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Research Article

Pharmacokinetic Boosting of Zidovudine for HIV Treatment

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ABSTRACT

The aim of the present study was to develop "Pharmacokinetic boosting model of Zidovudine for HIV treatment".Zidovudine was combined with Ketoconazole as once daily sustained release matrix tablets for pharmacokinetic boosting of Zidovudine, Ketoconazole inhibits CYP 3A4 enzyme responsible for metabolising Zidovudine hence boosts its plasma concentration , facilitate treatment of fungal infection which are prevalent during AIDS. Further this formulation increase therapeutic efficacy, reduce frequency of administration and improve patient compliance. The sustained release tablets were prepared by wet granulation method. By using different drug: polymer ratios, formulations F1 to F8 were prepared. Hydrophilic polymers like hydroxy propyl methyl cellulose (HPMC K4M), ethyl cellulose, PVPK-30 were used. Compatibility of the drug with various excipients was studied. The compressed tablets were evaluated and showed compliance with pharmacopoeial standards. Formulation containing 30% polymer mixture of HPMCK4M and Ethyl cellulose in ratio 1:1, with hardness 7.11±0.324 kg/cm^{2}showed the desired release profile which matched the theoretical release profile. In- vitro drug release characteristics were studied for a period of 12 hr using USP Type 2 dissolution apparatus. In Vivo studies of formulation F7 were performed on Rabbit.Plasma samples were analysed using HPLC. It was found that on administering single tablet of 300 mg AUC at t_p was found to be 237795 as in HPLC chromatogram and on administering F7 formulation containing Zidovudine and Ketoconazole in ratio 3:2, AUC at t_p was found to be 329095 . This shows significant pharmacokinetic boosting.

INTRODUCTION

AIDS (Acquired Immunodeficiency Syndrome or Acquired Immune Deficiency Syndrome, sometimes written Aids) is a devastating human disease that cripples the body's immune system by attacking and destroying helper T lymphocytes, making the affected persons susceptible to number of unusual infections and malignant tumour. In HIV infection several opportunistic infections appear due to weakening of immunity such as fungal infections, cancers, neurologic symptoms, and wasting syndromes. Zidovudine is mainly metabolised by cytochrome p3A4 enzymes hence less bioavailable so combination of Zidovudine with cytochrome p inhibitor prove to be suitable dosage form. Combination of Zidovudine with Ketoconazole can serve several purpose, first increase in bioavailability of nucleoside reverse transcriptase inhibitor due to inhibition of its metabolism, secondly due to weakening of immunity fungal infection attack HIV patient, this combination therapy is fruitful is this respect, further it is cost effective.

The oral route is the most often used for administration of drugs.Tablets are the most popular oral formulations available in the market and are preffered 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. 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. Zidovudine is soluble in water hence combination of hydrophilic polymer with hydrophobic prove to be useful.HPMCK4M is hydrophilic in nature and ethylcellulose is hydrophobic in nature

MATERIALS AND METHODS

Materials

Zidovudine – IP is procured by matrix labs, Hyderabad. Ketoconazole was gifted by Venus remedies. HPMC (hydroxy propyl methyl cellulose), ethyl cellulose, lactose, PVP k-30 was procured from Lobia chemia.

Formulation of Sustained Release Tablet: Matrix tablets were prepared by wet granulation method. Drug (specified dose) was blended with appropriate quantity of polymer(s) HPMCk4M, ethyl cellulose or carbopol and granulated using 5% w/v ethanolic solution of PVP-K90. Wet mass was passed through a No. 10 sieve. Wet granules were dried at 55°C ± 5°C for 1 hour and sieved (No. 44/22 sieve). Oversized granules (retained on No. 22 sieve) were kept aside. Undersize granules (passed from No. 44 sieve) were mixed with granules (retained on No. 22sieve) in a ratio of 1:9 as fines. This mixture was blended with magnesium stearate (1.2% w/w) and compressed using 16 station tableting machine, equipped with bevelled flat-faced punches of 12-mm diameter.

