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INVITRO & INVIVO STUDIES OF FDDS TABLETS FOR ZIDOVUDINE

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ABSTRACT Zidovudine inhibits the replication of HIV in human cells. The Zidovudine tablets were prepared by wet granulation technique by using different ratios of HPMC using other excipients. The prepared tablets were subjected to invitro & invivo studies. From study, it can be concluded that, the formulation retained for longer periods of time in the stomach and provides controlled release of the drug and increases its bioavailability. Sodium bicarbonate was added as a gas generating agent, induced carbon dioxide generating in presence of dissolution medium 0.1 N HCl. The combination of sodium bicarbonate & citric acid provided desired floating ability and therefore this combination was selected for the formulation. The present research work concludes that the formulation ZF9 consisting of HPMC K4M showed highest drug release in short duration of time.

KEYWORDS : Zidovudine, invitro, invivo drug release.

INTRODUCTION

Oral route is the most preferred route for administration of drugs[1]. Tablets are the most popular oral formulations available in the market and preferred by the patients and physicians. Conventional formulations are required to be administered in multiple doses and therefore have several disadvantages like accumulation of drug in multi□dose therapy, poor patient compliance and high cost[2,3]. Extended release formulations are much desirable and preferred for such therapy because they offer better patient compliance, maintain uniform drug levels, reduce dose and side effects and increase safety margin for high potency drugs. Hence, extended release formulations are preferred for such therapy[4,5]. This results in a significant fluctuations in drug levels[7]. Attempts to develop a single dose therapy for the whole duration of the treatment has focused attention on controlled or sustained drug delivery systems[6]. It also implies delayed therapeutic action and sustained duration of therapeutic effect whereas controlled release implies a predictability and reproducibility in the drug release kinetics[1,8].

Advantages of FDDS[9,10]:

- Sustained drug delivery: HBS type dosage forms remain in the stomach for several hours due to their modified GRT. Prolongation in the GRT sustains the drug release behaviour.
- HBS provides a better alternative for maintenance of systemic drug concentrations within the therapeutic window.
- These systems provides an easy way of maintaining constant blood level with an ease of administration and better patient compliance.
- Site specific drug delivery: Drugs having absorption sites in the stomach and upper parts of the intestine can be formulated to target the drug to the specific site.

MATERIALS & METHOD

Zidovudine was obtained from Emcure Pharma Pvt Ltd .pune, HPMC from AstraZeneca Pvt Ltd Bangalore & other excipients from S.D. Fine chemicals Mumbai.

Preparation Method[11]

Drug and polymers were mixed in a poly bag and the mixture was passed through a mesh No. 60. Granulation was done with a solution of PVP K30 in sufficient isopropyl alcohol. The wet mass was passed through mesh No. 12. The wet granules were dried at 60º for about 4 hours. The dried granules were sized by a mesh No. 18 and mixed with sodium bicarbonate, citric acid, magnesium stearate and talc. Granules thus obtained were compressed into tablets.

Table 1: Formulations Table (in mg)

	ZF1	ZF2	ZF3	ZF4	ZF5	ZF6	ZF7	ZF8	ZF9
Zidovudine	300	300	300	300	300	300	300	300	300
HPMC K100m	50	75	100						
HPMC K15m				50	75	100			
HPMC K4m							50	75	100
Carbopol 934	20	20	20	20	20	20	20	20	20
PVP K30	20	20	20	20	20	20	20	20	20
Mg Stearate	10	10	10	10	10	10	10	10	10
Talc	10	10	10	10	10	10	10	10	10
Sodium Bicarbonate	80	80	80	80	80	80	80	80	80
Citric acid	20	20	20	20	20	20	20	20	20
Lactose	10	60	110	60	110	160	110	160	85
Microcrystalline Cellulose	20	20	20	20	20	20	20	20	20

RESULTS & DISCUSSION

Invitro Dissolution Studes: Dissolution studies were carried out for Floating tablets using USP XXIII dissolution test apparatus-II at 50rpm, 900ml of 0.1N HCl used as dissolution media. Results are shown in Table 2 & Figure 2

Table 2: Invitro Release Data of Floating Tablets: ZF1-ZF9

Timings	ZF1	ZF2	ZF3	ZF4	ZF5	ZF6	ZF7	ZF8	ZF9
1 hr	13.85±0.52	12.80±0.36	10.14±0.45	20.23±0.22	19.15±0.51	16.45±0.45	28.15±0.19	23.45±0.14	20.22±0.13
2 hr	28.80±0.36	27.60±0.74	23.35±0.70	24.44±0.48	22.56±0.84	20.60±0.14	36.36±0.63	30.88±0.41	28.14±0.47
3 hr	37.50±0.47	36.50±0.96	31.77±0.13	31.85±0.63	29.16±0.16	27.80±0.71	45.84±0.31	41.23±0.77	36.98±0.36
4 hr	44.90±0.89	41.60±0.74	39.56±0.89	39.63±0.74	37.99±0.90	35.90±0.23	57.43±0.77	53.44±0.37	47.87±0.95
5 hr	53.90±0.88	52.55±0.36	50.50±0.67	48.65±0.89	47.99±0.89	45.49±0.19	67.12±0.24	62.80±0.48	58.22±0.36
6 hr	62.89±0.43	59.06±0.12	58.90±0.55	59.88±0.56	58.00±0.20	56.90±0.20	78.36±0.96	69.15±0.25	66.74±0.78
7 hr	69.80±0.50	67.90±0.36	66.50±0.36	69.99±0.23	68.46±0.54	64.87±0.48	88.11±0.38	78.55±0.49	76.23±0.58
8 hr	78.63±0.89	77.49±0.52	76.47±0.18	81.59±0.96	79.14±0.52	76.23±0.88	97.59±0.50	84.55±0.32	83.50±0.89
9 hr	87.50±0.35	84.50±0.96	82.66±0.11	92.54±0.74	91.66±0.13	84.60±0.87	100.00±0.00	93.44±0.44	90.80±0.90
10 hr	95.89±0.69	92.44±0.87	89.96±0.17	99.90±0.80	99.26±0.10	92.50±0.33	100.00±0.00	99.90±0.77	98,80±0.90
11 hr	99.90±0.80	99.00±0.56	98.97±0.60	99.90±0.80	99.26±0.10	99.97±0.13	100.00±0.00	99.90±0.77	98,80±0.90
12 hr	99.90±0.80	99.00±0.56	98.97±0.60	99.90±0.80	99.26±0.10	99.97±0.13	100.00±0.00	99.90±0.77	98,80±0.90

