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# Formulation and evaluation of zidovudine sustained release matrix tablets

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## ABSTRACT

The objective of the study was to design oral sustained release matrix tablets of zidovudine using Hydroxy Propyl Methyl Cellulose (HPMC) K4M, Guar Gum and Ethyl Cellulose as the retardant polymers and study the effect of various formulation factors such as polymer proportion, polymer type and effect of filler type on the in vitro release of the drug. Matrix tablets were prepared by wet granulation method and prepared tablets were evaluated for weight variation percentage friability, hardness thickness and in vitro dissolution studies. All the granules and formulations showed compliance with pharmacopieal standards .In vitro release studies revealed that the release rate decreased with increase polymer proportion and hydrophobic polymers retard the drug release more than hydrophilic polymers .The formulations F2 and F8 sustained release of drug for 12 hrs with 96%, 98% release but F5 (15% of HPMC) using MCC as diluent drug releases 10 hours only. Because of swelling property of MCC increased the drug release profile to a small extent due to change in swelling at the tablet surface. The kinetic treatment showed that the mechanism of drug release non-Fickian for HPMC and Ficikian–Diffusion process for guar gum. The developed sustained release matrix tablets of zidovudine with good initial release for first 2hrs(20-25%) and extended the release up to 12hrs can over come the disadvantages of conventional zidovudine tablets.

***Keywords:*** Zidovudine, Matrix tablet, Guar gum, Ethyl cellulose

## INTRODUCTION

The oral route is the route most often used for administration of drugs. Tablets are the most popular oral formulations available in the market and are preferred by patients and physicians alike. In long-term therapy for the treatment of chronic disease conditions, conventional formulations are required to be administered in multiple doses and therefore have several disadvantages.[1] Sustained release formulations are preferred for such therapy because they maintain uniform drug levels, reduce dose and side effects, better patient compliance, and increase safety margin for high potency drugs.[2]

Zidovudine (AZT), 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. It is crucial for the success of AIDS therapy to maintain the systemic drug concentration consistently above its target antiretroviral concentration throughout the course of the treatment.[3]

The main limitations to the therapeutic effectiveness of zidovudine are its dose-dependent hematological toxicity, narrow therapeutic index (0.4-4.0 µmol/L)[4], poor bioavailability (65% dose), and short biological half life (1 hr). After oral administration, zidovudine is rapidly absorbed from the gastro intestinal tract and exhibiting peak plasma concentration of 1.2µg/mL at 0.8 hrs. In the systemic circulation it is first converted to zidovudine-triphosphate, which is pharmacologically active. Although the biological half-life of zidovudine-triphosphate is 4 hrs, thus necessating frequent administration i.e. 3 to 4 times in a day to maintain constant therapeutic drug levels. Since AZT acts as a metabolic antagonist of thymidine and its antiviral effect is time dependent, an adequate zero-order delivery of AZT is desired for maintaining anti-AIDS effect and avoiding the strong side effects. The side effects are usually associated with excessive plasma level of AZT immediately after intravenous or oral administration.

HPMC, a semi synthetic derivative of cellulose, a swellable and hydrophilic polymer. Some research groups have worked on the usage of swellable HPMC as the retarding polymer to sustain the release of different drugs.[5] It is very suitable to use a retardant material in sustained release matrix tablets, as it is nontoxic and easy to handle.[6] Guar gum is a galactomann, obtained from the ground endosperm of guar seeds of plant Cyamopsis tetragonolobus. It has been investigated as controlled release carrier and regarded as a nontoxic and non-irritant material.[7] Ethyl cellulose has been evaluated as hydrophobic matrix to prolong the release of water-soluble drugs.[8]

The present study was designed to formulate matrix tablets using Guar gum, HPMCK4M and Ethyl cellulose polymers, and to investigate effect of various formulation factors such as polymer proportion, polymer type and effect of filler type (MCC and Talc) on the in vitro release of the water-soluble zidovudine matrix tablets.

## MATERIALSAND METHODS

Zidovudine was obtained as a gift sample from Matrix Labs, Hyderabad and Zydus Cadilla, Ahmedabad. Polymers Guar Gum and Ethyl Cellu-

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lose were obtained as gift samples from Dynamed Pharmaceuticals Pvt ltd., Hyderabad. HPMC K4M was a gift sample from Zydus cadila, Ahmedabad. All other chemicals and reagents used in the study were of analytical grade.

