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FORMULATION, DEVELOPMENT AND EVALUATION OF BI-LAYER TABLET OF ANTI HIV DRUGS

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Abstract:

In the last decade, interest in developing a combination of two or more Active Pharmaceutical Ingredients (API) in a single dosage form (bi-layer tablet) has increased in the pharmaceutical industry, promoting patient convenience and compliance. The present research work was envisaged to develop bilayer tablets to improve therapeutic efficacy of anti-HIV/AIDS drugs for the treatment of sexually transmitted diseases. The combination of two anti-HIV/AIDS drugs i.e. abacavir and lamivudine were used for the preparation of bilayer tablets which act HIV/AIDS infections. The formulations comprise of abacavir as immediate release layer formulated using different superdisintegrants and lamivudine as extended-release layer containing HPMC K4, K15. Evaluation of bilayer tablets were performed for the immediate release abacavir layer and sustain release lamivudine layer with optimization of excipients. The immediate release layer of abacavir showed complete release within 90 min and lamivudine release was extended up to 12 hours. The present study revealed that abacavir and lamivudine bilayer tablets were successfully developed for the use against sexually transmitted infections.

Keywords: *Bi-layer tablet, Abacavir, Lamivudine, HIV/AIDS, Superdisintegrants, HPMC*

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INTRODUCTION:

The curable sexually transmitted diseases (STDs) are the major public health problems worldwide which lead to illness with significant health, social and economic consequences, but except HIV no particular attention has been given to the prevalence of other infections [1,2]. It can lead to long-term, serious complications and sequelae [3]. In the year 2006, about 85% of the HIV infections have spread due to STD patients, which is alarming. STDs are among the most common infectious diseases. Annually, an estimated 19.7 million sexually transmitted infections occur in the United States alone. Worldwide, an estimated 499 million cases of chlamydia, gonorrhea, syphilis, and trichomoniasis occur each year. Some STDs are more prevalent in developing countries (chancroid, lymphogranuloma venereum [LGV], granuloma inguinale [donovanosis]) or in specific regions (gonorrhea with treatment failure and decreased susceptibility to cephalosporins in Asia) and may be imported into other countries by travelers returning from such locales [4]. There are various problems with the treatment of sexually transmitted disease (STDs) like increasing widespread resistance against individual drug, limited alternatives in pregnancy or allergy, lack of single agents possessing a broad spectrum of activity against multiple genital pathogens and higher dose of drug required for treatment with frequent dosing [5]. Fixed-dose combination drugs can be defined as two or more drugs in a single formulation, each drug having independent modes of action, or the combination of which are synergistic or additive, or complementary in their effect. Free combinations can be defined as two or more drugs in separate formulations, each taken usually at the same time. Fixed-dose combination (FDC) products are common in the treatment of hypertension, diabetes, human immunodeficiency virus, and tuberculosis. They make it possible to combine two or more drug molecules with different modes of pharmacological actions in a single dosing unit and optimize the treatment. From a patient perspective, they offer convenience, reduced dosing unit burden, and cost savings. From a clinical perspective, an aging population in developed countries will need multiple medications to treat age-related diseases and co-morbidities. Fixed-dose combination (FDC) products simplify dosing regimens and enhance patient compliance. The number of fixed-dose combination (FDC) products has grown over the years and the trend is likely to continue. While some formulation technologies such as multi-layer tablets, multiparticulate systems, active film coating, and hot-melt granulation. Historically, fixed-dose combination (FDC) products were developed for improved compliance, better efficacy, and reduced adverse events [6, 7]. In the current scenario, the strategies for developing a fixed-dose combination (FDC) are primarily based on the therapeutic requirements. The present research was carried out with the aim of developing bilayer tablets of abacavir and lamivudine for the treatment of sexually transmitted disease (STDs). Abacavir and lamivudine were selected as a combination of drugs against HIV/AIDS.

MATERIALS AND METHODS:

Abacavir and lamivudine were gifted by Mylan Pharmaceuticals Private Limited, Bangalore, India. HPMC K4M, K15M, PVP K30 was obtained from Mapromax, Life sciences Pvt. Ltd. Dehradun. Xanthan gum, magnesium stearate and talc were obtained from Loba Chemical Pvt Ltd (Mumbai, India). Crospovidone, Sodium starch glycolate, Croscarmellose sodium obtained from Danmed Pharmaceuticals Pvt Ltd, Hyderabad. Hydrochloric acid was obtained from S. D. Fine Chem. Ltd., Mumbai. All other chemical were purchased from Hi Media, Mumbai. Double distilled water was prepared freshly and used whenever required. All other chemicals used in this study including those stated were of analytical reagent (A.R.) grade.

