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Research Article

FORMULATION AND EVALUATION OF TABLETS OF LAMIVUDINE AND ZIDOVUDINE COMBINATION

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Abstract: Lamivudine and zidovudine, two widely prescribed anti retroviral drugs are official in IP 2010 and USP 2008. Combination of lamivudine and zidovudine is a preferred option for treating HIV and AIDS. Though this combination is used widely, there are only a few combined drug formulations available in the market. The objective of the present study is to develop tablet formulations containing lamivudine and zidovudine combination and to evaluate the prepared tablets. Tablets each containing lamivudine (150 mg) and zidovudine (300 mg) were formulated employing commonly used tablet excipients and were prepared by wet granulation method. All the prepared tablets were evaluated for drug content, hardness, friability, disintegration time and dissolution rate. All the combined drug tablets containing lamivudine and zidovudine prepared as well as commercial tablets fulfilled the official (IP 2010) specifications of uncoated tablets with regard to weight variation, hardness, friability, drug content and disintegration time. Tablets formulated with superdisintegrants, crospovidone and crosscarmellose sodium disintegrated rapidly within 1 min 30 seconds. Whereas the tablets formulated employing potato starch as disintegrant disintegrated relatively slowly and the disintegration time of these tablets was in the range 2 min 40 seconds - 4 min 50 seconds. The dissolution of both the drugs from the tablets formulated depended on the binder and disintegrant used. Lamivudine and zidovudine dissolution from the tablets followed first order kinetics with correlation coefficient (r) values in the range 0.9284 – 0.9804. Among the four binders, PVP K30 gave relatively rapid and higher dissolution and starch paste (gelatinized starch) gave low dissolution. The order of increasing dissolution rate (K1) observed with various binders was PVP K30 > Sucrose > Acacia > Starch paste. The same order was observed with both the drugs. Tablets formulated employing superdisintegrants gave faster dissolution of the two drugs than those formulated with potato starch as disintegrant. IP 2010 described a dissolution of NLT 70 % in 30 min for lamivudine and NLT 80% in 30 min for zidovudine. All formulated tablets except formulation F4 and commercial formulation tested fulfilled the official (IP 2010) dissolution rate test specification. Overall, formulations F3, F5 and F6 gave very rapid dissolution of both the drugs and as such they are considered as best combined drug formulations developed. The dissolution characteristics of these formulations are better than those of commercial formulations tested. Based on the results obtained, PVP K30, sucrose and acacia are recommended as binders and crospovidone and crosscarmellose sodium as disintegrants for the formulation development of combined drug tablets containing lamivudine and zidovudine.

Key words: Lamivudine, Zidovudine, Combined drug tablets, Formulation, Dissolution rate

INTRODUCTION

Lamivudine[1-4] and zidovudine[5-8], two widely prescribed anti retroviral drugs are official in IP 2010 and USP 2008. Lamivudine and zidovudine combination has significant therapeutic importance. The combination treatment is known as highly active antiretroviral therapy (HAART). Using a HAART protocol, HIV replication is inhibited, the presence of HIV-RNA in the plasma is reduced to undetectable levels and patient survival is greatly prolonged. Zidolam tablets (a commercial brand) contain lamivudine (150 mg) and zidovudine (300 mg). Zidolam tablets are used in antiretroviral combination therapy for the treatment of HIV infection. Zidolam tablet reduces the amount of HIV in the body and keeps it at a low level. It also increases CD4 cell counts. CD4 cells are a type of white blood cells that plays an important role in maintaining a healthy immune system to fight against infection.

Combination of lamivudine and zidovudine is a preferred option for treating HIV and AIDS. Though this combination is used widely, there are only a few combined drug formulations available in the market. The objective of the present study is to develop tablet formulations containing lamivudine and zidovudine combination and to evaluate the prepared tablets for various physical characteristics including dissolution rate. An RP HPLC method developed by the authors for the simultaneous estimation of lamivudine and zidovudine is applied in the dissolution rate study to estimate the two drugs simultaneously.

