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FORMULATION AND EVALUATION OF LAMIVUDINE AND TENOFOVIR DISPROXIL FUMARATE IR TABLETS

Patil Sagar Nanaji*, Swati Shailendra Rawat[1], D. Yashwanth Kumar[2]

Department of Pharmacy, MONAD University, Hapur, U.P, INDIA
[1]S N D College of Pharmacy, Yeola, Nashik, India
[2]Faculty of Pharmacy, Pacific University, Udaipur, India.

***Corresponding author e-mail:** psagarpharma@gmail.com

ABSTRACT

The main objective of the present study is to formulate and evaluate an immediate release tablet of Lamivudine and Tenofovir Disproxil Fumarate using different disintegrants. Lamivudine and Tenofovir Disproxil Fumarate belong to class of anti-retroviral drugs known as nucleotide analogue reverse transcriptase inhibitors. Pre formulation studies were performed prior to compression. The tablets were compressed using microcrystalline cellulose, crospovidone, crosscarmallosesodium, magnesium stearate and Aerosil. The fabricated tablets were evaluated for various micrometric properties like bulk density, tapped density, compressibility index, Hausner's ratio, angle of repose and post compression characteristics like thickness, hardness, friability, disintegration time and drug release. Crospovidone is found to be the better disintegrant when compared to crosscarmallosesodium in the formulation of immediate release tablets of Lamivudine and Tenofovir Disproxil Fumarate. The absorbance of Lamivudine and Tenofovir Disproxil Fumarate were screened in the UV region and the maximum absorbance was found to be 271 nm and 260nm respectively and this was used for UV analysis. Among the six different formulations developed F6 was found to be the best one with a drug release of 99.96% at the end of 30min.

Key words: Lamivudine, Tenofovir Disproxil Fumarate, Immediate release tablets.

INTRODUCTION

Oral drug delivery is the most desirable and preferred method of administering therapeutic agents for their systemic effects[1,2]. For many substances, conventional immediate release formulation provide clinically effective therapy maintaining the required balance of pharmacokinetic and Pharmacodynamic profiles with an acceptable level of safety to the patients. The Indian National AIDS Control Organization (NACO) projects that there will be 90 lakh HIV cases by 2010[3-5]. Tenofovir disproxilfumarate (TDF) belongs to class of anti-retroviral drugs knows as nucleotide analogue reverse transcriptase inhibitors (NtRTIs) which blocks reverse transcriptase an enzyme crucial to viral production in HIV-infected people[6]. Chemically, TDF is 9[(R)-2-[[bis [[(isopropoxycarbonyl) oxy] methoxy] phosphinyl] methoxy] propyl] adenine fumarate[7,8]. Lamivudine is a nucleoside reverse transcriptase inhibitor (NRTI) with activity against Human Immunodeficiency Virus Type 1 (HIV-1) and hepatitis B (HBV). It is phosphorylated intracellularly to its active 5'-triphosphate metabolite, Lamivudine triphosphate (L-TP). This nucleoside analogue is incorporated into viral DNA by HIV reverse transcriptase and HBV polymerase, resulting in DNA chain termination. Tenofovir is a nucleotide analog of deoxyadenosine monophosphate, Lamivudine is a synthetic nucleoside analogue. Their long half-lives in plasma and in peripheral blood mononuclear cells allow once-daily dosing in a single tablet, thus providing the nucleotide backbone for once-daily dosing, as a component of highly active antiretroviral therapy (HAART) [9,10.] An immediate release dosage form allows a manufacturer to extend market exclusivity, while offering patients a convenient dosage form or dosage regimen. Immediate Release Tablets are those tablets which are designed to disintegrate and release their medication with no special rate controlling features, such as special coatings and other techniques.

Immediate release and fast dispersing drug delivery system may offer a solution to these problems. Recently immediate release tablets have started gaining popularity and acceptance as a drug delivery system, mainly because they are easy to administer, has quick onset of action is economical and lead to better patient compliance [11].

