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FORMULATION AND DEVELOPMENT OF NOVEL AND STABLE DOSAGE FORMS OF LAMIVUDINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS BY WET GRANULATION TECHNIQUE

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ABSTRACT: Antiretroviral drugs are medications used for treatment of infection caused by retroviruses, primarily HIV. Different classes of antiretroviral drugs act at different stages of the HIV life cycle. No individual antiretroviral drug has been demonstrated to suppress an HIV infection for prolong treatment. Antiretroviral drugs must be taken in combinations in order to have a lasting effect. Combination of several (typically two or three or four) antiretroviral drugs were known to be defined as Highly Active Anti-Retroviral Therapy (HAART). These combinations create 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 arises, the other drugs continue to suppress reproduction of that mutation. In our Present study we aimed to develop a Stable Pharmaceutical dosage form with two different anti-retroviral drugs Lamivudine and Tenofovir Disoproxil Fumarate. Lamivudine and Tenofovir Disoproxil Fumarate were classified as High soluble and low permeable (BCS class 3) As per BCS classification system.

INTRODUCTION: The human immunodeficiency virus (HIV) is the causative agent of acquired immunodeficiency syndrome (AIDS). This disease is characterized by the destruction of immune system, particularly of the CD4 and T-cell making the host susceptible to opportunistic infections.

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HIV is also associated with a precursor AIDS-related complex (ARC), a syndrome characterized by symptoms such as persistent generalized lymphadenopathy, fever and weight loss [1].

One substantial and persistent problem in the treatment of AIDS was the ability of the HIV virus to develop resistance to the individual therapeutic agents employed to treat the disease. Thus, a need remains for an efficacious and long lasting therapy for AIDS which lowers HIV viral levels of patients to undetectable levels and raises CD4 cell counts for prolonged periods of time without the development of resistance.

Hence, there was a need to develop combination of drugs to treat AIDS called as fixed dose combinations (FDC). These treatments can effectively suppress viral production when used in combinations known as HAART (Highly Active Anti-Retroviral Therapy) [4]. Antiretroviral combination therapy defends against resistance by suppressing HIV replication as much as possible, thus reducing the potential pool of spontaneous resistance mutations.

Combinations of antiretrovirals create 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 arises, the other drugs continue to suppress reproduction of that mutation. With rare exceptions, no individual antiretroviral drug has been demonstrated to suppress an HIV infection for prolong treatment. Antiretroviral drugs must be taken in combinations in order to have a lasting effect. As a result, the standard of care was to use combinations of antiretroviral drugs. Combinations usually consist of two or three drugs from at least two different classes.

Advantages and Disadvantages of Combinations Drugs: The various advantages of FDCs when compared to the separate ARV regimens are ease of use, better adherences to the dosage schedules, reduced risk of drug resistance and increased affordability. Combination therapy reduces the daily dosages to be taken by patients and simplifies dosing schedule thereby increases patient compliance [2].

Incompatibility issues with respect to combination of Lamivudine and Tenofovir Disoproxil Fumarate can be overcome by selecting bi-layered tablet dose technology. Lamivudine and Tenofovir Disoproxil Fumarate when intimately mixed together to form a single layered tablet showed undesirable properties in stability testing. The appearance of tablets changed to brown colorat accelerated temperature (40 ºC) and controlled room temperature (25 ºC). In order to avoid the discoloration, Lamivudine and Tenofovir Disoproxil Fumarate granulated separately and can be compressed as a bi-layered tablet [3]. The major objective of this study was to develop a stable composition of Lamivudine and Tenofovir Disoproxil Fumarate tablets as a single layered tablet, which was found to be stable in its content and appearance. Hence the combination of tow drugs into a single dose was aimed to take advantages such as dosage schedules, reduced risk of drug resistance and increased affordability.

MATERIALS AND METHODS: Lamivudine and Tenofovir Disoproxil Fumarate (Aurobindo Pharma Limited), Croscarmellose Sodium (FMC biopolymers) and Microcrystalline cellulose (FMC bio polymers), Hypromellose (colorcon) and Magnesium Stearate (FACI asia / Barrington), Colloidal silicon dioxide (Evonik).

