INTERNATIONAL RESEARCH JOURNAL OF PHARMACY

www.irjponline.com ISSN 2230 – 8407

Research Article

FORMULATION DEVELOPMENT AND EVALUATION OF EFAVIRENZ AND LAMIVUDINE IMMEDIATE RELEASE TABLETS: A COMBINATION THERAPY

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Article Received on: 17/01/13 Revised on: 09/02/13 Approved for publication: 13/03/13

DOI: 10.7897/2230-8407.04328

IRJP is an official publication of Moksha Publishing House. Website: www.mokshaph.com

ABSTRACT

The present study outlines a systematic approach for Formulation and Evaluation of Immediate release Tablets of lamivudine and Efavirenz. The objective of this regimen is, to delay disease progression, to increase the duration of survival by achieving maximal and prolonged suppression of HIV replication, to restore and preserve immunological function. Combination therapy is more effective and has less chances of developing resistance than monotherapy. To achieve this goal various prototype formulation trials were taken and evaluated with respect to the various quality control tests such as Thickness, hardness, weight variation, dissolution, disintegration, hardness and assay. The formula was finalized by comparing the Invitro dissolution profile with that of the Marketed Tablets. The invitro release study was performed in 2%SLS in purified water upto30 min. Among all the formulations, formulation F5 release profile was good as compared to the marketed products. Stability studies (40±2ºC/75±5%RH) for 2 months indicated that no characteristics changes in formulation. There was no chemical interaction between drug and excipients.

Keywords: Lamivudine, Efavirenz, HAART-Highly Active Antiretroviral Therapy, Immediate Release tablet.

INTRODUCTION

Oral route is the most widely utilized route of administration among all the routes that have been explored for systemic delivery of drugs via pharmaceutical products of different dosage form. Oral route is considered most natural, uncomplicated, convenient and safe due to its ease of administration, patient acceptance and cost effective manufacturing process[1].

As a result the demand for the technologies has been increased 3 fold annually. Since the development cost of new chemical entity is very high, the pharmaceutical companies are focusing on the development of new drug delivery systems for existing drug with an improved efficacy and bioavailability together with reduced dosing frequency to minimize the side effects[2].

Combination therapy

When two or more drugs are used together to treat any disease, treatment is called as combination therapy. Now a day's various developed and developing countries move towards combination therapy for treatment of various diseases and disorders requiring long term therapy. Advantages of Combination therapy over monotherapy such as, problem of dose dependent side effects is minimized, a low dose combination of two different agents reduces the dose related risk, the addition of one agent may counteract some deleterious effects of the other, using low dosage of two different agents minimizes the clinical and metabolic effects that occur with maximal dosage of individual component of the combined tablet and thus dosage of the single component can be reduced, dosage form of two or more active ingredients in combination can show Synergistic cumulative effect and/or decreased side effects[3].

Fixed dose combinations are multiple antiretroviral drugs combined into a single pill. Combination of antiretroviral creates multiple obstacles to HIV replication to keep the number of offspring low and reduce the possibility of a superior mutation, if a mutation that conveys resistance to one of the drugs being taken, the other drugs continue to suppress reproduction of that mutation, no individual antiretroviral drug has been demonstrated to suppress an HIV infection for longer duration, so these agents must be taken in combinations in order to have a long lasting effect[4].

As a result, the standard of care is to use combinations of antiretroviral drugs, Current treatment for HIV infection consists of Highly Active Antiretroviral Therapy or HAART[5]. Current HAART options are combinations consisting of at least two drugs belonging to a different classes of antiretroviral agents, typically, these classes are two Nucleoside Analogue Reverse Transcriptase Inhibitors[6] (NARTIs).These different classes of antiretroviral drugs act at different stages of the HIV life-cycle, this two drug combination is commonly known as a double cocktail. Highly active antiretroviral therapy for HIV-AIDS. Lamivudine Reverse transcriptase Inhibitor. Efavirenz Non-nucleoside reverse transcriptase inhibitor (NNRTI)[7]. There is two major classes of ARVs based on their mechanism of action[8]; Reverse Transcriptase Inhibitors (RTIs).

MATERIALS AND METHODS

Lamivudine, Efavirenz (Heterolabs, India).Micro crystalline cellulose (JRS Pharma) Cross Carmellose Sodium (DMV International) Hydroxy Propyl Cellulose (Aqualon) Sodium Lauryl Sulfate (Stepan) Lactose Anhydrous (FMC biopolymer) Magnesium Stearate (Ferro) All other solvents and reagents were of analytical grade.

Drug-Excipient Compatibility Studies

It was observed that there was no characteristic change in Efavirenz and Lamivudine with Excipient binary mixture, drug-drug (Efavirenz + Lamivudine) mixtures; Drug-Purified water (Efavirenz + Lamivudine Purified water) directly exposed to 40°C/75%RH & 60°C for 1 month.