MATERIALS AND METHODS

Lamivudine and Tenofovir Disproxil Fumarate (Spectrum Pharma research solutions, Hyderabad), microcrystalline cellulose and magnesium stearate (SDfine chemicals, Hyderabad), crospovidone was obtained as gift sample from Nikko chemicals, Croscarmellose sodium (Richer Pharmaceuticals, Hyderabad), Aerosil (Richer Pharmaceuticals, Hyderabad) were commercially procured and used for this study.

Preparation of Lamivudine and TDF Immediate Release Tablets

Step 1: Weighing and Blending - the active ingredient, disintegration agents are Weighed and mixed.
Step 2: After the powder granules are passing through a screen and select granules of uniform size to allow even fill in the die cavity.
Step 3: A dry lubricant, gliding is added to the granules either by dusting over the spread-out granules or by blending with the granules. It reduces the friction between the tablet and the walls of the die cavity
Step 4: Last step in which the tablet is fed into the die cavity and then compressed between a lower and an upper punch. 12.5mm size punches were used for punching tablets.

Evaluation of immediate release tablets: Tablets were evaluated for hardness, weight variation, friability, thickness, disintegration time and percentage drug release as per the pharmacopoeia.
Hardness determination: The hardness of the tablets from each batch was measured by using hardness tester Monsanto hardness tester).
Friability test : Friability was determined by taking 20 tablets. Tablets samples were weighed accurately and placed in friabilator (Roche friabilator). After the given specification (4 min at 25 rpm), loose dust was removed from the tablets. Finally tablets were weighed. The loss in weight indicates the ability of the tablets to withstand this type of wear.
Disintegration test: The disintegration for Lamivudine and TDF immediate release layer was determined using the disintegration apparatus. One tablet was placed in each of six tubes placed in a beaker containing 1000 ml of purified water maintained at 37 ± 20oC and the apparatus was operated. The time taken for the tablets to disintegrate and pass through the mesh was noted.

Thickness: The thickness of tablet can vary without any change in weight. This is generally due to the differences of density of granules, pressure applied for compression and the speed of compression. It was measured by Vernier caliper (Mitutoyo, Japan).

Weight variation test: Twenty tablets were selected at random and their average weight was determined using an electronic balance (Shimadzu Aux200, Japan). The tablets were weighed individually and compared with average weight.

In- vitro dissolution study: The release rate of Lamivudine and Tenofovir Disproxil Fumarate from the tablets was determined using USP dissolution testing apparatus II (Electro lab, India). The dissolution testing was performed using 900ml of 0.01N HCl at 37±0.5°C temperature and speed 100 rpm. Sample of 10ml was withdrawn at regular intervals of 5, 10, 15, and 30 minutes and replaced with fresh medium to maintain sink condition and the percentage of drug release was determined using UV.

RESULTS AND DISCUSSION

Immediate release tablets of Lamivudine and Tenofovir Disproxil Fumarate were successfully prepared by direct compression using excipients like MCC101, crosscarmallosesodium, crospovidone, magnesium stearate and aerosil. Formulations were evaluated for pre and post compression parameters. In the FTIR spectral analysis , absence of any peaks other than characteristic peaks of pure drugs and excipients, confirmed the compatability of drug and excipients.

The prepared blend was evaluated for various physicochemical characteristics like angle of repose, Bulk and Tapped density, Compressibility index, Hausner's ratio. Bulk density and tapped density values of Lamivudine and Tenofovir immediate release granules were found to be between 0.593 to 0.640 and 0.720 to 0.771 respectively. Carr's index and Hausner's ratio were in the range of 11.11 to 19.32 and 1.14 to 1.24 respectively. Angle of repose was in the range of 27°44´ to 33°70'. These results indicated good flow property and compressibility ofthe blend. The compressed tablets were evaluated for various post compression parameters like weight variation, hardness, friability, thickness and

disintegration time. The results for these parameters of all formulations were found to be in the range of 550-559mg,4.4-6.5kg/cm^2, 4.4-4.9mm, and 3 - 7min respectively. The drug content and Invitro drug release values of Lamivudine and TDF from various formulations was found to be in the range of 96.0-98.2 ,48.23%-98.3% and 97.5-98.8% ,56.71-99.98% respectively. The formulationsF1, F3, and F5 were developed by using croscarmellosesodium and F2, F4, andF6 were using crospovidone with3%, 6%, and 8% concentrations respectively. Hence the formulation F6 with 8% crospovidone which showed maximum drug release at the end of 30min was selected as best one.

