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FORMULATION AND *IN VITRO* EVALUATION OF ZIDOVUDINE MATRIX TABLETS

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ABSTRACT

Zidovudine is Nucleoside Reverse transcriptase inhibitor and widely used in treatment of ART. In present study Zidovudine matrix tablets were formulated and evaluated using various natural and synthetic polymers. Sustained release matrix tablets were prepared by using HPMC k15m, Eudragit S100, Xanthan gum and Guar gum alone as rate controlling polymers by using direct compression method. Total four formulations were developed with 1: 0.25 drug polymer ratio. All the prepared tablets were evaluated for thickness, hardness, friability, weight variation, assay and in vitro drug release studies. From the data it was concluded that the formulations containing Eudragit shown 97% drug release within 12 hours.

KEYWORDS: Zidovudine, Matrix tablets, Eudragit, HPMC K15M.

INTRODUCTION

Oral route is the most convenient route of drug administration. So far so many oral dosage forms have been developed to improve the patient compliance. The drugs with less half life are eliminated from the body with in short period of time. Such drugs are needed to be administered frequently to get the required plasma drug levels. The increased dose frequency may reduce the patient compliance. This difficulty can be avoided by formulating the drugs as matrix type sustained release drug delivery systems.[1] Sustained Release dosage forms are most convenient dosage forms to improve the bioavailability of drugs. These dosage forms delay the release of drug by matrix formation there by allow the drug to get solubility and absorption completely from intestinal mucosa. These dosage forms are prepared by using rate retarding polymers which form network like matrix upon hydration. The drugs which are

sensitive to gastric environment can also be protected by formulating as matrix type dosage forms because of their ability to withstand the acidic environment. To get a successful sustained release product, the drug must be released from the dosage form at a predetermined rate and dissolve in the gastrointestinal fluids.[5]

The formulations of sustained-release drug delivery systems wish to achieve desired release rates, decrease the number of daily administrations, improve compliance and minimize side-effects.[6]

The major drawbacks of antiretroviral drugs for the treatment of AIDS are their adverse side effects during long-term therapy, poor patient compliance and huge cost of the therapy. 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. However, the main limitation to therapeutic effectiveness of AZT is its dose- dependent hematological toxicity, low therapeutic index, short biological half-life, and poorbioavailability. The biological half life of AZT is 4 hours, thus necessiating frequent administration(3 to 4 times a day) to maintain constant therapeutic drug levels. TreatmentofAIDS using conventional formulations of AZT is found to have many drawbacks such as adverse side effects due to accumulation of drugin multi-dose therapy, poor patient c ompliance and high cost. So, SR formulations of AZT can overcome some of these problems.

MATERIALS AND METHODS

Materials: Zidovudine was purchased from sura labs (Hyd, India). HPMC K15M, Eudragit S100, Xanthan gum and Guar gum were Purchased from sd fine chemicals and accord labs (secunderabad). All other chemicals and reagents used were of analytical reagent grade and purchased from Himedia, (Hyderabad, India).

Matrix tablets Preparation

Zidovudine mixed manually in polybag with different ratios of HPMC K15M as rate controlling polymer and micro crystalline cellulose as diluent for 10 minutes and the blend was lubricated with magnesium stearate for 3-5mins and talc was added as glidant then compressed into tablets by direct compression method using 6mm diameter punches in a four station rotary tablet-punching machine. Similarly zidovudine matrix tablets were prepared by using different concentrations of Eudragit S100, Guar gum, Xanthan gum as rate controlling polymer. Compositions of matrix tablet formulations are given in table 1. Each tablet

(500mg) contained 200mg of zidovudine. The mass of tablets were determined using a digital balance (Shimadzu, India) and thickness with digital vernier calipers.

Table No: 1 Formulation of zidovudine matrix tablets

INGREDIENTS	F1	F2	F3	F4
Zidovudine	200	200	200	200
Hpmck15m	50	-	-	-
Eudragit s100	-	50	-	-
Guar gum	-	-	50	-
Xanthangum	-	-	-	50
MCC	230	230	230	230
Mg stereate	10	10	10	10
Talc	10	10	10	10

Evaluation of prepared tablets

1. Hardness test: The tablets to be tested are held between a fixed and a moving jaw of hardness test apparatus (Monsanto) and reading of the indicator is adjusted to zero. The screw knob was moved forward until the tablet breaks and the force required to break the tablet was noted.