Preparation of Immediate release tablets

Lamivudine, Efavirenz granules are prepared by direct compression method. The composition of each tablet is shown in table 1.Formulations are prepared first Sifting of Lamivudine, Efavirenz, Microcrystalline Cellulose, Cross Carmellose Sodium, Hydroxy Propyl Cellulose, Sodium Lauryl Sulfate were sifted together and the material were loaded into octagonal Blender and mixed for 10 minutes. The granules were passed through # 20 prelubricated with Lactose Anhydrous and lubricated with magnesium stearate by further blending for 5 mins. Compression was done on Cadmach tablet compression machine (Ahmadabad) using 24.00×11.00 mm punches.

In-vitro Evaluation of the powdered blend

Angle of repose

It is the maximum angle that can be obtained between the free standing surface of the powdered heap and the horizontal plane. It was determined by height cone method. A funnel was fixed at a desired height and powdered blend was filled in it and then allowed to flow down freely onto a graph paper fixed on a horizontal surface and the height and radius of the heap formed were noted. Angle of repose was calculated using the formula,

$$\theta = \tan^{-1} (h/r)$$

Where, h = height of the heap obtained,
r = radius of the heap obtained.

Bulk Density

The powder sample equivalent to 5gms was filled in a 25ml graduated cylinder and powder was leveled and the unsettled volume (V_b) was noted. The bulk density was calculated in gms/cm^3 by the formula,

$$\text{Bulk density } (\rho_b) = \frac{M}{Vb}$$

Where, M = Mass of powder taken, V_b = Bulk volume.

Tapped Density

The powder sample equivalent to 5gms was filled in a 25ml graduated cylinder. The mechanical tapping of the cylinder was carried out using tapped density tester at a constant rate for 100 times. Volume was considered as tapped volume (V_t). The tapped density was calculated in gms/cm^3 by the formula,

$$\text{Tapped density } (\rho_t) = \frac{M}{Vt}$$

Where, M = Mass of powder taken, V_t = Tapped volume.

Compressibility Index (Carr's Index)

Compressibility index of the powder can be computed based on the bulk and tapped densities, using the formula

$$\text{Carr's index } (\%) = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

Hausner's Ratio

It indicates the flow properties of the powder and was measured by the ratio of tapped density to the bulk density.

$$\text{Hausner's Ratio} = \frac{\text{Tapped density}}{\text{Bulk density}}$$

In-vitro Evaluation of the prepared tablets

Tablet thickness

A vernier calipers was used to determine thickness of 5 randomly selected tablets. Results were expressed as mean values as shown in table 2.

Tablet Hardness

Hardness indicates the ability of a tablet to withstand mechanical shocks while handling. The hardness of the tablets was determined using Monsanto hardness tester. It is expressed in kg/cm^2. Three tablets were randomly picked and mean hardness of the tablets was determined which was given in the table 2.

Friability

The friability of tablets was determined using Roche friabilator. It is expressed in percentage (%). Twenty tablets were initially weighed (W_o) and transferred into the friabilator's chamber. The friabilator was operated at 25rpm for 4 minutes (or run up to 100 revolutions). The tablets were dedusted and reweighed (W). The% friability was then calculated as

$$\text{Percentage of Friability} = 100 \left(1 - \frac{W}{W_o}\right)$$

Percentage friability of tablets less than 1% was considered acceptable. The results were shown in the table 2.

Table 1: Composition of different batches of tablets (mg per tablet)

API/Excipients	F1	F2	F3	F4	F5
Efavirenz	300	300	300	300	300
Lamivudine	150	150	150	150	150
MCC(Vivapur-101)	60	52	56	49	51
CCS-(Primllose)	18	24	30	34	30
HPC-(Klucel-LF)	24	24	16	16	18
SLS-(Stepanol)	10	12	12	15	15
Pre/Lubrication					
Lactose(DCL-21)	30	28	26	26	26
Magnesium Sterate	8	10	10	10	10
Core Weight of Tablet	600	600	600	600	600
Coating					
Opadry Yellow **	15	15	15	15	15
Tablet Weight	615	615	615	615	615

Table 2: Flow properties of the Compressed tablets of Efavirenz and Lamivudine formulations

Formulation	Weight variation (mg)	Thickness (mm) mean±SD	Hardness (Kp) mean±SD	Friability (%)	Disintegration time (Min)
Limits	**600-620**	**7.6±0.5**	**11±4**	**NMT 1.0% W/W**	**NMT 30**
F1	-	-	-	-	-
F2	612±2.5	9.1	11±3	0.4±0.01	22±1
F3	612±2.5	8.5	11±3	0.3±0.05	15±2
F4	612±2.5	7.7	11±4	0.4±0.09	13±2
F5	612±2.5	7.5	11±2	0.3±0.04	12±4