CONCLUSION

The immediate release tablets of Lamivudine and Tenofovir Disproxil Fumarate have been developed with direct compression method. The Dissolution studies were performed in media pH 0.1N HCl and F6 formulation was concluded as optimized formula based on the drug release profile. Finally the identified formula shall be utilized for the process development studies.

Table 1: Formulation of Lamivudine and Tenofovir Immediate Release granules

S. No.	Ingredients	F-1 mg/tab	F-2 mg/tab	F-3 mg/tab	F-4 mg/tab	F-5 mg/tab	F-6/tab
1.	Lamivudine	150	150	150	150	150	150
2.	Tenofovir	300	300	300	300	300	300
3.	Microcrystalline cellulose pH 102	qs	qs	qs	qs	qs	qs
4.	Cross carmellose sodium	17	--	28	--	39	--
5.	Povidone	--	17	--	28	--	39
6.	Colloidal Silicon Dioxide	2.5	2.5	2.5	2.5	2.5	2.5
7.	Magnesium stearate	7.5	7.5	7.5	7.5	7.5	7.5
Average Weight		550	550	550	550	550	550

Table 2 : Micromeritic properties of Granules of L+TDF (IR)

Formulation code	Bulk density (g/cc)	Tapped density (g/cc)	Carr's index (%)	Hausner's ratio	Angle of repose(degree)
F-1	0.593	0.735	19.32	1.24	31.42
F-2	0.635	0.771	17.64	1.21	33.70
F-3	0.639	0.729	12.35	1.14	27.44
F-4	0.633	0.721	12.21	1.14	25.35
F-5	0.640	0.720	11.11	1.13	27.69
F-6	0.634	0.770	17.12	1.21	33.50

Table 3: Post compression parameters of L+ TDF immediate release tablets

Formulation	Uniformity of Weight mg ± SD (n=20)	Hardness Kg/cm2 ± SD (n=10)	Thickness mm ± SD (n=5)	Friability (%)	Disintegration time in mints	% drug content	
						Lamivudine	TDF
F1	557	5.5	4.5	0.21	7.0	96.2	97.8
F2	555	6.5	4.9	0.18	6.0	96.0	98.1
F3	559	4.6	4.5	0.29	4.5	97.1	97.5
F4	550	4.4	4.4	0.19	4.35	98.2	97.9
F5	558	5.9	4.6	0.21	4.5	97.1	96.5
F6	554	5.2	4.5	0.44	3.0	97.2	98.8

Table 4: Percentage drug release of Lamivudine at 271nm

time (min)	F1 (3%CCS)	F2 (3%CP)	F3 (6%CCS)	F4 (6%CP)	F5 (8%CCS)	F6 (8%CP)
0	0	0	0	0	0	0
5	13.1	15.55	19.43	22.25	25.52	29.92
10	20.19	25.53	28.45	35.29	42.45	49.23
15	28.29	38.26	49.31	55.77	68.71	65.2
30	48.23	55.5	63.59	72.21	86.49	98.3

Table 5: percentage drug release of (TDF) Tenofovir Disproxil Fumarate at260nm

time (min)	F1 (3%CCS)	F2b (3%CP)	F3 (6%CCS)	F4 (6%CP)	F5 (8%CCS)	F6 (8%CP)
0	0	0	0	0	0	0
5	15.23	20.25	27.54	28.23	30.12	29.35
10	23.45	32.33	35.23	37.5	40.23	48.85
15	33.44	49.47	52.03	62.4	73.95	69.29
30	56.71	61.36	76.19	79.12	90.84	99.98