**Preparation of the Matrix Tablets: -**

Matrix tablets were prepared by wet granulation method as reported by Bettini et.al[9]. Zidovudine (300 mg) was dry blended with appropriate quantity of polymer(s) and diluent talc and granulated using 5% wt/vol ethanolic solution of PVP-K30. The wet mass was passed through a No.10 sieve. The wet granules were dried at 55º C ± 5 ºC for one hour and sieved through No.18 sieve. Granule mixtire was blended with 1% magnesiumstearate and mixed for 5 minutes. This granule mixture was compressed using 16 stations rotary tableting machine (Cadmach Machinery Co, Ahmedabad.) equipped with round, concave faced punches of 13-mm diameter.Polymer ratio was varied to get matrix tablets of varying polymer concentrations of 10%, 15%, 20% for Guar gum,ethyl cellulose and HPMCK4M. Polymers . The same method described above was followed microcrystalline cellulose (MCC) powder in place of Talc for HPMC polymer for observing the diluent effect.

The composition of variuous formulations is summarized in Table-1.

**Evaluation of Matrix Tablets [10]: -**

All prepared matrix tablets were evaluated for Hardness (Monsanto hardness tester), Weight variation, assay, percentage friability (Roche friabilator), Thickness (Screw gauge).
The values of evaluation parameters are given in table-2.

**In –Vitro Release Studies**

The in vitro dissolution study was carried out using 8 station dissolution rate test apparatus (Electro lab, TDT-08L) USP (apparatus 1) basket method at 50 rpm. The dissolution medium consisted of 900ml simulated gastric fluid (pH 1.2) for first 2hrs followed by simulated intestinal fluid (pH 7.4) from 2-12 hrs. Aliquots of 5ml were withdrawn every one-hour and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced. Aliquots withdrawn were diluted suitably, filtered and analyzed at 266nm spectrophotometrically[11]. All the release studies were conducted in triplicate and the mean values were plotted verses time with standard deviation less than three indicating reproducibility result.
The plot of percentage cumulative drug release against time (Hrs.) is shown in
Figure1, 2 and 3.

**Calculation of Theoretical Release Profile of Zidovudine from Sustained Release Formulations**

Theoretical release profile of a drug is constructed to check whether the formulations are releasing the drug similar to the predicted profile. The total dose of Zidovudine for twice-daily sustained release formulation was calculated by the following equation

$$D_t = Dose[1+0.693\ X\ t/\ t_{1/2}] \text{——————(1)}$$

Where, $D_t$ = total dose of drug; Dose = dose of the immediate release part (35.04 mg); t = time (hours) during which the sustained release is desired (12 hours); $t_{1/2}$ = half-life of the drug (1.1 hours).

**Kinetic Analysis of Dissolution Data: -**

The order and mechanism of zidovudine release from the matrix tablets were determined by fitting the release rate studies data into Equations 1, 2, and 3:Equation 2, the zero order Equation; and Equation 3 Higuchi's square root equation; and equation 4 Korsmeyer and Peppas equation.

$$M_t/M_8 = K_0 t \text{……(2)}$$
$$M_t/M_8 = K_H t^{1/2} \text{. ……(3)}$$
$$M_t/M_8 = Kt^n \text{……(4)}$$

Where $M_t/M_8$ is the fraction of drug released at any time t and $K_0$,$K_H$,K are release rate constants for Equation 2,3,and 4,respectively. In equation 2, n is the diffusional exponent indicative of drug release. The values of K, $K_H$, $K_o$, n, t50% (time required for 50% of drug release), and r (correlation coefficient) were determined. Equations 2 and 3 fail to explain the drug release mechanism from polymeric matrices that undergo swelling and/or erosion during dissolution. In such cases, based on the value of n obtained by fitting the data into Equation 4, we can describe the mechanism of drug release from the formulation. A value of n-0.45 indicates Fickian (case-1) release: n>0.45 but >0.89 for non-Fickian (anomalous) release; and >0.89 indicates super case-II type of release. Case-II generally refers to the erosion of the polymeric chain and anomalous transport (Non-Fickian) refers to a combination of both diffusion and erosion controlled drug release.[12]
The values of mathematical modeling and drug release kinetics are given in Table 3.

**RESULTS AND DISCUSSION: -**

All the batches were evaluated for the Physical properties, Hardness of the tablet in the range of 4.62±0.25 to 6.0±0.7kg/cm2, (Table-3) thickness 4.24±0.08 to 4.54±0.01mm, Percentage weight loss in the Friability test was less than 0.7% in all batches and all the batches contained zidovudine within 100 ± 5% of the labeled content. Overall the prepared tablet batches of good quality with regard to hardness, friability and drug content.