Lamivudine and Tenofovir Disoproxil Fumarate Tablets were prepared as a single layer tablet by using wet granulation technique. In the present study, Lamivudine and Tenofovir Disoproxil Tablets were prepared using different approaches and finally were studied for physical appearance and active contents in stability. Lamivudine, Tenofovir Disoproxil Fumarate granules were prepared from wet granulation separately and variation in blending and lubrication was aimed to overcome the incompatibility issues during stability.

Couples of trial batches were executed and were studied for physical and chemical parameters in stability. Trial-1 includes, Lamivudine and Tenofovir granules were prepared separately and together blended with extra granular, lubricated and materials then compressed to tablets. Trial-2 includes Lamivudine and Tenofovir granules were prepared separately, first Tenofovir granules were lubricated with magnesium stearate, then blended with Lamivudine granules and extra granular, finally the combined blend lubricated with magnesium stearate and then compressed to tablets.

Manufacturing Process: The trial batches were aimed for 1000 tablets batch size. The manufacturing process for both trials is similar up to the preparation of dried granules (Lamivudine and Tenofovir). Lamivudine was sifted and blended with microcrystalline cellulose and croscarmellose sodium, and was granulated using binder solution which was prepared by dissolving hypromellose in water and then the wet mass was dried and screened. Tenofovir Disoproxil Fumarate was

sifted and blended with microcrystalline cellulose and croscarmellose sodium, and was granulated using binder solution which was prepared by dissolving hypromellose in water, and then the wet mass was dried and screened. The Lamivudine granules and Tenofovir Disoproxil Fumarate granules were blended together along with extra granular in microcrystalline cellulose and croscarmellose sodium and then lubricated with magnesium stearate (Tiral - 1).

The manufacturing process for Trial - 2 was similar to Trial - 1 up to preparation of lamivudine and Tenofovir dried granules. For blending step, first, the Tenofovir granules were lubricated with Magnesium stearate and then blended with Lamivudine granules and extra granular materials together. The resultant mixture finally lubricated with magnesium stearate. Both trials (1 and 2) were compressed into tablets and were coated using Opadry II blue.

TABLE 1: COMPOSITION OF LAMIVUDINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS [5, 6]

S. no.	Ingredient	Trial-1 Quantity/ tablet in mg	Trial-2 Quantity/ tablet in mg
	Granulation Part 1 (Lamivudine)		
1	Lamivudine, USP	300.00	300.00
2	Microcrystalline cellulose, NF	119.75	119.75
3	Croscarmellose Sodium, NF	40.00	40.00
4	Hypromellose, NF	9.00	9.00
5	Purified water, USP	Sufficient quantity	Sufficient quantity
	Granulation 2 (Tenofovir Disoproxil Fumarate part)		
6	Tenofovir Disoproxil Fumarate, USP	300.00	300.00
7	Microcrystalline cellulose, NF	135.25	120.25
8	Croscarmellose Sodium, NF	40.00	40.00
9	Hypromellose, NF	12.00	12.00
10	Purified water	Sufficient quantity	Sufficient quantity
	Lubrication for Tenofovir Disoproxil Fumarate part		
11	Magnesium Stearate, NF	0.00	15.0
	Extra granular part (Blending)		
12.	Colloidal silicon dioxide, NF	10.00	10.00
13	Croscarmellose sodium, NF	50.00	50.00
14	Magnesium Stearate, NF	20.00	20.00
	Core Total weight	1035.00	1035.00
15	Opadry-II Blue	34.50	34.50
	Coated Tablet weight	1069.5	1069.5

RESULTS AND DISCUSSION: Trail 1 and Trial 2 were studied for physical description (Core tablets and coated tablets) where the tablets were dissolution and Assay exposed to stability at Room Temperature and Accelerated condition.

Dissolution: As per the office of generic drugs guidance, the official media for dissolution was 0.1N HCl using USP Apparatus II with 900 ml at 75 rpm speed.

