eISSN: 2231-0541 CAS CODEN: PHARN8 An ELSEVIER Covered Journal

PHARMANEST

An International Journal of Advances in Pharmaceutical Sciences

Volume 4 | Issue 6 | November-December 2013 | Pages 1361-1382

Original Research Article

FORMULATION AND EVALUATION OF EFAVIRENZ TABLETS DEVELOPED BY MOISTURE ACTIVATED DRY GRANULATION

P.NITHIN*

Scient institute of Pharmacy, Department of Pharmaceutics, Ibrahimpatnam, Hyderabad- 501506, Andhra Pradesh- India

Author for Correspondence: nithinpallepati@gmail.com

Received: 03-09-2013 Revised: 11-09-2013

Accepted: 17-10-2013 Available online: 01-11-2013

ABSTRACT

The aim of present work is to formulate and evaluate efavirenz tablets. Efavirenz tablets were prepared by using Moisture Activated Dry Granulation. Efavirenz is a non-nucleoside reverse transcriptase inhibitor (NNRTI) used to treat HIV-1 infection and AIDS. As with other anti-retroviral drugs, HIV rapidly develops resistance if efavirenz is used alone. So recommended therapy consists of combinations of three or more anti-retroviral. Objective is to monitor the manufacturing process of efavirenz tablets to facilitate the formulation, evaluation, optimization and confirmation of the critical product / process parameter identified during the developmental stage of the formulation so that the final product at pilot scale / test batch will produce consistent results.

Key words: Efavirenz, NNRTI, Formulation, Evaluation, MADG.

INTRODUCTION

Use of efavirenz can produce a false positive result for HIV infection that has not previously been treated, The United States Department of Health and Human Services Panel on Anti-retroviral Guidelines currently recommends the use of efavirenz in combination with lamuvidine /zidovudin (Combivir) or tenofovir /emtricitabin as the preferred NNRTI-based regimens in adults and adolescents. Efavirenz is also used in combination with other antiretroviral agents as part of an expanded post exposure prophylaxis regimen to reduce the risk of HIV infection in people exposed to a significant risk (e.g. needle stick injuries, certain types of unprotected sex etc.).

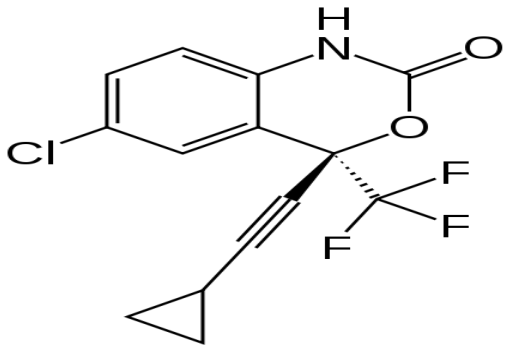
The usual adult dose is 600 mg once a day. It is usually taken on an empty stomach at bedtime to reduce neurological and psychiatric adverse effects. Efavirenz was combined with the popular HIV medication truvada, which consists of tenofovir and emtricitabin, all of which are reverse transcriptase inhibitor. This combination of three medications approved by the U.S Food & Drug Administration (FDA) in July 2006 under the brand name Atripla, provides HAART in a single tablet taken once a day. It results in a simplified drug regimen for many patients.

Drug Details

Molecular weight :315.675

Brand name : sustiva

Molecular structure:



Adverse Effects:

- Psychiatric symptoms, including insomnia, confusion in some urine test for marijuana.
- Memory loss and depression are common, and more serious symptoms such as psychosis may occur in patients with compromised liver or kidney function.
- Rash, nausea, dizziness and headache may occur.

- Efavirenz can cause birth defects and should not be used in women who are pregnant.

MATERIALS AND METHODS

Materials

Efavirenz is obtained from Aurobindopharma limited, Microcrystalline cellulose from FMC biopolymer, Croscarmellose sodium and Lactose monohydrate from DMV international, Hydroxypropyl cellulose from Gls polymers pvt ltd, Magnesium stearate from Pentagon Laboratories, Purified water from Aurobindopharma limited. Equipments required are Vibro sifter, Multimill, Rapid mixer granulator (25 lts), Fluidizes bed drier (20 kgs), Octagonal blender, Compression machine, Digital balance, Sieves, Friabilator, Hardness tester, Digimaticvernier calipers, Disintegration tester, Digital Tablet dissolution apparatus.