2. Friability: Friability test was performed using Roche friabilator. Ten tablets were weighed and placed in the friabilator, which was then operated for 25 revolutions per minute. After 100 revolutions the tablets were dusted and reweighed. The percentage friability was determined using the formula.

$$\text{Percentage friability} = \frac{\text{Initial weight - Final weight}}{\text{Initial weight}} \times 100$$

3. Weight Variation: For weight variation test, twenty tablets were selected at random and weighed individually. The individual weights were compared with average weight for determination of weight variation.

4. Drug Content Ten tablets were weighed and powdered. Powder equivalent to 200mg of zidovudine was dissolved in 10ml of 0.1N HCl, then make upto 100ml with 0.1N HCl in 100ml standard flask. From this 10µg/ml, equivalent solution was prepared and analyzed at 270 nm using UV double beam spectrophotometer.

5. Dissolution Studies Invitro release study was performed using USP apparatus type II at 50 rpm. The dissolution medium was 900ml of 0.1N HCl for 2 hrs. It was maintained at a

temperature of 37±0.5^{o} C. The drug release was evaluated by taking 5ml sample (which was replaced with fresh medium) every half- an-hour interval upto 2 hours and suitably diluted with 0.1N HCl and absorbance was measured at 270 nm using UV spectrophotometer. After 2 hrs 900 ml of 0.1N HCl was replaced with 900 ml of dist water and the dissolution was carried out up to 12 hours by taking 5ml of samples every 1 ing it with fresh medium. The collected samples were analysed by UV spectrophotometer at 270nm.

6. Kinetic Analysis To analyze the mechanism of drug release rate kinetics of all the formulations, the results of invitro release profiles were fitted into first order kinetic model, Higuchi model, zero order kinetic model and Korsmeyer model. The results of invitro release profiles were plotted in models of data treatment as follows:

1. Log cumulative percent drug remaining versus time (first order kinetic model)
2. Cumulative percent drug release versus square root of time (Higuchi model)
3. Log cumulative percent drug released versus time (zero order kinetic model)
4. Log cumulative percent drug released versus log time (korsmeyers model).

7. Stability Studies Stability studies were carried out to assess the stability of all formulated controlled release zidovudine tablets. The prepared tablets were kept at 45^{o} ±2^{o}C, 75±5% RH for 45 days. At 15 days intervals the tablets were evaluated for all physical parameters. The percentage of zidovudine content and invitro drug release studies were also determined.

RESULTS AND DISCUSSION

Evaluation of zidovudine powder mixture and matrix Tablets The powder prepared for compression of matrix tablets were evaluated for their flow properties. The bulk density was within the range of 0.37 to 0.50 gm/cm3 . Tapped density ranged between 0.43-0.62 gm/cm3. Angle of repose was within the range of 28. 10 to 34. 96. Compressibility index was found to be 11.11-20.0 and Hausner ratio ranged from 1.12-1.27 for powder of different formulations (Table-2). These values indicate that the prepared granules exhibited good flow properties.

Table no:2 Physical Properties of powder blends

Formulation	Bulk density (g/ml)	Tapped density (g/ml)	Compressability index (%)	Hausners ratio	Angle of repose (Ɵ)
F1	0.50	0.62	20.0	1.27	32^{0}.4’
F2	0.37	0.47	21.2	1.25	28^{0}.3’
F3	0.38	0.43	11.6	1.13	28^{0}.7’
F4	0.40	0.45	11.11	1.12	29^{0}.3’

Table no: 3 Physical properties of prepared tablets.

Formulation	Weight variation test (mg)	Thickness test (mm)	Hardness test (kg/cm^2)	Friability test (%)	Drug content (%)
F1	500.3	3.74	5.2	0.10	98.73
F2	501.4	4.15	5.6	0.26	99.85
F3	502.8	4.14	5.4	0.68	97.85
F4	498.6	4.14	5.1	0.30	98.23

All the prepared tablets showed good elegance in appearance. The hardness of the tablets of all formulations was within the range of 5.1 to 5.6 kg/cm^2, indicating good mechanical resistance of the tablets. The variation in weight was within the range of ±1.5% complying with Pharmacopoeial specifications. The percentage of zidovudine in all formulations was ranging from 97.85-99.85% indicating content uniformity was within the limits (±10%). The thickness and diameter of zidovudine tablets was found to be in the range of 3.74 to 4.14mm and 6.1 to 6.2 mm respectively, which showed uniform thickness and diameter. (Table-3). The particle loss in the friability test was below 1% for all the formulations, which is an indication of good mechanical resistance of tablets.