**Effect of Polymer Concentration on the Release Profile**

Rate of drug release from the matrix tablets was found to decrease with increase in polymer ratio. This was because an increase in polymer concentration caused an increase in the viscosity of the gel (by making it more resistant to drug diffusion and erosion) as well as the formation of a gel layer with a longer diffusion path. This could have caused a decrease in the effective diffusion coefficient of the drug and therefore a reduction in the drug release rate. (Figure-1)

**Effect of Polymer Type on the Release Profile**

From the Figure-4 it can observed that, the release was highest from guar Gum matrix where as lowest drug release was found with Ethyl Cellulose. Ethyl Cellulose was extensively hydrophobic in nature with lower wettability and formation of pores and cracks did not occur to facilitate drug release. Hydrophilic polymers when exposed to the dissolution medium they swells and the formation of a gel-like network surrounding the tablet.

**Table 1: Formulation table of Zidovudine tablets**

| Code | HPMCK4M | Guar Gum | Ethyl Cellulose | Talc | MCC |
|---|---|---|---|---|---|
| F1 | 30 | - | - | 65 | - |
| F2 | 45 | - | - | 50 | - |
| F3 | 60 | - | - | 35 | - |
| F4 | 30 | - | - | - | 65 |
| F5 | 45 | - | - | - | 50 |
| F6 | 60 | - | - | - | 35 |
| F7 | - | 30 | - | 65 | - |
| F8 | - | 45 | - | 50 | - |
| F9 | - | 60 | - | 35 | - |
| F10 | - | - | 30 | 65 | - |
| F11 | - | - | 45 | 50 | - |
| F12 | - | - | 60 | 35 | - |

◆Tablet weight 400mg,All the formulations had Magnesium Stearate 1% as a lubricant

