic levels. A sustained release formulation will be beneficial as it would avoid multiple dosing. In the present study a gastro-retentive formulation having sustained release was developed using two formulations, tablet and film. Tablet of Zidovudine were prepared by wax based technology using different combinations of white bees wax and hard paraffin (G1-G4). The formulations were evaluated for various physical parameters, buoyancy studies & dissolution. It was found that the .G1 formulation showed maximum floating time of more than 12 hrs & drug release was for 12 hours. Gastro-retentive film of Zidovudine was prepared by using cellulose acetate as a gastro-retentive polymer in five different concentrations (ZV1-ZV10). The prepared film was evaluated for various physical parameters & buoyancy studies. The formulation ZV5 was having floating time of more than 12 hours. It was concluded that Zidovudine could be formulated as a tablet and film formulations for a sustained release action up to 12 hours.

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## 1. Introduction

Gastro-retentive dosage forms are used for sustained release of drugs [1]. In the present study we have designed two gastro-retentive dosage formulations of zidovudine that is tablet and film. Tablet was prepared through wax based technology and film was prepared by solvent evaporation technique. Zidovudine is the first effective antiretroviral agent. It is a synthetic thymidine analog. It absorbs rapidly &reaches peak plasma concentration within 1 hour. The elimination half life of parent compound is considerably shorter than that of the intracellular tri-phosphate which is 3-4 hour. A sustained release formulation will be beneficial as it would avoid multiple dosing [3-5].. Zidovudine the first anti-HIV compound approved for clinical use is widely used for treatment of AIDS either alone or in combination with other antiviral agents. However, the main limitation to therapeutic effectiveness of Zidovudine is its dose-dependent hematological toxicity, low therapeutic index, short biological half-life, and poor bioavailability [6]. After oral administration, it is rapidly absorbed from the gastrointestinal tract (GIT) exhibiting a peak plasma concentration of 1.2 μg/mL at 0.8 hours [7].

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## 2. Experimental

Zidovudine and Xanthan gum was gifted from Sun Pharma Industries Jammu and Cipla Mumbai, HPMC K4 and HPMC K100 was gifted by Colorcon Asia Pvt. Ltd. other reagents were obtained from laboratory. It is one of the important prerequisite in development of any drug delivery system. Preformulation studies were performed on the drug, which included melting point determination, solubility and compatibility studies. Compatibility with excipients was conformed by carried out IR studies. The pure drug and its formulations along with excipients were subjected to IR studies. In the present study, the Sodium Chloride disc (pellet) method was employed Compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and polymer were studied. The characteristic absorption peaks of were obtained at 1856.72 $cm^{-1}$, 1243.49 $cm^{-1}$, 857.61 $cm^{-1.}$

### Evaluation of Powder Blend [8-10]

Angle of repose: The angle of repose of powder blend was determined by the funnel method. The accurately weight powder blend were taken in the funnel. The height of the funnel was adjusted in such a way the tip of the funnel just touched the apex of the powder blend. The powder blend was allowed to flow through the funnel freely on to the surface. The diameter of the powder cone was measured and angle of repose was calculated using the following equation.

$$\tan \theta = h/r$$

Where, h and r are the height and radius of the powder cone. Bulk density: Both loose bulk density (LBD) and tapped bulk density (TBD) was determined. A quantity of 2 gm of powder blend from each formula, previously shaken to break any agglomerates formed, was introduced in to 10 ml measuring cylinder. After that the initial volume was noted and the cylinder was allowed to fall under its own weight on to a hard surface from the height of 2.5 cm at second intervals. Tapping was continued until no further change in volume was noted.
LBD and TDB were calculated using the following equations.
LBD= Weight of the powder blend/Untapped Volume of the packing
TBD=Weight of the powder blend/Tapped Volume of the packing

Compressibility Index: The Compressibility Index of the powder blend was determined by Carr's compressibility index. It is a simple test to evaluate the LBD and TBD of a powder and the rate at which it packed down. The formula for Carr's Index is as below:

$$\text{Carr's Index (\%)} = [(TBD-LBD)\ x100]/TBD$$

Total Porosity: Total porosity was determined by measuring the volume occupied by a selected weight of a powder (Vbulk) and the true volume of the powder blend (The space occupied by the powder exclusive of spaces greater than the intermolecular spaces, V)

$$\text{Porosity (\%)} = Vbulk-V/Vbulk\ x\ 100$$

### Method of Preparation of Tablet

Beeswax, hard paraffin & liquid paraffin were melted in a large petridish & the required quantity of zidovudine was added to the molten mass. Previously prepared geometric mixture of starch, sodium bicarbonate was added to the molten mixture and stirred well to mix. The mass was removed from hot plate & subjected to scrapping untill it attained room temperature. The coherent mass is passed through 22 mesh sieve & was resifted on a 40 mesh sieve to remove the fines. The granules (5 g) from both the 22 and 40 mesh sieves were collected and mixed with 2% w/w talc and 1% w/w magnesium stearate. This lubricated blend was compressed into tablets using tablet punching machine (Jyoti Scientific industries Gwalior M.P.).Compression force was adjusted to

obtain tablets with hardness in range of 5 to 10 kg/cm2.Tablets weighed 625 ± 2 mg, and was round flat-face with an average diameter of 12 mm and thickness of 9 mm.