EXPERIMENTAL

Materials:

Lamivudine and zidovudine were gift samples from M/s Hetero Pharmaceuticals, Hyderabad. Crospovidone and Crosscarmellose soduim were gift samples M/s Natco Pharma Ltd., Hyderabad. Potato Starch (SD Fine Chem), Acacia IP, Sucrose, PVP K30 (Loba Chemie), Lactose I.P, Talc and Magnesium stearate were procured from commercial sources.

Zidolam, a commercial tablet formulation containing lamivudine and zidovudine was procured from local market. All other materials used were of Pharmacopoeial grade.

Methods:

Formulation and Preparation of Tablets:

Tablets each containing lamivudine (150 mg) and zidovudine (300 mg) were formulated employing commonly used tablet exciepients. A total of six tablet formulations were prepared by wet granulation method as per the formulae given in Table 1.

Preparation of Tablets:

The required quantities of lamivudine, zidovudine, lactose, half the quantity of potato starch and the binder were mixed thoroughly in a mortar by following geometric dilution technique. Water was added and mixed thoroughly to form dough mass. The wet mass was pressed through mesh No. 12 to obtain wet granules. The wet granules were dried at 60^{o} C for 4 h. Dried granules were passed through mesh No. 16 to break aggregates. Crospovidone or Crosscarmellose sodium and lubricants talc and magnesium stearate were passed through mesh No. 100 on to dry granules and blended in a closed polyethylene bag. The tablet granules were then compressed into 600 mg tablets on a 16- station tablet punching machine (M/s Cadmach machineries Pvt. Ltd., Ahmedabad) to a hardness of 5- 6 kg/cm^2 using 11 mm flat punches. In each case 100 tablets were compressed.

Evaluation of Tablets:

Hardness of the tablets was tested using a Monsanto hardness tester. Friability of the tablets was determined in a Roche friabilator. Disintegration time of the tablets prepared was determined using a Thermonic tablet disintegration test machine using water as test fluid.

Dissolution Rate Study:

Dissolution rate of (i) lamivudine and (ii) zidovudine from the tablets prepared was studied in water (900 ml) employing USP 8 station Dissolution Rate Test Apparatus (M/s Labindia Disso 8000) with a paddle stirrer at 50 rpm. A temperature of 37±1°C was maintained throughout the study. One tablet containing 150 mg of lamivudine and 300 mg of zidovudine was used in each run. Samples of dissolution fluid (5 ml) were withdrawn through a filter (0.45 µm) at different intervals of time, suitably diluted with the mobile phase and assayed for lamivudine and zidovudine by the HPLC method developed. Dissolution samples (2.0 ml) were suitably diluted with the mobile phase and injected into the HPLC column for the simultaneous determination of lamivudine and zidovudine.

The dissolution fluid withdrawn at each sampling time was replaced with fresh dissolution fluid and suitable correction is made in calculating the amount of drug dissolved. For comparison dissolution of lamivudine and zidovudine from Zidolam tablets was also studied. All dissolution rate experiments were conducted in triplicate (n=3).

Analysis of Results:

Dissolution data were subjected to analysis as per zero order and first order kinetics. Three dissolution parameters namely PD_{10} (Percent dissolved in 10 min), T_{50} (Time for 50 % dissolution) and K_1 (First order dissolution rate constant) were calculated from the dissolution data.

RESULTS AND DISCUSSION

The objective of the present study is to develop tablet formulations containing lamivudine and zidovudine combination and to evaluate the dissolution rate of combined drug formulation by using the HPLC method developed for simultaneous determination of lamivudine and zidovudine in the dissolution study.

Tablets each containing lamivudine (150 mg) and zidovudine (300 mg) were formulated employing commonly used tablet excipients. Binder is a critical ingredient in tablet formulation influencing the disintegration time and dissolution rate of the tablets. Four binders namely (i) acacia, (ii) sucrose, (iii) PVP K30 and (iv)starch paste (i.e., gelatinized starch) were used in the formulation of combined drug tablets. Their influences on various physical properties and dissolution rate of combined drug tablet formulations were evaluated. Disintegrant is another critical ingredient in tablets. The effect of three disintegrants namely (i) potato starch, (ii) crospovidone and (iii) croscarmellose sodium on the disintergration and dissolution rate of combined drug tablet formulations was also evaluated. A total of six tablet formulations were prepared as per the formulae given in Table 1. The tablets were prepared by wet granulation method.