Dissolution Studies Invitro release studies were performed to determine the percentage of drug released from zidovudine matrix tablet formulations with polymer. Results of the invitro release studies of zidovudine matrix tablet formulations with polymer are presented in (Table 4). The percentage drug release of all formulations after 12 hours using polymers was found to be 64% (F1), 99% (F2) and 95%(F3) and 97% (F4).It was found that the cumulative percentage drug release of the formulation F2 was more than other formulations. The cumulative percentage of drug release in the formulation F3 showed controlled release than other formulations. The type of polymer concentration played a major role in drug release with eudragit, the drug release was prolonged. The graphical representation data of the zidovudine matrix tablet formulations with polymer is shown in (Figure I).

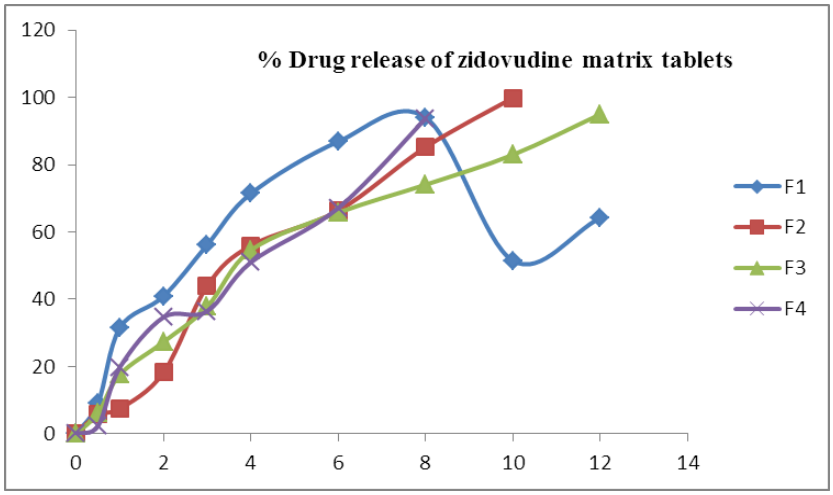

Figure 1: % drug release of zidovudine matrix tablets,

Kinetic Analysis The release rate kinetic data for all the formulations were shown in Table-5. When the data were plotted according to zero order, the formulations showed a high linearity, with regression coefficient values ($\mathbf{r^2}$) between 0.91-0.97. Diffusion is related to transport of drug from the dosage matrix into the invitro study fluid depending on the concentration. This is explained by Higuchi's model. The release profiles of drug from all the formulations could be best expressed by Higuchi's equations, as the plot showed high linearity with regression co-efficient values ($\mathbf{r^2}$) between 0.97-0.64.By using korsmeyer model, if n = less than 0.45 it is Fickian diffusion, if n = 0.45-0.89 it is non-Fickian transport. The result of all the formulations showed 'n' values between 0.611-0.843. It showed that all the formulations follow non- Fickian transport mechanism and also follow the mechanism of both diffusion and erosion (Table-5).

Table no:5 Mechanism of drug release from zidovudine matrix tablets

Formulation	Zero order r^2	First order r^2	Higuchi r^2	Korsmeyer r^2	Hixoncrowel r^2	N
F1	0.916	0.368	0.649	0.482	0.362	0.46
F2	0.941	0.674	0.953	0.775	0.980	0.57
F3	0.945	0.674	0.979	0.965	0.149	0.84
F4	0.973	0.037	0.951	0.169	0.165	0.64

Stability Studies zidovudine matrix tablets from all the formulations were stored at $45^{o} \pm 2^{o}C$, 75 ± 5% RH upto 30 days. Tablet evaluation tests were carried out at every 15 days intervals. All the formulations are physically stable. There were no deviations found in the tests and all are within the limits. There were no significant change in the drug content and invitro drug release profiles. It showed that all the formulations are chemically stable.

CONCLUSION

The results of experimental studies of zidovudine matrix tablets proved that the powder of zidovudine showed good flow properties, tablet evaluation tests are within the acceptable limits, the kinetic studies revealed that all the formulations followed zero order drug release and stability studies revealed that all the formulations were found to be stable after storing at $45^{o} \pm 2^{o}C$, 75 ± 5% RH for 30 days. The drawbacks of the conventional dosage forms of zidovudine can be minimized by zidovudine matrix tablets. Thus the results of the above study clearly indicated that zidovudine may be formulated as sustained release tablets using eudragit S100 as rate controlling polymer using direct compression method, which will provide continuous release of drug at a predetermined rate and for a predetermined time.

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