Methods

As the name implies, this is a process where moisture is used to activate the granule formulation, but the granules are not heat dried.

The MADG Process:

The Moisture Activated Dry Granulation involves two major stages:

1. Agglomeration
2. Moisture distribution and Absorption Stage

Success depends on the selection and order in which the formulation ingredients are added, as well as how the process is carried out.

1. Agglomeration:

- In this stage, all or part of the drug is mixed with filler(s) and an agglomerating binder to obtain a uniform mixture.
- During mixing, a small amount of water (1–4%) is sprayed onto the powder blend, water droplets hydrate the dry binder and create tacky nuclei or tacky wet mass.
- The binder functions as the drug and excipients move in the circular motion caused by the mixer impellers or blades.
- Dry powder particles adhere to the wet nuclei or wet tacky mass to

create moist agglomerates.

- The resulting agglomerates are small and spherical because the amount of water used in the MADG process is much lower than that in conventional wet granulation.
- The agglomerates therefore cannot grow into large, wet lumps. The particle size of the agglomerates generally is in the range of 150–500 μm.
- It is possible, based on the drug loading technique, to add only part of the drug to the formulation during the agglomeration stage.
- The remaining drug can be added after the moist agglomerates have been formed. The added drug particles adhere to the wet agglomerates and become incorporated into them.
- The process does not create large granules, which would need milling, and because very little water is used in the process, the endpoint is not sensitive to blending.

2. Moisture Absorption and Distribution Stage:

- In this stage, moisture absorbents such as microcrystalline cellulose or silicon dioxide are added as mixing continues.
- When these agents come into contact with the moist agglomerates, they pick up moisture from the agglomerates and redistribute moisture within the mixture.
- The entire mixture thus becomes relatively dry. Although some of the moisture is removed from the wet agglomerates, some of these agglomerates remain almost intact, and some, usually the larger particles, may break up.
- This process results in a granulation with uniform particle-size distribution.
- The process continues with the addition of a disintegrant to the mixture, followed by blending for a few minutes.
- Then, during mixing, lubricant is added and blended for sufficient time to achieve adequate lubricity.
- This step completes the MADG granulation process.
- Excluding material loading, the actual processing time for the MADG process is only 10–20 min. Even for a commercial scale batch, the

processing time is essentially the same as it would be for a laboratory or pilot-scale batch.

- Beginning with the premixing of the drug and excipients, the final granulation could be ready for tablet compression, encapsulation, or powder filling in about an hour.

TRAILS

Trail -1

Sifting:

Sieve efavirenz, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate separately through #20 mesh. Hydroxypropyl cellulose sifted through #30, sodium lauryl sulfate through #60.

Dry mixing:

Sifted materials are loaded to rapid mixer granulator and dry mixing was carried out up to 15 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate after 5, 10, 15 minutes of mixing intervals and submitted for analysis.

Granulation:

I. Agglomeration: The granulating fluid was sprayed over a period of 1 minute with impeller at slow speed.

II.Rapid Adsorption: Kneading was done with impeller and chopper at slow speed for 30 seconds, followed by impeller and chopper at fast speed for 30 seconds.

Extra granular materials sifting: Sieve remaining microcrystalline cellulose, croscarmellose sodium, and lactose monohydrate separately through #20 mesh. Magnesium stearate was sifted through #60 mesh.

Rapid adsorption:

This step is unique for MADG, extra granular material except magnesium stearate are mixed for adsorption and equal distribution of granulating fluid with impeller at slow speed for 2 minutes. 6 point unit dose samples collected in duplicate after 2 minutes.

Blending (Lubrication):

Load magnesium stearate along with granules into octagonal blender and blend for 3min, 5 min and 7 min.

Compression:

Compression of efavirenz tablets as per the following specifications.