The physical characteristics of the tablets prepared are given in Table 2. Hardness of the tablets was in the range 4.5 – 6.5 Kg/sq.cm. Friability of the tablets was less than 1.05% in all the cases. Tablet weight variation was within ±2.5%. The tablets contained both the drugs, lamivudine and zidovudine within 100±3 % of the labeled claim. Tablets formulated with superdisintegrants, crospovidone and crosscarmellose sodium (F5 and F6) disintegrated rapidly within 1 min 30 seconds. Whereas the tablets formulated employing potato starch as disintegrant (F1, F2, F3, F4) disintegrated relatively slowly and the disintegration time of these tablets was in the range 2 min 40 seconds - 4 min 50 seconds. All the tablets prepared as well as commercial tablets fulfilled the official (IP 2010) specifications of uncoated tablets with regard to weight variation, hardness, friability, drug content and disintegration time.

Dissolution rate of lamivudine and zidovudine from the formulated and commercial tablets was studied in water as prescribed in IP 2010 for zidovudine tablets. As lamivudine is a water soluble drug its dissolution was also studied in water. Lamivudine and zidovudine content of the dissolution samples were determined by the HPLC method developed. The dissolution profiles are shown in Figs. 1 – 2. The dissolution parameters are summarized in Tables 3– 4.

Table 1: Formulae of Lamivudine and Zidovudine Tablets Prepared

Ingredient (mg/Tablet)	F1	F2	F3	F4	F5	F6
Lamivudine	150	150	150	150	150	150
Zidovudine	300	300	300	300	300	300
Potato Starch	90	90	90	90	--	--
Acacia	12	--	--	--	12	12
Sucrose	--	12	--	--	--	--
PVP K30	--	--	12	--	--	--
Gelatinized Starch	--	--	--	12	--	--
Crospovidone	--	--	--	--	30	--
Crosscarmellose Sodium	--	--	--	--	--	30
Lactose	24	24	24	24	84	84
Talc	12	12	12	12	12	12
Magnesium Stearate	12	12	12	12	12	12
Total Weight (mg)	600	600	600	600	600	600

Table 2: Physical Characteristics of the Tablets Prepared

Formulation	Hardness (Kg/sq.cm)	Friability (% wt. loss)	D.T. (min-sec)	Weight Variation (%)	Drug Content (mg/tablet)	
					Lamivudine	Zidovudine
F1	5.0 – 6.0	0.85	2 - 40	± 2.5	148.5	295.5
F2	5.5 – 6.0	0.62	3 - 40	± 1.5	149.2	297.4
F3	4.5 – 5.5	0.91	3 - 20	± 2.4	150.8	301.6
F4	5.0 – 5.5	0.74	4 - 50	± 1.2	151.2	302.7
F5	5.5 – 6.5	1.05	1 - 25	± 2.2	149.7	301.9
F6	5.0 – 6.0	0.95	1 - 30	± 1.8	148.2	298.6
C	6.0 – 6.5	0.87	2 - 50	± 2.5	148.8	298.8