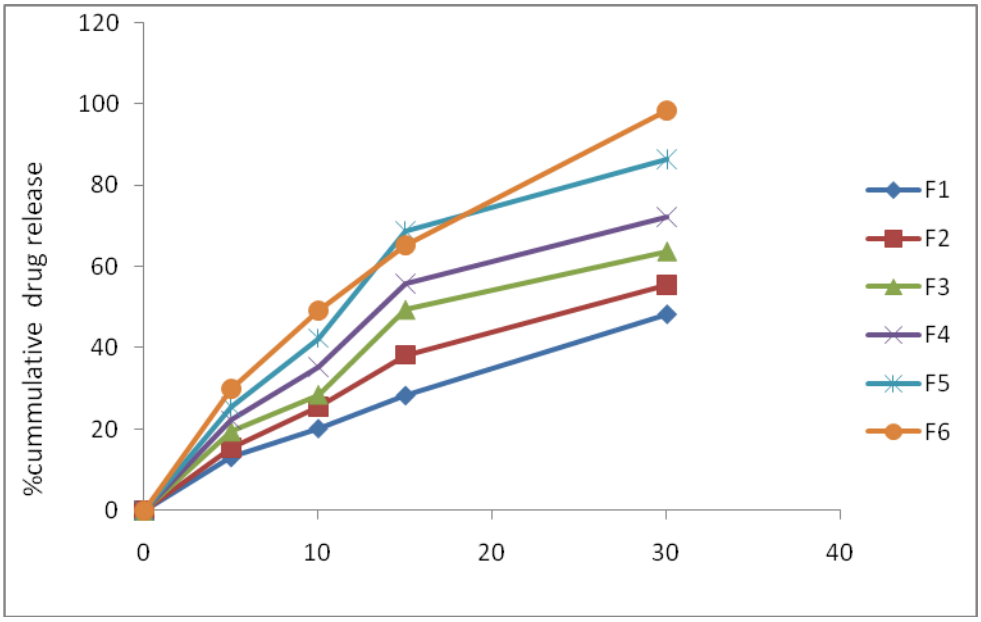

Fig.1 % Cumulative drug release of Lamivudine

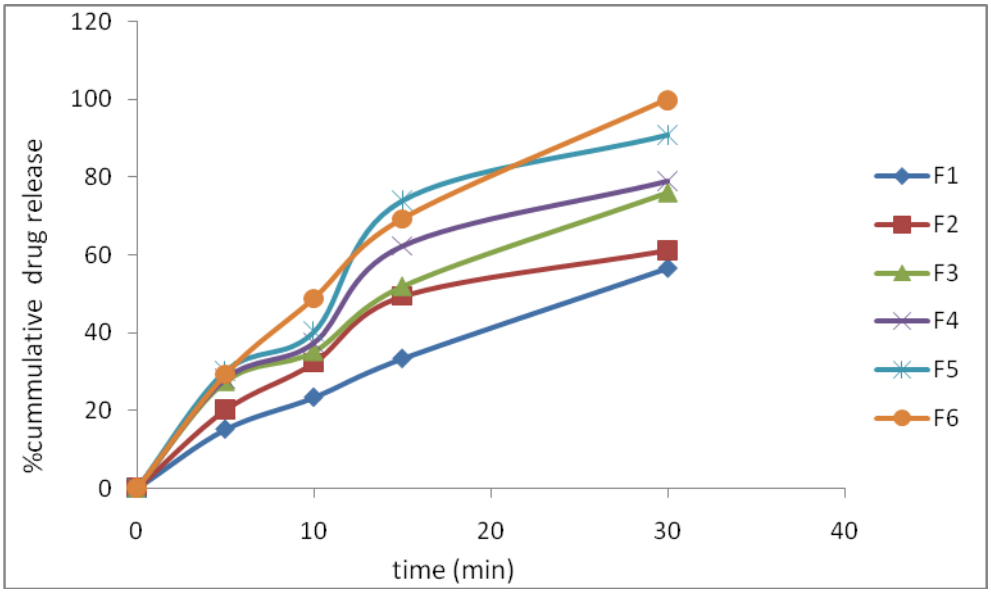

Fig.2 % Cumulative drug release of TDF

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