TABLE 2: PHYSICAL DESCRIPTION [3]

Product: Lamivudine and Tenofovir Disoproxil Fumarate Tablets, 300 mg / 300 mg						
Batch Number		**Trial-1**			**Trial-2**	
Condition Parameters	**Initial**	**25 °C/60% RH 1M***	**40 °C/75% RH 1M**	**Initial**	**25 °C/60% RH 1M & 3M**	**40 °C/75% RH 1M & 3M**
Appearance (Core)	White colored	No change in color	Brown colored	White colored	No change in color	No change in color
Appearance (Coated)	Blue colored	No change in color	No change in color	Blue colored	No change in color	No change in color

*****M: Month

In our study, Lamivudine and Tenofovir Disoproxil Fumarate were tried to formulate in two different variations as, Trial-1 includes lamivudine and Tenofovir granules blended together to compress for tablets. Due to its intimate contact, the tablet tends to change in color and failed for description during accelerated stability. The assay and dissolution profiles of Tenofovir for the Trial-1 are degraded in stability when compared with initial results.

Whereas the Trial-2 includes an additional step to lubricate the Tenofovir granules and then together blended with Lamivudine granules to compress for Tablets. The lubrication of Tenofovir granules has given a hydrophobic nature, which has prevented to undergo degradation when it was together blended with Lamivudine granules. Hence the assay and dissolution profiles for the Trial-2 were stable up to 3 Months in accelerated stability condition.

TABLE 3: DISSOLUTION PROFILES OF LAMIVUDINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS OF TRIAL-1 (MEDIA: 0.1N HCl, USING USP APPARATUS II WITH 900 ml AT 75 rpm (AVERAGE OF 6 UNITS), INITIAL AND ONE MONTH (RT AND ACCELERATED STABILITY) [7]

Time points in minutes	% Drug dissolved					
	Initial		25 °C/60% RH-1M		40 °C/75% RH-1M	
	Lamivudine	Tenofovir	Lamivudine	Tenofovir	Lamuvidine	Tenofovir
5	52	46	50	44	52	46
10	95	90	94	88	94	55
15	100	96	99	95	95	65
20	100	96	100	95	96	67
30	100	95	100	95	97	68
45	100	95	100	95	99	69

TABLE 4: DISSOLUTION PROFILES OF LAMIVUDINE AND TENOFOVIR DISOPROXIL FUMARATE TABLETS OF TRIAL-2 (MEDIA: 0.1N HCl, USING USP APPARATUS IIWITH 900 ml AT 75 rpm (AVERAGE OF 6 UNITS), INITIAL AND THREE MONTH (RT AND ACCELERATED STABILITY) [7]

Time points in min	% Drug dissolved					
	Initial		25 °C/60% RH-1M		40 °C/75% RH-3M	
	Lamivudine	Tenofovir	Lamivudine	Tenofovir	Lamivudine	Tenofovir
5	52	46	52	46	52	46
10	98	90	95	89	94	86
15	103	96	99	94	96	93
20	103	96	101	95	97	95
30	103	95	102	95	99	95
45	104	95	103	95	100	95

TABLE 5: STABILITY COMPILATION OF ASSAY OF TRIAL 1 AND 2 (ACCELERATED CONDITION)

	Tablet Assay					
	Triail-1			Trail-2		
	Initial	40 °C/75% RH 1M	Initial	40 °C/75% RH		
				1M	2M	3M
Lamivudine	99.5	98.3	98.3	100.4	98.2	99.1
Tenofovir Disoproxil Fumarate	99.0	89.0	98.6	102.4	100.5	96.9

CONCLUSION: In the present study, a satisfactory attempt has been made to formulate stable novel combinations into dosage form of Lamivudine and Tenofovir Disoproxil Fumarate Tablets using wet granulation technique and was aimed to lubricate first Tenofovir granules protect from degradation, blended with Lamivudine granules and then compressed into single layered tablet. From our experimental study, it was concluded that complete release of both Lamivudine and Tenofovir Disoproxil Fumarate from the formulation was observed. The Formulation was subjected to the stability studies for three months and found that there was no drop in the Assay and dissolution values compared to the initial. Finally, a stable dosage form has been developed with combination of Lamivudine and Tenofovir Disoproxil Fumarate.

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CONFLICT OF INTEREST: Nil

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