F1-F6: Formulated Tablets; C: Commercial Tablets

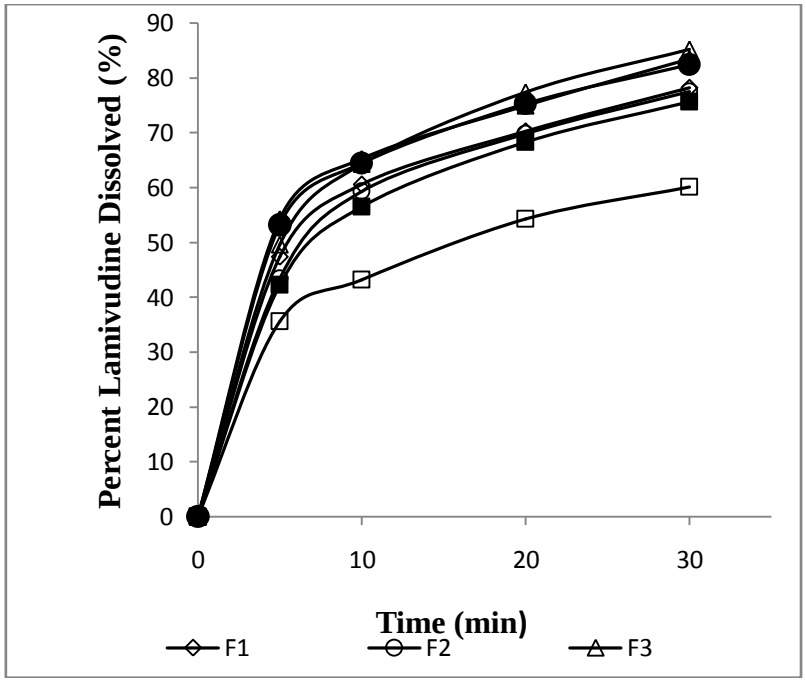

Fig.1: Lamivudine Dissolution Profiles of Formulated and Commercial Tablets

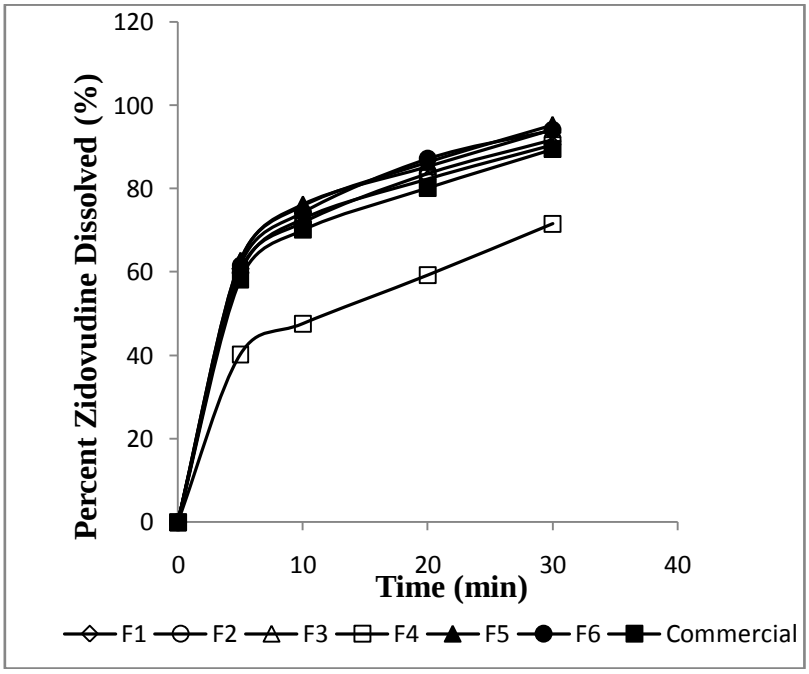

Fig. 2: Zidovudine Dissolution Profiles of Formulated and Commercial Tablets

Table 3: Lamivudine Dissolution Parameters of the Tablets Formulated and Commercial

Formulation	Dissolution Parameter			
	PD_{10} (%)	T_{50} (min)	$K_1 \times 10$ (min^{-1})	Correlation Coefficient (r) in First Order Model
F1	60.60	15.2	0.4559	0.9429
F2	59.28	15.2	0.4569	0.9521
F3	64.35	11.7	0.5918	0.9684
F4	43.25	25.3	0.2741	0.9284
F5	65.25	13.0	0.5316	0.9449
F6	64.46	13.3	0.5210	0.9437
C	56.51	15.9	0.4333	0.9534

Table 4: Zidovudine Dissolution Parameters of the Tablets Formulated and Commercial