Formulation development

Formulation of immediate release (IR) layer

Fast dissolving tablets of abacavir were prepared by direct compression method after incorporating different superdisintegrants such as, crosscarmellose sodium (Ac-Di-Sol), crospovidone and sodium starch glycolate in different concentrations. All the ingredients given in table 1 were weighed and mixed in geometric progression in a dry and clean mortar. Then the ingredients were passed through mesh #60. The Blend was compressed on 8 mm (diameter) fat punches on a ‘Rimek mini press 16 station rotary compression machine. Nine formulations of abacavir granules were prepared and each formulation contained one of the three disintegrate in different concentration. Each tablets weighing 350 mg, were obtained.

Table 1 Composition of Abacavir immediate release (IR) tablets

Ingredients(mg)	Formulation code								
	IF1	IF 2	IF 3	IF 4	IF 5	IF 6	IF 7	IF 8	IF 9
Abacavir	300	300	300	300	300	300	300	300	300
Sodium Starch glycolate	10	15	20	-	-	-	-	-	-
Croscarmellose sodium	-	-	-	10	15	20	-	-	-
Crospovidone	-	-	-	-	-	-	10	15	20
Microcrystalline cellulose	25	20	15	25	20	15	25	20	15
Talc	5	5	5	5	5	5	5	5	5
Magnesium stearate	10	10	10	10	10	10	10	10	10
Total weight	350	350	350	350	350	350	350	350	350

Formulation of extended release (ER) layer

Direct compression was followed to manufacture the extended-release layer tablets of lamivudine. Eight different formulations (F1, F2, F3, F4, F5, F6, F7, & F8) were prepared by direct compression. All the polymers selected, drug and excipients were passed through sieve no. 40 before using into formulation. The amount and ratio of drug and polymers were weighed as per given in table 2 and all the formulation were used for further evaluations parameters.

Table 2 Various formulations of lamivudine extended-release layer

Excipients (mg)	F1	F2	F3	F4	F5	F6	F7	F8
Lamivudine	150	150	150	150	150	150	150	150
HPMC K4	90	120	-	-	-	-	30	40
HPMC K15	-	-	90	120	-	-	30	40
Xanthan gum	-	-	-	-	90	120	30	40
PVP K30	15	15	15	15	15	15	15	15
Talc	5	5	5	5	5	5	5	5
Magnesium Stearate	10	10	10	10	10	10	10	10
Lactose	80	50	80	50	80	50	80	50
Total Weight	350	350	350	350	350	350	350	350

Formulation development of bilayer tablet

Optimized formulation IF-8 of immediate release layer and optimized formulation of F-7 for extended release used for formulation of Bi-layer tablet.

Evaluation of Precompression Parameter

Angle of Repose (θ)

The angle of repose was determined by using fixed funnel method. The physical mixtures of drug with different excipients were prepared and the accurately weighed drug powder or its physical mixture was taken in a funnel. The height of the funnel was adjusted in such a way that the tip of the funnel just touches the apex of the heap of the drug powder. The powder was allowed to flow through the funnel freely onto surface. The angle of repose was calculated using the following equation**.**

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

Where, h and r are the height and radius of the powder cone respectively.

Bulk Density/Tapped Density

Both loose bulk density (LBD) and tapped density (TBD) were determined were calculated using the following formulas.

LBD = Powder weight/volume of the packing

TBD = Powder weight /tapped volume of the packing

Compressibility Index

The compressibility index of the granules was determined by Carr's compressibility index**.**

Carr's index (%) = [(TBD – LBD)/TBD] × 100.

Hausner's ratio

Hausner's ratio is an indirect index of ease of measuring the powder flow. It was calculated by the following formula [8, 9].

Hausner's ratio = Tapped density/Bulk density.

Evaluation of post compression Parameter

Shape and color of tablets

Uncoated tablets were examined under a lens for the shape of the tablet and colour was observed by keeping the tablets in light [10].

Thickness

Three tablets were picked from each formulation randomly and thickness was measured individually. It is expressed in mm and standard deviation was also calculated. The tablet thickness was measured using dial-caliper (Mitutoyo, Japan).

Hardness

For each formulation, the hardness of five tablets was determined using the Monsanto hardness tester (Cadmach) and measured in terms of kg/cm^2.

Weight variation

Twenty tablets were selected randomly from each formulation and average weight was determined. The tablets were weighed individually and compared with average weight. The U.S Pharmacopoeia allows a little variation in the weight of a tablet.