Table.1.Tablet Compression Parameters

Description	White, oval, biconvex tablets debossed with a D on one side and 37on other side break line on both side
Tooling	19.20 X 9.30mm
Embossing	Break line between D on one side and 37 on other side break line on the both sides
Average mass	1200 ± 2 % (1176.00 – 1236.00 mg)
Hardness	18-29 kp
Thickness	7.60 ± 0.3 mm
Disintegration time	NMT 15 minutes
Friability	NMT 1 % w/w
Uniformity of mass	± 5 % of average weight

Observation:

- Sticking observed during compression on the upper punch.
- Dry mixing optimum time found out to be 10 minutes.
- Lubrication time is optimised to 3 minutes.

Further batches have been planned to reduce the sticking problem and to improve the flow.

Trail -2

Sifting:

Sieve efavirenz, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate separately through #20 mesh. Hydroxypropyl cellulose sifted through #30, sodium lauryl sulfate through #60.

Dry mixing: Sifted materials are loaded to rapid mixer granulator and dry mixing was carried for 10 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate and submitted for analysis.

Granulation:

I. Agglomeration: The granulating fluid was sprayed over a period of 2 minutes with impeller at slow speed.

II.Rapid Adsorption: Kneading was done with impeller and chopper at slow speed for 1 minute, followed by impeller and chopper at fast speed for 30 seconds.

Extra granular materials sifting:

Sieve remaining microcrystalline cellulose, croscarmellose sodium, and lactose monohydrate separately

through #20 mesh. Magnesium stearate was sifted through #60 mesh.

Rapid adsorption:

This step is unique for MADG, extra granular material except magnesium stearate are mixed for adsorption and equal distribution of granulating fluid with impeller at slow speed for 3 minutes. 6 point unit dose samples collected in duplicate after 3 minutes.

Blending (Lubrication):

Load magnesium stearate along with granules into octagonal blender and blend for 3min.

Compression:

Compression of efavirenz tablets are maintained same.

Observation:

- Increase in kneading time and rapid adsorption time solved the sticking problem.
- Rapid adsorption time optimised to 3 minutes.
- The flow problem was solved by more fluid uptake.
- No sticking problem observed during compression.

Dissolution observed to be in the lower limit. So, further batch planned to overcome the problem.

Trail- 3

Sifting:

Sieve efavirenz, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate separately through #40 mesh. Hydroxypropyl cellulose sifted through #30, sodium lauryl sulfate through #60.

Dry mixing:

Sifted materials are loaded to rapid mixer granulator and dry mixing was carried for 10 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate and submitted for analysis.

Granulation:

I. Agglomeration: The granulating fluid was sprayed over a period of 2 minutes with impeller at slow speed.

II.Rapid Adsorption: Kneading was done with impeller and chopper at slow speed for 1 minute, followed by impeller and chopper at fast speed for 30 seconds.

Extra granular materials sifting:

Sieve remaining microcrystalline cellulose, croscarmellose sodium, and lactose monohydrate separately through #20 mesh. Magnesium stearate was sifted through #60 mesh.

Rapid adsorption:

This step is unique for MADG, extra granular material except magnesium stearate are mixed for adsorption and equal distribution of granulating fluid with impeller at slow speed for 3 minutes. 6 point unit dose samples collected in duplicate after 3 minutes.

Blending (Lubrication):

Load magnesium stearate along with granules into octagonal blender and blend for 3min.

Compression:

Compression of efavirenz tablets are maintained same.

Observation: Dissolution is found to be normal by changing the mesh size.

Further trials are done to optimize the turret speed of the tablet compression machine.

Trail- 4

Sifting:

Sieve efavirenz, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate separately through #40 mesh. Hydroxypropyl cellulose sifted through #30, sodium lauryl sulfate through #60.

Dry mixing:

Sifted materials are loaded to rapid mixer granulator and dry mixing was carried for 10 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate and submitted for analysis.

Granulation:

I. Agglomeration: The granulating fluid was sprayed over a period of 2 minutes with impeller at slow speed.

II.Rapid Adsorption: Kneading was done with impeller and chopper at slow speed for 1 minute, followed by impeller and chopper at fast speed for 30 seconds.

Extra granular materials sifting: Sieve remaining microcrystalline cellulose, croscarmellose sodium, and lactose monohydrate separately through #20 mesh. Magnesium stearate was sifted through #60 mesh.