**Evaluations of Powder Blend of Tablet**

The powder blend of tablet was evaluated for the bulk density, tapped density and angle of repose. The formulation GI has bulk density of 4.1, tapped density of 2.4 & angle of repose of 14.5.

**Evaluation of Prepared Tablet:**

The prepared tablet was evaluated for uniformity of weight, hardness, friability, In vitro disintegration, in vitro dissolution, lag time & floating time [11] . And the formulation GI has hardness 5 , friability 0.58 % , lag time 0.23 sec , floating time more than 15 hour , In vitro disintegration time more than 1.5 hour & showed drug release for more than 16 hours.

**Drug content [12]**

Five tablets were weighed individually and powdered. The powder equivalent to average weight of tablets was weighed and drug was extracted in 0.1 N HCl, the drug content was determined measuring the absorbance at 317.4 nm after suitable dilution using a Shimadzu UV-1701 UV/Vis double beam spectrophotometer.

**Friability Test**

The friability of tablets were determined using Roche Friabilator. It is expressed in percentage (%). Ten tablets were initially weighed (W initial) and transferred into friabilator. The friabilator was operated at 25rpm for 4 minutes or run up to 100 revolutions. The tablets were weighed again (Wfinal). The % friability was then calculated by –

% Friability = 100 (1-Winitial/ Wfinal)

% Friability of tablets less than 1% are considered acceptable.

**In vitro buoyancy studies** [13]

The in vitro buoyancy was determined by floating lag time method described by Dave B.S.10The tablets were placed in 250 ml beaker containing 0.1 N HCl. The time required for the tablets to rise to the surface and float was determined as floating lag time. The time between introduction of dosage form and its buoyancy in 0.1 N HCl and the time during which the dosage form remain buoyant were measured. The time taken for dosage form to emerge on surface of medium called Floating Lag Time (FLT) or Buoyancy Lag Time (BLT) and total duration of time by which dosage form remain buoyant is called Total Floating Time (TFT).

**In Vitro dissolution studies [14]**

The release rate of Zidovudine from floating tablets was determined using *The United States Pharmacopoeia* (USP) XXIV dissolution testing apparatus II (paddle method). The dissolution test was performed using 900 ml of 0.1 N HCl, at 37 ± 0.5°C and 60 rpm A sample (5 ml) of the solution was withdrawn from the dissolution apparatus hourly for 12 hours, and the samples were replaced with fresh dissolution medium. The samples diluted to a suitable concentration with 0.1N HCl. Absorbance of these solutions was measured at 317.4 nm using a Shimadzu UV-1701 UV/Vis double beam spectrophotometer. Cumulative percentage of drug release was calculated using the equation obtained from a standard curve.

**Swelling index**

The swelling index of tablets was determined n 0.1 N HCl (pH 1.2) at room temperature. The swollen weight of the tablets was determined at predefined time intervals. The swelling index was calculated by the following equation:

Swelling index WU = (Wt - W0) X100/ W0

Where, Wt = Weight of tablet at time t.
W0 = Initial weight of tablet

**Effect of hardness on buoyancy lags time**

Formulation ZV10 was selected to study the effect of hardness on buoyancy lag time. The tablets of batch 10 were compressed at different compression pressures to get the hardness of 4kg/cm$^2$, 6kg/cm$^2$ ,8kg/cm$^2$ ,10kg/cm$^2$and 12 kg/cm$^2$. The tablets were evaluated for Buoyancy Lag Time. The method followed is same as that of Buoyancy test.

**Stability study [15-17]**

Gastro retentive tablets of Zidovudine formulated in the present study were subjected to accelerated stability studies. Stability studies of the prepared formulations were performed at ambient humidity conditions, at room temperature, at 40$^o$C period up to 30 days. The samples were withdrawn after periods of 15 days, and 30 days and were analyzed for its appearance, hardness, and friability, floating time, drug content and in vitro release.

**Preparation of Gastro Retentive Film of Zidovudine:**

For the preparation of floating film of Zidovudine we have mixed an equal amount of cellulose acetate and Zidovudine and dissolved it in acetone. This solution was poured in a perti dish, after evaporation of the solvent a smooth film was formed.

**Evaluation of Gastro Retentive Film of Zidovudine:**

The prepared film of Zidovudine was evaluated for lag time floating time & In vitro disintegration time. The results for the best formulation were lag time 0.02 sec, floating time more than 12 hour, In vitro disintegration time more than 1 hour.

**3. Result and discussion**

Angle of Repose (q):- The angle of repose for the formulated blend was carried out.It concludes all the formulations blend was found to be in the range 64.88' to 69.30'.

Compressibility Index: - Compressibility index was carried out, it found between 22.34% to 26.30% indicating the powder blend have the required flow property for compression

Friability Test :- The % friability was less than 1% in all the formulations ensuring that the tablets were mechanically stable.