Formulation	Dissolution Parameter			
	PD_{10} (%)	T_{50} (min)	$K_1 \times 10$ (min^{-1})	Correlation Coefficient (r) in First Order Model
F1	72.80	9.7	0.7097	0.9616
F2	71.90	9.1	0.7588	0.9715
F3	76.25	8.0	0.8588	0.9730
F4	47.60	18.6	0.3730	0.7617
F5	75.92	7.4	0.9305	0.9803
F6	74.35	7.9	0.8782	0.9804
C	70.12	10.2	0.6746	0.9634

The dissolution of both the drugs from the tablets formulated depended on the binder and disintegrant used. Lamivudine and zidovudine dissolution from the tablets followed first order kinetics with correlation coefficient (r) values in the range 0.9284 – 0.9804. The dissolution rate (K_1) values were calculated from the slopes of the first order linear plots in each case. Dissolution rate (K_1) of both lamivudine and zidovudine depended on the binder used. Though all the binders were used at the same concentration as the formulae (2%), variations were observed in the dissolution rate of the drugs from the tablets. Among the four binders PVP K30 gave relatively rapid and higher dissolution and starch paste (gelatinized starch) gave low dissolution. The order of increasing dissolution rate (K_1) observed with various binders was PVP K30 > Sucrose > Acacia > Starch paste. The same order was observed with

both the drugs. Tablets formulated employing super disintegrants (F5, F6) gave faster dissolution of the two drugs than those formulated with potato starch (F1) as disintegrant.

All formulated tablets, except formulation F4, gave higher dissolution rate of the medicaments than the commercial formulation. IP 2010 described a dissolution of NLT 70 % in 30 min for lamivudine and NLT 80% in 30 min for zidovudine. All formulated tablets except formulation F4 and commercial formulation tested fulfilled the official (IP 2010) dissolution rate test specification. Overall, formulations F3, F5 and F6 gave very rapid dissolution of both the drugs and as such they are considered as best combined drug formulations developed. Formulation F3 contains PVP K30 as binder and potato starch as disintegrant. Formulation F5 contains acacia as binder and crospovidone as disintegrant. Formulation F6 contains acacia as binder and crosscarmellose sodium as disintegrant. The dissolution characteristics of these formulations are better than those of commercial formulations tested.

Based on the results obtained, PVP K30, sucrose and acacia are recommended as binders and crospovidone and crosscarmellose sodium as disintegrants for the formulation development of combined drug tablets containing lamivudine and zidovudine.

CONCLUSIONS

1. All the combined drug tablets containing lamivudine and zidovudine prepared as well as commercial tablets fulfilled the official (IP 2010) specifications of uncoated tablets with regard to weight variation, hardness, friability, drug content and disintegration time.
2. Tablets formulated with superdisintegrants, crospovidone and crosscarmellose sodium disintegrated rapidly within 1 min 30 seconds. Whereas the tablets formulated employing potato starch as disintegrant disintegrated relatively slowly and the disintegration time of these tablets was in the range 2 min 40 seconds - 4 min 50 seconds.
3. The dissolution of both the drugs from the tablets formulated depended on the binder and disintegrant used. Lamivudine and zidovudine dissolution from the tablets followed first order kinetics with correlation coefficient (r) values in the range 0.9284 – 0.9804.
4. Among the four binders, PVP K30 gave relatively rapid and higher dissolution and starch paste (gelatinized starch) gave low dissolution. The order of increasing dissolution rate (K_1) observed with various binders was PVP K30 > Sucrose > Acacia > Starch paste. The same order was observed with both the drugs.
5. Tablets formulated employing superdisintegrants gave faster dissolution of the two drugs than those formulated with potato starch as disintegrant.
6. IP 2010 described a dissolution of NLT 70 % in 30 min for lamivudine and NLT 80% in 30 min for zidovudine. All formulated tablets except formulation F4 and commercial formulation tested fulfilled the official (IP 2010) dissolution rate test specification.
7. Overall, formulations F3, F5 and F6 gave very rapid dissolution of both the drugs and as such they are considered as best combined drug formulations developed. The dissolution characteristics of these formulations are better than those of commercial formulations tested.
8. Based on the results obtained, PVP K30, sucrose and acacia are recommended as binders and crospovidone and crosscarmellose sodium as disintegrants for the formulation development of combined drug tablets containing lamivudine and zidovudine.

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