Rapid adsorption: This step is unique for MADG, extra granular material except magnesium stearate are mixed for adsorption and equal distribution of granulating fluid with impeller at slow speed for 3 minutes.

Blending (Lubrication):

Load magnesium stearate along with granules into octagonal blender and blend for 3min.

Compression:

Compression of efavirenz tablets are maintained same.

Compression is carried out at 20, 25 and 30 rpm turret speed.

OBSERVATION:

- All the physical and compression parameters found to be satisfactory.
- Compression at 20-25 rpm observed to be satisfactory.

Trail- 5

Sifting:

Sieve efavirenz, microcrystalline cellulose, croscarmellose sodium, lactose monohydrate separately through #40 mesh. Hydroxypropyl cellulose sifted through #30, sodium lauryl sulfate through #60.

Dry mixing:

Sifted materials are loaded to rapid mixer granulator and dry mixing was carried for 10 minutes with impeller at slow speed, 6 point unit dose samples collected in duplicate and submitted for analysis.

Granulation:

I. Agglomeration: The granulating fluid was sprayed over a period of 2 minutes with impeller at slow speed.

II.Rapid Adsorption: Kneading was done with impeller and chopper at slow speed for 1 minute, followed by impeller and chopper at fast speed for 30 seconds.

Extra granular materials sifting:

Sieve remaining microcrystalline cellulose, croscarmellose sodium, and lactose monohydrate separately through #20 mesh. Magnesium stearate was sifted through #60 mesh.

Rapid adsorption: This step is unique for MADG, extra granular material except magnesium stearate are mixed for adsorption and equal distribution of granulating fluid with impeller at slow speed for 3 minutes. 6 point unit dose samples collected in duplicate after 3 minutes.

Blending (Lubrication):

Load magnesium stearate along with granules into octagonal blender and blend for 3min.

Compression: Compression of efavirenz tablets are maintained same. Compression is carried out at 20-25 rpm turret speed.

Pre-Compression Characteristics

1) Organoleptic Properties: The color, odor and taste of the drug were recorded using descriptive terminology.

2) Bulk Density: Bulk density of a compound various substantially with the method of crystallization, milling or formulation. Bulk density is determined by pouring pre-sieved granules into a graduated cylinder via a large funnel and measure the volume and weight.

Bulk density = weight of granules/ Bulk volume of granules

3) Tapped Density: Tapped density is determined by placing a graduated

cylinder containing a known mass of granules and mechanical tapper apparatus, which is operated for a fixed number of taps until the powder bed volume has reached a minimum volume. Using the weight of the drug in the cylinder and this minimum volume, the taped density may be computed.

Tapped density =weight of granules/ Tapped volume of granules

4) Compressibility Index and Hausner Ratio: The compressibility index and Hausner ratio may be calculated using measured values of bulk density and tapped density as follows:

Compressibility index = 100 × tapped density / bulk density

Hausner ratio = tapped density / bulk density

5) Particle Size Analysis:

Particle size: Particle size is a notion introduced for comparing dimensions of solid particles (flecks), liquid particles (droplets), or gaseous particles (bubbles).

Methods for particle size analysis: Microscopy,Sieving,Sedimentation.

6) Solubility: Solubility is the property of a solid, liquid, or gaseous chemical substance called solute to dissolve in a solid, liquid, or gaseous solvent to form a homogeneous solution of the solute in the solvent. The solubility of a substance fundamentally depends on the physical and chemical properties of the solute and solvent as well as on temperature, pressure and the pH of the solution.

7) Flow Ability: Capability of a liquid or loose particulate solid to move by flow.

8) Moisture Content (Or) Water By Kf: Take around 50ml of methanol in titration vessel of Karl Fischer titrator and titrate with Karl Fischer reagent to end point. In a dry mortar grind the pellets to fine powder .Weigh accurately about 0.5 g of the sample, transfer quickly to the titration vessel, stir to dissolve and titrate with Karl Fischer reagent to end point.