*Table 1. Composition of Zidovudine Floating Tablets*

| **Ingredients** | **ZV1** | **ZV2** | **ZV3** | **ZV4** | **ZV5** | **ZV6** | **ZV7** | **ZV8** | **ZV9** | **ZV10** |
|---|---|---|---|---|---|---|---|---|---|---|
| Zidovudine | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 | 25 |
| HPMCK4M 40 | 45 | ----- | 45 | 65 | - | 15 | ----- | 25 | 65 | 65 |
| HPMC K100M | 60 | 60 | 60 | 60 | --- | 60 | ---- | 40 | 40 | 40 |
| Xanthan gum | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 | 15 |
| Sodium bicarbonate | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 | 5.5 |
| Citric acid | 13.5 | 13.5 | 13.5 | 13.5 | 13.5 | 13.5 | 13.5 | 13.5 | 13.5 | 13.5 |
| PVP-K-30 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 | 35 |
| Magnesium Stearate | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 | 18 |
| Talc | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Avicel | 2.20 | 2.20 | 2.20 | 2.20 | 2.20 | 2.20 | 2.20 | 2.20 | 2.20 | 2.20 |

# All quantities were in milligrams.

Drug Content Uniformity: - The percentage of drug content for ZV1 to ZV 10 was found to be between 97.11% to 105.69% of Zidovudine, it complies with official specifications

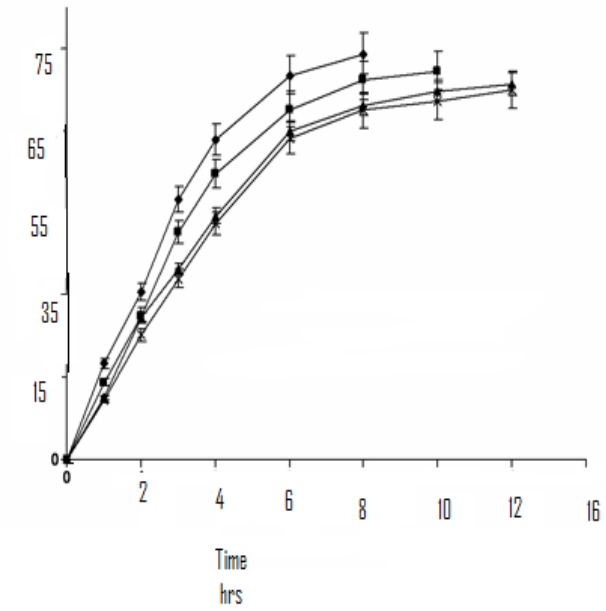


*Fig. 1. In vitro dissolution profile for tablets of batches ZV1 to ZV 10*

**In vitro buoyancy study**

On immersion in 0.1N HCl solution pH (1.2) at 37.$^0$C, the tablets floated, and remained buoyant without disintegration. From the results it can be concluded that the batch containing only HPMC polymer showed good Buoyancy lag time (BLT) and Total floating time (TFT). Formulation containing HPMC K4M, HPMC K100M and Xanthan gum showed good BLT of 55 sec, while the formulation containing Xanthan gum did not float more than 2.5 hrs. This may be due to the nature of polymer and gas generating agent, which were kept constant in the present study.

*Table 2. Effect of hardness on Buoyancy lag time of formulation ZV 1-ZV 10*

| **Hardness in kg/cm $^2$** | **Buoyancy Lag Time (sec)** |
|---|---|
| 4 | 25 |
| 6 | 43 |
| 8 | 63 |
| 10 | 75 |
| 12 | 98 |

**In-vitro Dissolution Study and Kinetic modelling of drug release [18-21]**

The release data obtained for formulations ZV1 to ZV10 were tabulated in IV shows the plot of cumulative % drug released as a function of time for different formulations. The in-vitro release of all ten batches of floating tablets showed the release with an initial effect. In the first hour % drug released were 41.9, 37.30, 32.41, 30.44, 29.66, 34.23, 39.79, 24.66, 35.66 and 25.51.

*Table 3. Kinetic values obtained from invitro released data of formulation*

| Kinetic Model | Intercept | Slope | R2 |
|---|---|---|---|

| | | | |
|---|---|---|---|
| Zero-order plot | 23.16 | 7.51 | 0.9843 |
| First-order plot | 12.64 | 2.85 | 0.9651 |

## 4. Conclusions

In the present study an attempt was made to develop a gastro retentive dosage form of Zidovudine. Two gastro retentive dosage forms were developed in this study that is tablet & film. Tablet was prepared by using hard paraffin & white beeswax as a matrixing agent & floating enhancer. Results of analysis indicated that low levels hard paraffin and a high level of white bees wax should be used to manufacture the tablet formulation with desired in vitro floating time and dissolution. Formulation GI was selected as a promising formulation. Film was prepared by using cellulose acetate and it has floated for more than 12 hours thus it can also be used to prepare a sustained release formulation of zidovudine.After present study it can be concluded that a gastro retentive dosage form of zidovudine can be used for its sustained release.

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