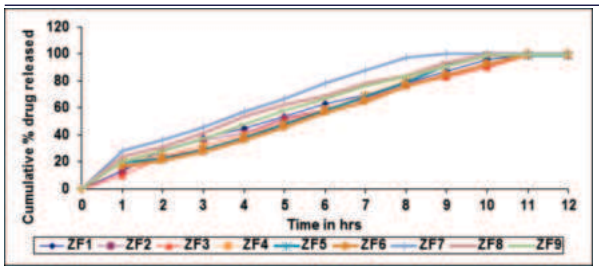

Fig 1: Invitro Release Curves of Floating Tablets: ZF1-ZF9

Invivo Studies

The study was carried out as per the ICH-guidelines. Healthy 12 rabbits weighing 2.8-3.2 kg were selected & divided into 2 groups, consisting of 6 animals. In fasting condition of all the 12 rabbits, First group administered with conventional marketed Zidovudine tablet. Second group with the optimized Zidovudine tablet formulation of 100mg till 24hrs with access to water during the study period. From marginal ear vein the blood samples were collected at specified time intervals and content was estimated in plasma using a validated HPLC analytical method and pharmacokinetic parameters t_{max}, C_{max}, AUC_{0-t}, k_{el} and $t^{1/2}$.

Comparative Plasma Concentration Profiles

Mean peak plasma concentration of test (T) C_{max} 1280.83 ng/mlwas gradually reached in 3 hr. In case of reference (R) Zidovudine conventional tablet the C_{max} was 1923.83 ng/ml which was reached in 2 hr. The Cmax of the Test formulation (T) was less when compared with Reference (R) formulation. The increase in t_{max} was clearly indicating the drug availability for longer period. The reference (R) was rapidly absorbed and the t_{max} reached in about 1.40h. After reaching the t_{max} the drug starts elimination and the plasma concentration gradually decreased. In case of test (T) the t_{max} achieved slowly and the drug availability was found for longer period. The AUC_{0-t} of the reference (R) was found to be 5797.57ng.min/ml. The increase in AUC_{0-t} was observed in the test (T) formulation, which was around 14192.55 ng.min/ml. This clearly indicates the drug availability for long duration. The plasma half life ($t^{1/2}$) of the reference (R) and test (T) formulations were 1.43 hr and 3.86 hours, respectively, which were significantly different. Thus the increased $t^{1/2}$ is another indication on the in vivo performance of the Zidovudine controlled release formulation. There is a difference in t_{max} and C_{max} was observed when compared among individual subjects which may be due to the subjective variability. This was observed in both test and reference formulations. The overall C_{max}, t_{max}, AUC_{0-t} and $t^{1/2}$ were completely different between both test and reference formulation. Therefore the prepared formulation was releasing the drug for a prolonged period of time.

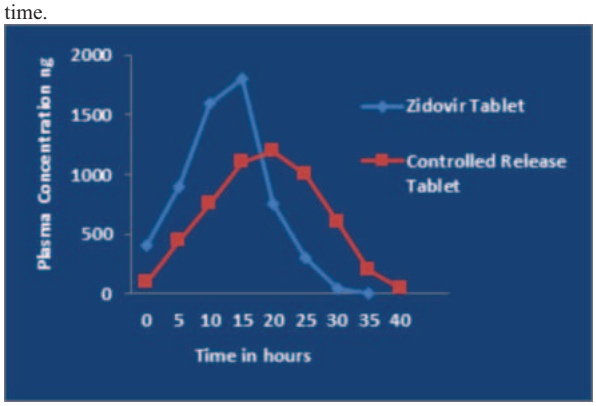

Fig 2: Comparative Plasma Concentration Profiles Of Zidovudine Conventional Tablet 100 Mg (R) With Zidovudine 100 Mg Controlled Release Tablet Formulation (T).

CONCLUSION

From the present study, the following conclusions can be drawn:

- ✓ Floating tablets of Zidovudine can be developed to increase gastric residence time and thereby increasing its bioavailability.
- ✓ As the amount of polymer in the tablet formulation increases, the drug release rate decreases and as the concentration of gas generating agent (NaHCO3) increases the drugs releases increases and at the same time floating lag time decreases.
- ✓ $NaHCO_3$ has predominant effect on the buoyancy lag time, while HPMC K4M, has predominant effect on total floating time and drug release.
- ✓ Sodium alginate and Xanthan gum has given extra adhesion property and helped to maintain the integrity of the tablet.
- ✓ The Invivo evaluation studies for formulation ZF9 with the commercial formulation of Zidovir, the results for parameters, t_{max}, C_{max}, AUC_{0-t}, k_{el} and $t^{1/2}$ indicated better bioavailability when compared to commercial marketed formulation. There is a significant increase in the oral bioavailability of Zidovudin. This might be due to increased gastric residence time of the experimental dosage form which allowed for the maximum absorption of the Zidovudine from the stomach & upper part of the small intestine.

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