Experimental work: Simultaneous estimation- Corrected interference method used **.**Several mixed standards of drugs Zidovudine : Ketoconazole were prepared in ratio of 3:2 in HCl and buffer separately. Absorbance was measured both at 267 nm and 226 nm. This is apparent absorbance. Absorbance in mixture is equal to sum of

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Table1.Formulation and optimization of sustained release tablet of Ketoconazole and Zidovudine

Ingredients	F1	F2	F3	F4	F5	F6	F7	F8
Zidovudine	300	300	300	300	300	300	300	300
Ketoconazole	200	200	200	200	200	200	200	200
HPMCK4M	70	140	210	280	168	140	105	84
Ethyl cellulose					42	70	105	126
Lactose	q.s	q.s	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Avicel	1%	1%	1%	1%	1%	1%	1%	1%
Magnesium stearate	2%	2%	2%	2%	2%	2%	2%	2%
Talc	1%	1%	1%	1%	1%	1%	1%	1%

Table 2 Evaluation of Granules

Batch code	Bulk density Gm/ml	Tapped density Gm/ml	Compressibility index%	Hausner's ratio	Angle of repose
F1	0.40	0.55	27.2	1.37	31°.8′
F2	0.46	0.55	14.5	1.16	32°.4′
F3	0.50	0.62	20.0	1.24	28°.3′
F4	0.36	0.48	21.2	1.12	28°.7′
F5	0.38	0.44	10.6	1.24	27°.7
F6	0.40	0.45	11.11	1.23	27°.9′
F7	0.38	0.48	12.1	1.17	25°.7
F8	0.40	0.45	16.5	1.19	30°.9′

Table 3 Post compression parameters of tablet

Batch code	Average weight	Hardness	Friability
F1	705.25±6.25	5.84±0.337	0.551
F2	695.79±6.63	5.79±0.288	0.543
F3	707.33±6.63	5.77±0.265	0.548
F4	694.10±6.94	6.11±0.188	0.532
F5	707.12±6.24	6.16±0.219	0.531
F6	693.49±5.49	6.42±0.223	0.530
F7	705.39±6.03	7.11±0.324	0.523
F8	696.33±6.41	9.28±0.356	0.515

All values are expressed as mean±SD, (n=3)