Moisture content =V X F X 100/ Weight of Sample in mg

9)Assay: Assay is an indicative of the amount of the drug present in the dosage form. Ten tablets were weighed and powdered. The equivalent 600mg of efavirenz was weighed and transferred into a 250 ml volumetric flask with 1.5% SLS in distilled water. The solutions were filtered, suitably diluted and analyzed at 247 nm in a UV Spectro photometer.

10) Angle of Repose: Angle of repose is used to determine the flow properties

of powders, pellets or granules. The method to find angle of repose is to pour the powder on a conical heap on a level, flat surface and measure the included angle with the horizontal.

$$\mathbf{Tan\ \theta = h/r}$$

Post-Compression Characteristics

1) Drug Content: Three tablets were crushed and quantity equivalent to 45mg will be taken and determined using 0.1M Hcl with UV spectrophotometer.

2) Weight Variation: The USP weight variation test will be run by weighing 20 tablets individually, calculating the average weight, and comparing the individual tablet weights to the average. The tablets met the USP tests that were not more than 2 tablets were outside the percentage limit and no tablets differed by more than 2 times the percentage limit.

3) Hardness: Hardness of the tablets will be determined by breaking it between the second and third fingers with thumb being as a fulcrum. There will be a sharp snap the tablet will be deemed to have acceptable strength. Hardness of the tablets will be determined by Stokes Monsanto Hardness Tester and the hardness should be found within the range of 3.5-5.5 kg/cm^2.

4) Friability: The friability of tablets will be determined by Roche Friabilator. 20 tablets were taken and weighed. After weighing the tablets were placed in the Roche Friabilator and subjected to the combined effects of abrasion and shock by utilizing a plastic chamber that revolves at 25 RPM for minutes dropping the from a distance of six inches with each revolution. After operation the tablets were de-dusted and reweighed.

$$\mathbf{F=100(1-Wo/Wt)}$$

5) Content Uniformity: In this test, 30 tablets were randomly selected contained for sample, and 10 the tablets Efavirenz should contain not less than 85.0 % and not more than 115.0 % of the label claim. If one unit outside the range of 85 to 115% of the label claim and no units is outside 75 to 125% or if RSD> 6% or if both conditions prevail, test 20 additional units.

6) Thickness: The thickness of a tablet will be the only dimensional variable related to the process. 10 tablets were measured for their thickness and diameter with a Caliper, Thickness

Gauge. Average thickness and diameter were calculated.

7) Disintegration Test: Disintegration time is considered to be one of the important criteria in selecting the best formulation. For most tablets the first important step toward solution is break down of tablet into smaller particles or granules, a process known as disintegration.Place one tablet into each tube and suspend the assembly in to the 1000ml beaker containing water maintained at 37 ± 2°C and operate the apparatus for 30 seconds. Remove the assembly form the liquid. Observe the tablets, if one or two tablets fail to disintegrate completely; repeat the test on 12 additional tablets. The requirement is met if not less than 16 of the total of 18 tablets tested are disintegrated.

8) Dissolution by UV spectroscopy: Dissolution means the process by which solid substance enters in the solvent to yield a solution. It is controlled by the affinity between the solid substance and the solvent. It is a process in which a solid substance solubilizes in a given solvent that is mass transfer from the solid surface to the liquid phase.

Types of dissolution apparatus:

Different types of dissolution apparatus are used. They are:

i) Apparatus 1 or rotating basket type
ii) Apparatus 2 or paddle assembly type
iii) Apparatus 3 or reciprocating cylinder type
iv) Apparatus 4 or flow through cell type
v) Apparatus 5 or paddle over disk type
vi) Apparatus 6 or cylinder type
vii) Apparatus 7 or reciprocating holder type.