Friability

A sample of twenty randomly selected tablets were accurately weighed and placed in a Roche friabilator. The friabilator was operated for 4 min at a speed of 25 rpm. The tablets were removed from the friabilator, de-dusted and reweighed. The percent loss in weight due to abrasion and impact was calculated as,

%Friability= (Loss in weight/ Initial weight) x 100

Hardness test

The hardness of tablet was measured by Pfizer hardness tester and results were expressed in Kg/cm^2**.**

Uniformity of drug content IR layer

The test is mandatory for tablets with 10mg or less weight of active ingredient. Ten randomly selected tablets from each formulation (F1 to F9) were finely powdered and Drug equivalent to 10 mg of drug dissolved in 10 ml 0.1 N HCl (Simulated gastric fluid of pH 1.2 without enzymes) sonicate it for 20 minutes, till the entire drug leached out from complex, then the solution was filtered through whatman filter paper No. 41. From this Solution take 1 ml and Diluted up to 100 ml with 0.1 N HCl and the drug content was determined spectrophotometrically at 286nm for Abacavir.

Uniformity of drug content ER layer

Twenty tablets were taken and amount of drug present in each tablet was determined. The tablets were crushed in a mortar and the powder equivalent to 100mg of drug was transferred to 100ml standard flask. The powder was dissolved in 50 ml of 0.1 N HCl and made up to volume with of 0.1 N HCl. The sample was mixed thoroughly and filtered through a 0.45µ membrane filter. The filtered solution was diluted suitably and reacts with dye and analyzed for drug content by UV spectrophotometer at a λ max of 276nm using of 0.1 N HCl as blank.

Dissolution rate studies

In vitro drug release of the sample was carried out using USP- type II dissolution apparatus (Paddle type). The dissolution medium, 900 ml 0.1N HCl was placed into the dissolution flask maintaining the temperature of 37±0.50ºC and rpm of 75. One lamivudine tablet was placed in each basket of dissolution apparatus. The apparatus was allowed to run for 12 hours. Sample measuring 5 ml were withdrawn after every 1 hour up to 12 hours using 10ml pipette. The fresh dissolution medium (37^0C) was replaced every time with the same quantity of the sample. From this take 0.5 ml and dilute up to 10 ml with 0.1 N HCl and take the absorbance at 276nm using spectroscopy.

RESULTS AND DISCUSSIONS:

λ_{max} of Abacavir and lamivudine was found to be 286 and 276nm by using U.V. spectrophotometer (Labindia-3000+). The powdered blends of different formulations of immediate and extended-release tablets were evaluated for angle of repose, bulk density (BD), tapped density (TBD), compressibility index and Hausner's ratio was founds within the range, which shows good flow properties of the powdered blend Table 3 & 4. The prepared tablets were evaluated for different physico-chemical properties and the results are summarized in Table 5 & 6. The tablets were white, circular in shape and were found to be uniform with respect to weight variation, hardness; thickness, friability and content uniformity of different batch of tablets were found within acceptable range and the distribution of drug in all the formulations was uniform. The prepared bilayer tablets were evaluated for different physico-chemical properties and the results are summarized in Table 7 & 8. The tablets were found to be uniform with respect to weight variation and hardness (6.5 kg/cm^2). The thickness (5.23 mm) and friability (0.754%) of optimized batch of tablets were found within acceptable range. Content uniformity of formulations was found to be 99.45 and 99.12 %, where the distribution of drug in all the formulations was uniform. A dissolution study shows the release of abacavir and lamivudine. The immediate layer of abacavir release approx 98.85 percent drug within 1.5 Hrs. and extended layer lamivudine shows release up to 12 Hours Approx 99.85 percent of drug release in 12 hours. The release of bilayer tablet is shown in Figure 1.

Table 3: Results of pre-compressional parameters of Abacavir

Formulation code	Parameters			
	Loose Bulk density(gm/ml)	Tapped bulk density(gm/ml)	Carr's Index (%)	Hausner's Ratio
IF1	0.365	0.452	19.248	1.238
IF2	0.358	0.465	23.011	1.299
IF3	0.362	0.472	23.305	1.304
IF4	0.374	0.482	22.407	1.289
IF5	0.369	0.476	22.479	1.290
IF6	0.347	0.456	23.904	1.314
IF7	0.356	0.462	22.944	1.298
IF8	0.374	0.485	22.887	1.297
IF9	0.352	0.465	24.301	1.321

Table 4: Result of pre-compression properties of lamivudine tablets

F. Code	Bulk density(gm/ml)	Tapped density(gm/ml)	Compressibility index	Hausner ratio
F1	0.452	0.562	19.573	1.243
F2	0.465	0.574	18.990	1.234
F3	0.454	0.565	19.646	1.244
F4	0.474	0.579	18.135	1.222
F5	0.465	0.572	18.706	1.230
F6	0.472	0.582	18.900	1.233
F7	0.458	0.571	19.790	1.247
F8	0.465	0.577	19.411	1.241

Table 5: Results of post-compression parameters of all formulations (Abacavir)