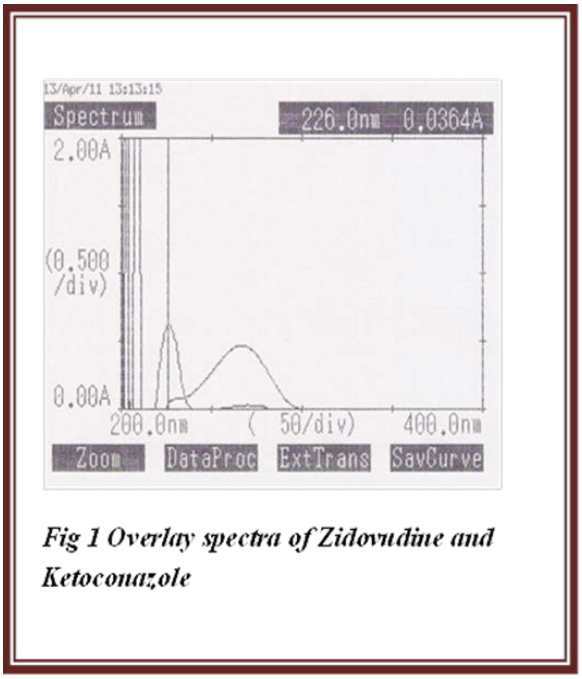


Fig 1 Overlay spectra of Zidovudine and Ketoconazole

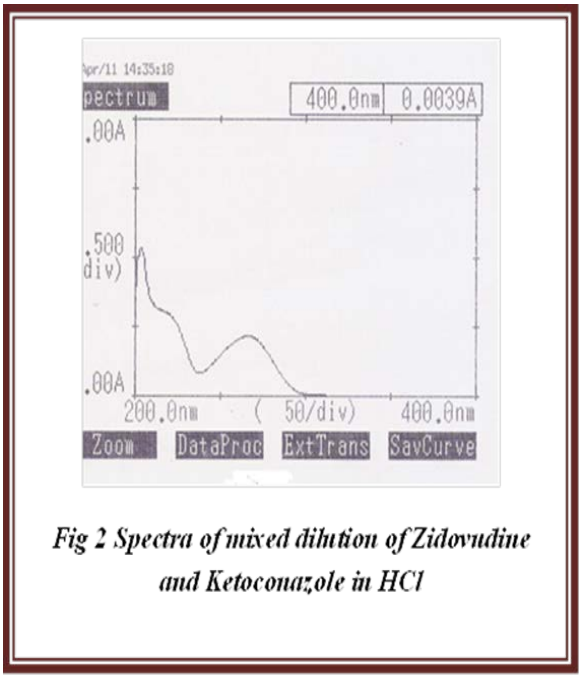
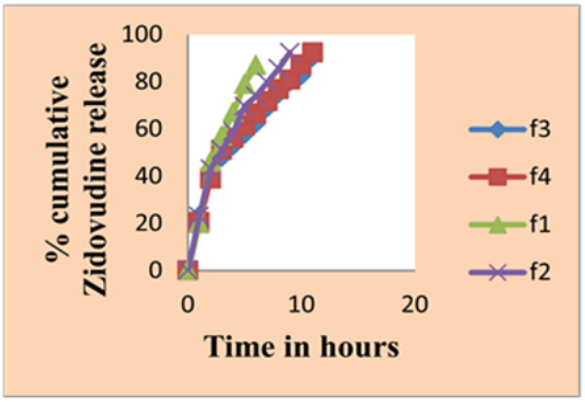


Fig 2 Spectra of mixed dilution of Zidovudine and Ketoconazole in HCl

Fig. 3 In vitro release profile showing the effect of various concentrations of HPMC K4M on Release of Zidovudine from matrix tablet



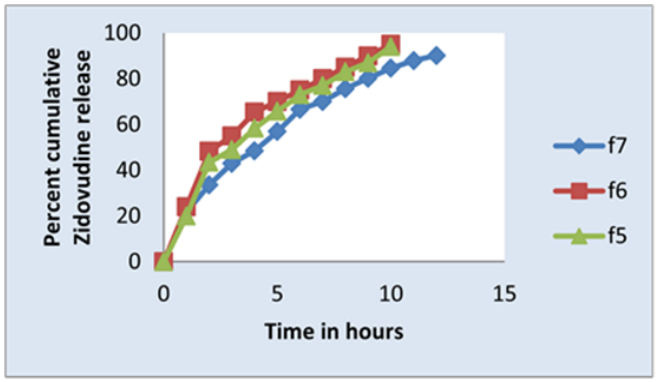


Fig 4 In vitro release Profile showing effect of different ratio of HPMC K4M and ethyl cellulose on Zidovudine release from matrix tablet

individual absorbances. To find out the actual absorbance of each drug in mixture, absorbance of second drug is subtracted from apparent absorbance of first drug.

In vivo analysis of Plasma sample: The quantitative determination of drug in plasma was performed by HPLC assay using C-18 reverse phase column, a mobile phase consisting of a mixture of sodium acetate buffer (55mM) with pH adjusted to 7.0 and acetonitrile (91:9 v/v) used and UV detection set at 267 nm. Twenty microliters of injection volume was eluted in C-18 column (4.6 × 150 mm) at room temperature. The column eluant was monitored at 267 nm using diode array UV detector.