RESULTS

Pre-Compression Characteristics

Table.2. Preformulation Studies of Tablets for Different Tests

S.No	Test	Test results
1	Description	white granules
2	Bulk density	0.5gm/ml
3	Tapped density	0.68gm/ml
4	Compressibility index	26.40%
5	Particle size analysis	Cumulative %
	#20	1
	#30	3
	#40	8
	#60	15
	#80	18
	#100	22
	#120	25
	#140	31
	Plate	100
6	Solubility Analysis	Freely soluble in methanol and practically insoluble in water
7	Flow ability	29
8	LOD at 105˚c (on moisture balance)	3.85%
9	Assay	100.20%

Post-Compression Characteristics

PHYSICAL PROPERTIES OF GRANULES

Table.3.Physical Properties of Granules for Different Trail Batches

Trail	Loss on drying (% w/w)	Bulk density (g/ml)	Tapped density (g/ml)	Carr's index	Hausner's ratio
1	1.45	0.489	0.683	28.358	1.396
2	1.25	0.563	0.722	22.022	1.282
3	1.39	0.569	0.727	21.733	1.277
4	1.32	0.566	0.725	21.931	1.280
5	1.35	0.565	0.724	21.918	1.281

PARTICLE SIZE DISTRIBUTION

Table.4.Particle Size Distribution for Different Trail Batches

Trail	% cumulative retainsMesh (ASTM)							
	20	30	40	60	80	100	120	200
1	8.40	13.80	23.80	39.80	54.20	66.00	90.60	99.40
2	7.28	14.32	28.06	37.82	53.07	67.59	90.95	98.62
3	9.36	16.28	27.37	39.41	54.14	72.19	90.11	99.00
4	7.73	16.66	27.81	36.34	56.93	73.28	91.91	98.83
5	8.28	16.69	27.78	36.67	54.36	72.25	91.84	98.71

BLEND UNIFORMITY

STAGE: Dry Mixing

Table.5.Dry Mixing Optimization for Different Trail Batches

Location	Trail 1 (Percentage label claim)			Trail 5
	5 minutes	10 minutes	15 minutes	10 minutes
1	100.7	101.0	102.1	97.6
2	102.8	101.5	101.5	98.1
3	102.7	101.5	100.7	98.7
4	100.7	102.0	101.0	98.7
5	101.2	101.4	102.8	97.9
6	101.8	100.8	100.9	98.5
Average	101.7	101.4	101.5	98.3
Minimum	100.7	100.8	100.7	97.6
Maximum	102.8	102.0	102.8	98.7
R.S.D	0.94	0.42	0.81	0.45

STAGE: Pre-Lubrication

Table.6.Rapid Adsorption Optimization for Different Trail Batches

Location	Trail 1 (Percentage label claim)			Trail 5
	2 minutes	3 minutes	5 minutes	3 minutes
1	99.5	100.6	99.1	98.5
2	98.6	101.2	99.2	99.7
3	101.1	100.2	99.3	99.9
4	99.9	99.5	99.6	100.1
5	99.1	100.3	99.8	99.9
6	101.2	99.7	99.7	99.8
Average	100.2	100.14	99.57	99.88
Minimum	98.6	99.5	99.1	97.9
Maximum	101.2	101.2	100	100.7
R.S.D	0.86	0.54	0.32	0.59

STAGE: Lubrication

Table.7.Lubrication Optimization for Different Trail Batches

Location	Trail 1 (Percentage label claim)			Trail 5
	3 minutes	5 minutes	7 minutes	3 minutes
1	97.7	105	108	99.5
2	99.3	101.2	105	100.8
3	100.1	103	103	99.8
4	99.7	93	93	100.3
5	100.9	102.2	102.2	98.1
6	100.7	95	95	100.4
7	97.1	104.4	104.4	97.9
8	100.4	100.4	100.4	101.4
9	97.4	103.1	103.1	99.3
10	99.3	93	103	100.8
Average	99.3	100.3	101.71	99.83
Minimum	97.1	93	93	97.9
Maximum	100.9	104.4	108	101.4
R.S.D	1.39	4.62	4.54	1.15

COMPRESSION PARAMETERS

Table.8.Tablet Compression Parameters at Different Turret Speeds

Trail	Averageweight (mg)		Uniformity of weight (mg)		Thickness (mm)	Hardness (kp)		Disintegration Time (min)			Friability (% w/w)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Limits	(1174 -1236.00 mg)		± 5 % of average weight		(7.30 – 7.90 mm)	(18.0 – 29.0 kp)		NMT 15 minutes			NMT 1.0	
4 (20 rpm)	1185	1212.3	1196.5	1209.6	6.92	7.01	19.5	23.5	5'53”	7’04”	0.01	0.14
4 (25 rpm)	1192.6	1215.9	1200.8	1214.9	6.94	7.08	22.2	25.0	4'59”	6’07”	0.05	0.06
4 (30 rpm)	1179.0	1224.0	1193.9	1218.4	6.98	7.10	22.4	25.8	5'41”	6'50”	0.07	0.12
5 (20-25 rpm)	1199.0	1217.0	1201.3	1209.3	6.98	7.05	22.1	24.5	5'51”	7’04”	0.05	0.07