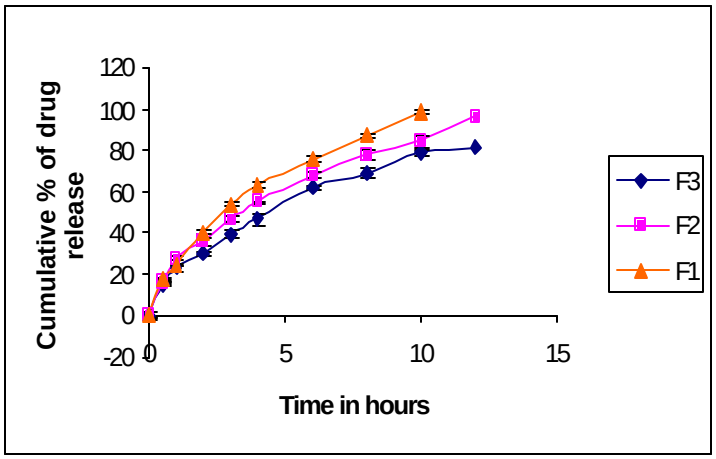



**Figure1. Percentage cumulative drug release of batches F1 to F3(HPMC K4M)**

**Table 2: Evaluation parameters of different formulations**

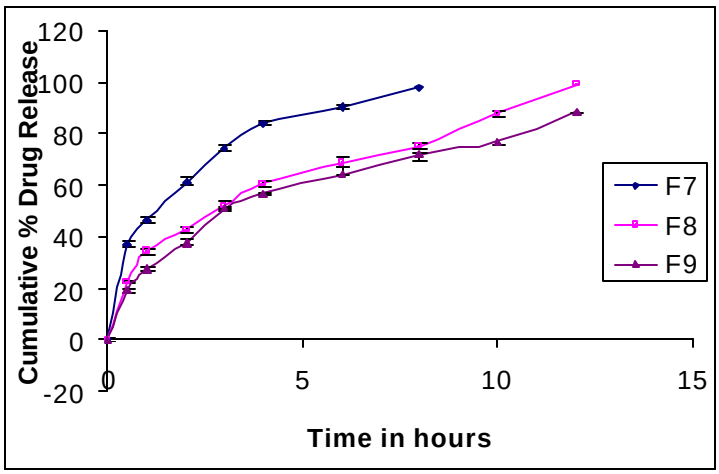
| Code | Hardness †(kg/cm²) | Thickness (mm) * Ariation‡(%) | Deviation in Weight | Friability† (%) | Content uniformity *(%) |
|---|---|---|---|---|---|
| F1 | 4.63±0.42 | 4.31±0.07 | 1.169±0.02 | 0.26±0.06 | 95.41±0.72 |
| F2 | 4.5±0.41 | 4.39±0.23 | 1.027±0.08 | 0.33±0.04 | 93.75±0.55 |
| F3 | 4.72±0.61 | 4.42±0.13 | 1.357±0.04 | 0.62±0.14 | 98.66±1.90 |
| F4 | 5.25±0.28 | 4.54±0.01 | 1.462±0.05 | 0.34±0.04 | 97.7±0.96 |
| F5 | 4.75±0.64 | 4.48±0.08 | 0.7460.05 | 0.43±0.08 | 95.41±2.96 |
| F6 | 5.5±0.41 | 4.54±0.11 | 0.804±0.02 | 0.53±0.12 | 97.75±0.43 |
| F7 | 5.375±0.25 | 4.5±0.09 | 1.443±0.15 | 0.48±0.04 | 94.25±1.52 |
| F8 | 5.375±0.47 | 4.5±0.09 | 0.568±0.08 | 0.44±0.08 | 96.85±1.21 |
| F9 | 4.625±0.47 | 4.32±0.35 | 0.835±0.02 | 0.25±0.12 | 96.58±1.77 |
| F10 | 5.25±0.64 | 4.63±0.34 | 0.563±0.08 | 0.27±0.08 | 95.66±0.611 |
| F11 | 5.25±0.28 | 4.4±0.18 | 0.927±0.05 | 0.38±0.04 | 94.85±1.03 |
| F12 | 5.12±0.47 | 4.37±0.20 | 0.536±0.12 | 0.30±0.17 | 97.5±1.2 |

***All values represent mean ± SD, n=6,† All values represent mean ± SD, n=6,‡ All values represent mean ± SD, n=20**

**Figure2. Percentage cumulative drug release of batches F7 to F9 (Guar gum)**

**Table-3. Mathematical modeling and drug release kinetics of sustained release tablets of zidovudine**

| Formulation | Zero Order | First Order | Higuchi | Peppas | Peppasn | t50 |
|---|---|---|---|---|---|---|
| F1 | 0.9486 | 0.9374 | 0.9959 | 0.9943 | 0.588 | 2.2 |
| F2 | 0.9585 | 0.9546 | 0.9972 | 0.9959 | 0.544 | 3.2 |
| F3 | 0.9569 | 0.9956 | 0.9941 | 0.9959 | 0.544 | 5.1 |
| F4 | 0.9705 | 0.9925 | 0.9955 | 0.995 | 0.544 | 1.3 |
| F5 | 0.957 | 0.9419 | 0.9879 | 0.9904 | 0.553 | 2.3 |
| F6 | 0.9519 | 0.9003 | 0.99 | 0.9858 | 0.507 | 4.9 |
| F7 | 0.9942 | 0.9896 | 0.9794 | 0.9717 | 0.457 | 1.6 |
| F8 | 0.9825 | 0.9939 | 0.9876 | 0.9911 | 0.454 | 3.6 |
| F9 | 0.8917 | 0.9635 | 0.9717 | 0.9898 | 0.364 | 5.6 |
| F10 | 0.8998 | 0.98 | 0.9764 | 0.9861 | 0.450 | 8.3 |
| F11 | 0.9248 | 0.9764 | 0.9836 | 0.9752 | 0.492 | 9.1 |
| F12 | 0.9098 | 0.9621 | 0.9805 | 0.9822 | 0.487 | 9.6 |




**Effect of diluent on release profile**

Figure-5 shows the comparative dissolution profile of 10%, 15%, 20% HPMC polymer using Talc and MCC as diluent of formulations F1 and F6. In the release of zidovudine there is significant divergence was observed. due to difference in solubility of diluent and their subsequent effect to their tortuosity factor. The t50 of the two formulations was 2.2 and 1.35 of F1 and F4 respectively. The t50 values are more when MCC used as diluent.