RESULT AND DISCUSSION

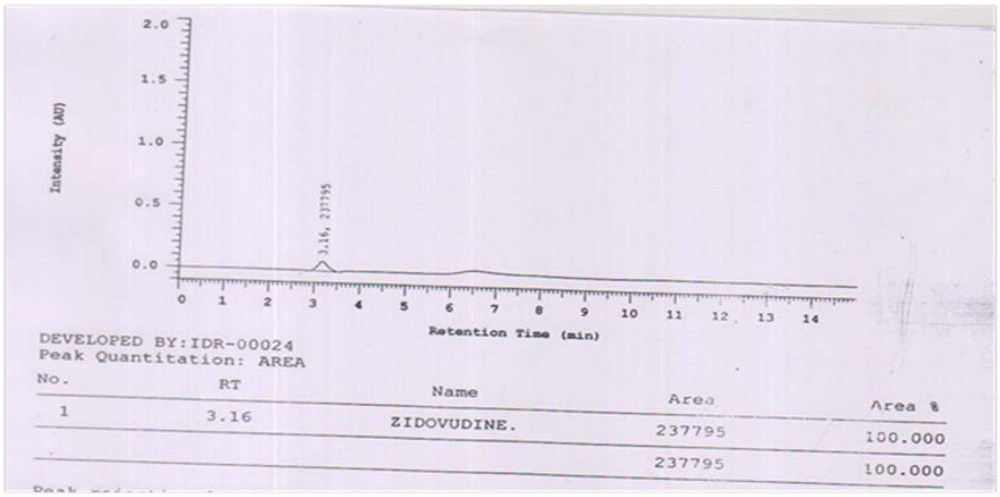
Preformulation studies: Solubility- Zidovudine was found soluble in water, phosphate buf fer pH 6.8 ,ethanol, methanol,0.1 N HCl. Ketoconazole was found to be soluble in 0.1 N HCl, slightly soluble in buffer, soluble in ethanol.

Bulk density- The bulk density for formulated blend were carried out for all formulations and found in the range 0.36- 0.50g/ml

Tapped density-

The tapped densities for the formulated blend was carri

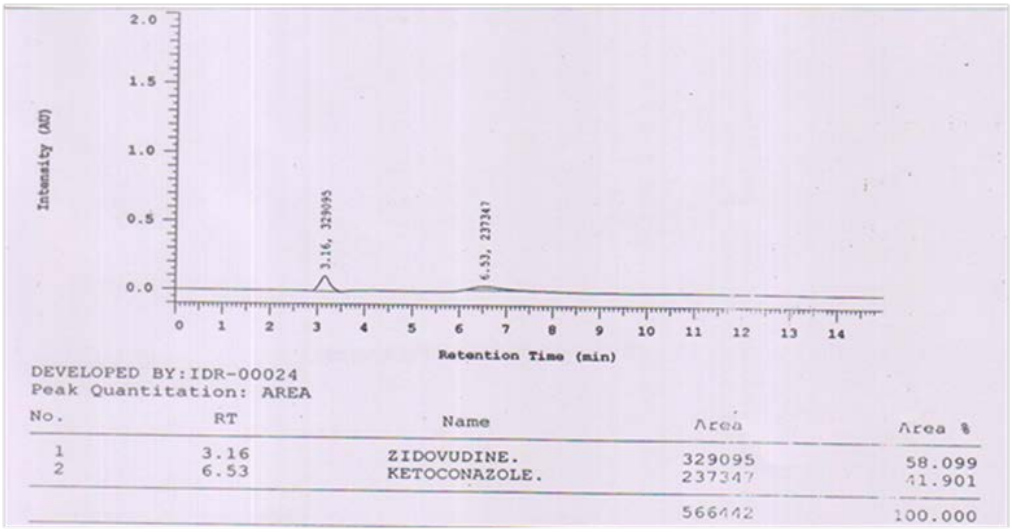
Fig 5 Chromatogram of plasma sample when only Zidovudine sustained release 300 mg tablet administered to rabbit



DEVELOPED BY:IDR-00024
Peak Quantitation: AREA

No.	RT	Name	Area	Area %
1	3.16	ZIDOVUDINE.	237795	100.000
			237795	100.000

Fig 6 Chromatogram of Plasma sample when F7 formulation administered



DEVELOPED BY:IDR-00024
Peak Quantitation: AREA

No.	RT	Name	Area	Area %
1	3.16	ZIDOVUDINE.	329095	58.099
2	6.53	KETOCONAZOLE.	237347	41.901
			566442	100.000

ed out for all formulations and found in the range of 0.44 – 0.62 g/ml.