F. Code	Hardness test (kg/cm^2)	Friability (%)	Weight variation (%)	Thickness (mm)	Drug content (%)
IF1	3.4±0.1	0.658±0.014	355±4	2.4±0.2	98.85±0.45
IF2	3.5±0.2	0.652±0.021	352±6	2.3±0.2	98.87±0.65
IF3	3.6±0.1	0.612±0.032	354±5	2.3±0.1	99.12±0.25
IF4	3.5±0.1	0.715±0.025	348±4	2.4±0.3	99.45±0.36
IF5	3.5±0.1	0.689±0.015	352±2	2.5±0.1	99.65±0.41
IF6	3.5±0.2	0.775±0.042	349±3	2.4±0.2	99.78±0.32
IF7	3.6±0.1	0.645±0.032	353±2	2.5±0.1	99.74±0.26
IF8	3.5±0.2	0.658±0.022	354±1	2.4±0.3	99.18±0.41
IF9	3.5±0.1	0.622±0.035	352±2	2.5±0.1	99.25±0.33

Table 6: Results of post compression properties of all formulations (Lamivudine)

F. code	Thickness (mm)	Hardness (kg/cm^2)	Weight variation (mg)	Friability (%)	Drug content (%)
F1	3.5	5.2	348	0.858	98.89
F2	3.4	5.3	352	0.658	99.85
F3	3.5	5.1	345	0.489	98.89
F4	3.6	5.4	355	0.558	99.56
F5	5.5	5.3	348	0.658	99.28
F6	3.4	5.4	350	0.856	99.56
F7	3.4	5.2	348	0.658	99.23
F8	3.4	5.1	352	0.758	99.12

Table 7: Post-compression parameters of optimized formulation

Formulation	Hardness test (kg/cm^2)	Friability (%)	Weight variation	Thickness (mm)
1.	6.5	0.754	Passes	5.23

Table 8 Results of Drug content analysis of optimized formulation

Formulation	Abacavir (% Label Claim)	Lamivudine (% Label Claim)
In-house Bilayer tablet	99.45	99.12

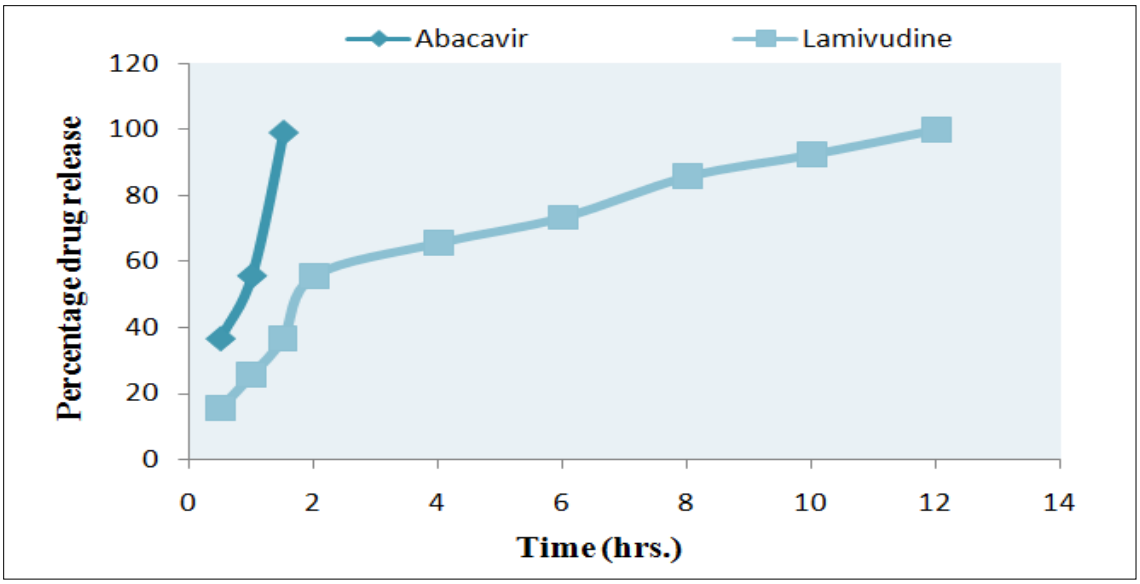

Figure 1: Graph of Release of Bilayer tablets

CONCLUSION:

The Experiment relates to formulation and development of oral pharmaceutical bilayer tablet of abacavir and lamivudine for administration of therapeutically and prophylactically effective amount of drug substance to obtain both a relatively fast or quick onset of therapeutic effect and mainatainence of a therapeutically active plasma concentration for relatively long period of time. Experiment conclude that Bi-layer tablet is suitable for delivering drugs with different release pattern like one layer of drug as immediate release to get quick relief and second drug as extended release of drug which gives effect of drug for sufficient long time and reduce frequency of dose. The results of current study clearly show that bilayer tablet was developed as a stable dosage form. Abacavir and lamivudine bilayer tablet has a promising potential as an alternative to the conventional dosage form. This new dosage form has commercial marketing potency as no such delivery systems are presently available in market.

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