**Release Kinetics**

.As clearly indicated in Figure -1, the formulations did not follow a zero-order release pattern. When the data were plotted according to the first-order equation, the formulations showed a fair linearity, with regression values between 0.9358 and 0.9957. Release of the drug from

**Figure3. Percentage cumulative drug release of batches F7 to F9 (Ethyl cellulose)**

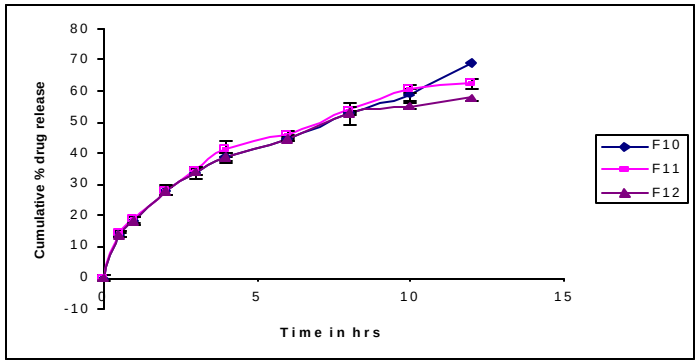



**Figure-4.Effect of Polymer Type on Cumulative % Drug Release**

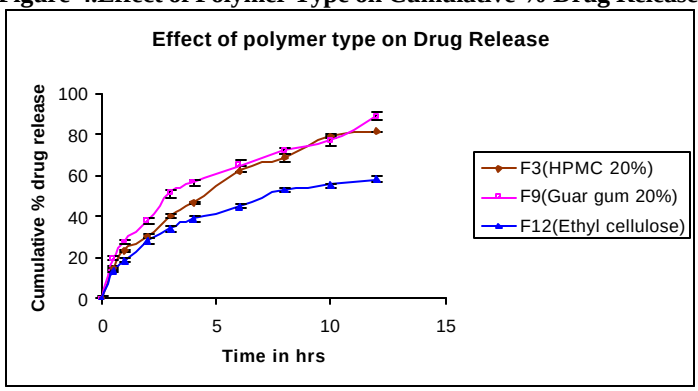



**Figure-5.Effect of Diluents on Cumulative % Drug Release**

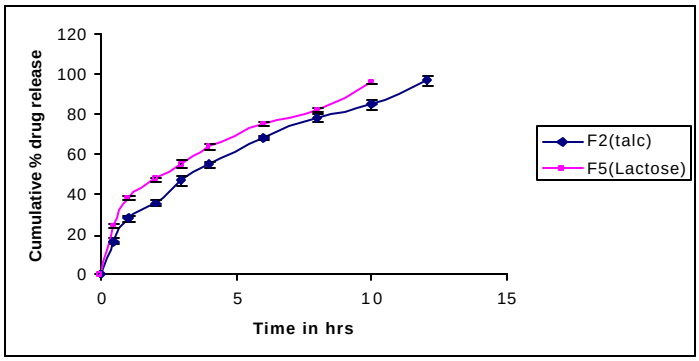
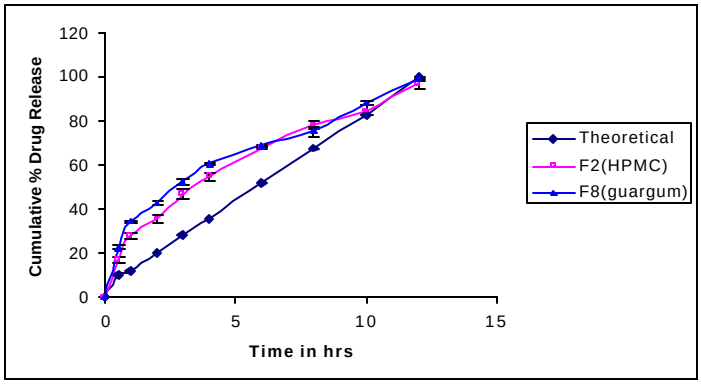



**Figure-6.Mean (±SD) Drug Release from Theoretical and Optimized formulations**




a matrix tablet containing hydrophilic polymers generally involves factors of diffusion.. This could explain why the drug diffuses at a comparatively slower rate as the distance for diffusion increases, which is referred as square-root kinetics or Higuchi's kinetics [13] In our experiments, the in vitro release profiles of drug from all the formulations could be best expressed by Higuchi's equation, as the plots showed high linearity ($R^2$: 0.9707 to 0.9967). To confirm the diffusion mechanism, the data were fit into Korsmeyer et al's equation. The formulations F1 to F8showed good linearity ($R^2$: 0.9856 to 0.9981), with slope (*n*) values ranging from 0.517 to 0.588, indicating that diffusion is the dominant mechanism of drug release with these formulations. This *n* value, however, appears to indicate a coupling of diffusion and erosion mechanisms—so-called anomalous diffusion.

Based on the similarity with theoretical release profile (Figure-6) evident by the f2 factor, formulations F2, F8, were selected as optimized formulations.

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