Angle of repose - It was concluded that entire formulation blend was carried out in the range25^{o}.7-32^{o}.4´

Compressibility index- It was found between 10.6 to 27.2 indicating that powder blends has required flow property

Hausner's Ratio – It was found between1.12 -1.37 indicating good flow properties In vitro dissolution- In vitro dissolution was carried out of all the formulation and it was found that 10 % showed 98% release in 7 hour, 20% showed 95 release in 8 hour, 30 % and 40% showed 96 and 97 release in 10 and 12 hour respectively showing more sustained action.

Different ratio of HPMC: ethyl cellulose taken 1:0.25(F5), 1:0.5(F6), 1:1(F7), 1:1.5(F8). 1: 1 ratio showed better release among all the formulation. Ratio 1:0.5 and 1:0.25 showed 94-95 percent release in tenth hour while 1:1 ratio showed 97 percent release in 12 hour thereby by showing more sustained action. The ratio 1:1.5 HPMC: ethyl cellulose shows insignificant release hence not useful therapeutically. It can be concluded from

Table 4 Percent cumulative release of Zidovudine

Time in hours	F1	F2	F3	F4	F5	F6	F7
0	0	0	0	0	0	0	0
1	20.13±0.36	23.66±0.30	23.05±0.24	20.5±0.19	24.21±0.72	20.34±0.43	21.67±0.47
2	46.56±0.46	43.75±52	40.13±0.44	38.87±0.36	48.45±41	43.23±0.37	33.54±0.19
3	57.33±0.42	53.81±58	51.33±0.68	51.02±0.59	55.98±0.38	51.15±0.56	43.95±0.27
4	69.29±0.56	64.79±43	60.68±0.76	56.19±0.63	66.34±0.73	62.34±0.58	54.44±0.25
5	81.54±0.67	73.58±36	72.83±0.73	61.36±0.88	70.76±0.33	69.08±0.65	63.89±0.45
6	89.41±0.48	85.89±67	81.33±0.76	66.53±0.75	75.72±0.78	74.38±0.79	70.58±0.49
7	98.23±0.72	90.67±59	85.99±0.58	71.71±0.57	80.03±0.71	79.10±0.26	75.88±58
8		95.58±51	90.89±0.39	76.88±0.39	85.18±0.76	84.67±0.55	79.64±0.61
9			96.10±0.81	80.89±0.65	90.64±0.62	89.39±0.52	85.21±0.52
10			96.37±0.64	87.22±0.31	95.58±0.68	94.43±0.64	90.57±0.77
11				92.39±0.28	96.32±0.81	95.11±0.35	95.88±0.66
12				97.56±0.49			96.97±0.71

All values are expressed as mean±SD, (n=3)

Table 5. Stability study of formulation F7(40°C ± 2°C, 75% ± 5% RH)

Parameters	At 0 day	30days	60 days	90 days
Physical appearance	White , circular	No change	No change	No change
Weight variation(mg)	695.421±6.743	695.433±5.281	706±6.343	694±5.343
Hardness (Kg/cm^2)	6.91±0.258	6.84±0.275	6.78±0.313	6.73±0.413
Friability(%)	0.560	0.559	0.548	0.546
Drug content(%)	Z=96.97±1.34 K=96.24±1.28	Z=96.92±1.23 K=96.17±1.46	Z=97.23±1.45 K=96.37±1.39	Z=96.33±1.22 K=96.47±1.64

above data that as the concentration of ethylcellulose was increase from 0.25 to 1, release become more sustained because of hydrophobic nature of ethylcellulose

Bioequivalence study was carried out. The release of Zidovudine and Ketoconazole in combined formulation was compared with their individual marketed formulation Ketoconazole immediate release formulation and Zidovudine sustained release formulation .It was found that release pattern was similar to these individual formulation.

Stability Studies: Stability studies carried out as per ICH guidelines and formulation was found to be appropriate and stable.

In Vivo Studies: In vivo studies of optimized formulation F7 performed on Rabbit.Plasma samples were withdrawn at regular intervals and analysed using HPLC.When Plasma sample was analysed using HPLC, it was found that that on administering single tablet of 300 mg AUC at t_p was found to be 237795 as in graph and on administering F7 formulation containing Zidovudine and Ketoconazole in ratio 3:2, AUC at t_p was found to be 329095. This shows significant pharmacokinetic boosting.

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