Table 3: Assay values of all formulation

Formulation	Assay (%)	
	Efaverinz	Lamivudine
F1	-	-
F2	102±0.5	91±0.8
F3	100±1.2	94±0.3
F4	102.3±1	95±1
F5	103±1	97±0.5
Innovator	104±1	97±7

Table 4: Dissolution data of all formulations

Time (min)	Sustiva	F2-Efavirenz	Epivir	F2-Lamivudine
0	0	0	0	0
10	89	45	98	60
20	97	68	98	80
30	98	81	98	89
45	98	89	99	94

Table 5: Dissolution graph of optimised formulations

Time	10(min)	20(min)	30(min)	45(min)
SUSTIVA	89	97	98	98
F2	45	68	81	89
F3	68	77	84	95
F4	80	84	89	94
F5	89	95	95	99
EPIVIR	98	98	98	99
F2	60	80	89	94
F3	71	82	95	97
F4	96	98	99	100
F5	98	99	99	100

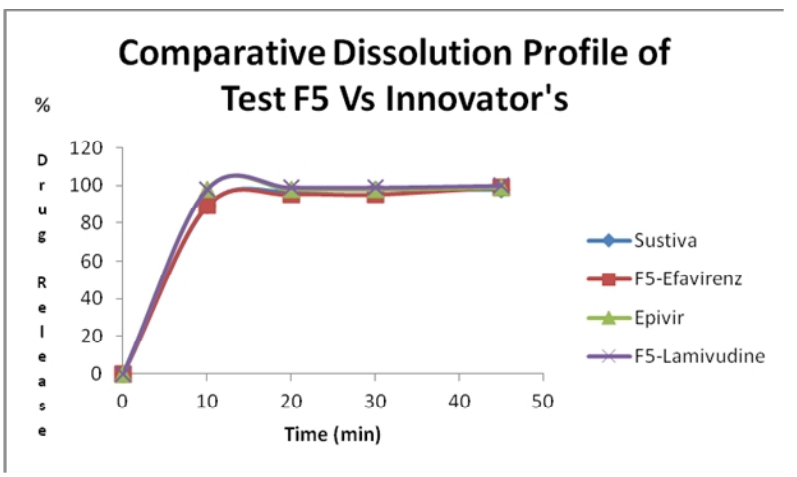

Figure 1: Comparative dissolution graph of test F5 vs. standard

In-vitro drug release study

An in-vitro drug release study was carried out using tablet dissolution test apparatus USP type- II (Paddle) at 100 rpm[9, 10]. The dissolution medium consisted of 900ml 2% SLS in purified water, maintained at a temperature 37.0°C±0.5°C.A sample of 5ml was withdrawn at predetermined time intervals and an equivalent amount of fresh dissolution fluid equilibrated at the same temperature was replaced, and then measure absorbance by HPLC technique. The assays of all the formulations are tabulated in table 3.

The dissolution data of all formulations is tabulated in table 4, followed by the dissolution graph of optimised formulation F5 tabulated in table 5.

RESULTS AND DISCUSSION

In the present study, Lamivudine and Efavirenz Immediate release tablets were prepared by direct compression process by using ingredients shown in table 1. A total number of five formulations were prepared. The data of evaluated tablets such as thickness, weight variation, hardness and friability are shown in table 2. The hardness was found to be in the range of 11kp to13kp, the normal acceptance criteria for hardness are not more than 15.00kp.The dissolution data of all formulations is tabulated in table 4, followed by the dissolution graph of optimised formulation F5 tabulated in table 5.

In F2, it was observed that the dissolution profile of the test product was on lower side when compared to the innovator, so in order to increase the dissolution it was decided to do the formulation by increasing the concentration of Cross Carmellose Sodium from 3%-4%in F3 to match the initial release of Efavirenz.

In F3, observed that the decreasing the concentration of binder (HPC) from increasing the concentration of Disintegrant (Croscarmellose Sodium) improved the dissolution profile of the test product but it was still on lower side when compared to the innovator. So in order to increase the dissolution further, it was decided to the formulation by decreasing the concentration of binder (HPC) from 24mg/tab to 16mg/tab.

In F4 observed that the optimization of binder (HPC) the dissolution profile was improved by the addition of Disintegrant (Croscarmellose Sodium) of the test product so in order to match innovator release profile.

In F5 observed that the dissolution profile of the test product was matching with the dissolution profile of the innovator – Optimised batch.

CONCLUSION

F5 formulation was concluded as optimized formula based on the drug release profile and other evaluation parameters compared with Innovator. Finally, the identified formula shall be utilized for the process development studies for successful launching of the product as it was proved to be stable and robust, cost effective.

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Cite this article as:

Pradeep Pagidimarri, PM Vasanth, K Ramesh. Formulation development and evaluation of Efavirenz and Lamivudine immediate release tablets: A combination therapy. Int. Res. J. Pharm. 2013; 4(3):145-148

Source of support: Nil, Conflict of interest: None Declared