Table.9.Tablet Compression Parameters at Different Hardness

Different hardness	Averageweight(mg)		Uniformity of weight (mg)		Thickness (mm)		Hardness (kp)		Disintegration Time (min)		Friability (% w/w)	
	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max	Min	Max
Limits (Kp)	(1174.00 - 1236.00 mg)		± 5 % of average weight		(7.30 – 7.90 mm)		(18.0– 29.0 kp)		NMT 15 minutes		NMT 1.0	
18.0–22.0	1195	1221	1195	1221	7.70	7.79	19	20.9	5'49"	6'02"	0.26	0.31
22.0–25.0	1199	1210	1199	1210	7.60	7.67	23	25	6'56"	7'15"	0.03	0.05
25.0-29.0	1200	1205	1200	1205	7.45	7.50	25	26.8	6'32"	7'40"	0.01	0.02

Table.10.Invitro Dissolution Studies of (Trail 2)

Unit no.	Cumulative drug release					
	5 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	41.02	59.34	60.54	63.21	64.90	66.79
2	47.22	52.66	63.50	64.79	66.20	67.21
3	43.31	55.09	63.22	65.05	61.09	65.55
4	49.01	51.89	58.74	63.95	66.89	69.50
5	47.80	61.03	59.21	68.80	64.25	65.95
6	44.70	54.97	60.79	66.20	64.85	73.05
Mean	45.51	55.83	61.00	65.30	64.60	68.33
Minimum	41.02	51.89	58.74	63.21	61.09	65.55
Maximum	49.01	61.03	63.50	68.80	66.89	73.05

Table.11.Invitro Dissolution Studies of Efavirenz (Trail 3)

Unit no.	Cumulative drug release					
	5 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	61.05	80.21	88.52	96.22	98.10	98.09
2	67.95	86.79	92.48	100.01	100.95	99.05
3	62.21	80.25	84.25	91.78	92.55	93.80
4	61.79	78.75	84.75	91.99	92.45	92.20
5	64.33	80.50	85.05	92.22	92.16	93.80
6	61.71	78.50	85.95	93.78	94.84	95.03
Mean	63.17	80.83	86.83	94.33	95.17	95.32
Minimum	61.05	78.50	84.25	91.78	92.16	92.20
Maximum	67.95	86.79	92.48	100.01	100.95	99.05

Table.12.Invitro Dissolution Studies of Efavirenz (Trail 4 - Turret 20 Rpm)

Unit no.	Cumulative drug release					
	5 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	53.25	69.06	88.06	95.44	98.55	98.05
2	51.05	72.94	88.05	90.05	95.45	98.10
3	57.75	69.61	89.10	90.10	94.25	97.12
4	51.95	71.39	81.79	92.60	97.75	99.55
5	54.25	73.21	86.22	93.96	94.40	97.20
6	55.75	76.79	85.78	92.02	95.60	96.10
Mean	54.00	72.16	86.50	92.36	96.00	97.68
Minimum	51.05	69.06	81.79	90.05	94.25	96.10
Maximum	57.75	76.79	89.10	95.44	98.55	99.55

Table.13.Invitro Dissolution Studies of Efavirenz (Trail 4 - Turret 25 Rpm)

Unit no.	Cumulative drug release					
	5 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	52.05	74.09	79.05	90.06	94.05	96.21
2	55.70	72.99	82.09	92.04	97.10	97.79
3	59.10	70.06	77.12	88.10	92.12	93.21
4	52.15	70.15	79.14	90.12	96.22	97.78
5	56.77	70.16	77.55	89.52	93.51	94.94
6	54.41	72.60	80.10	90.06	96.21	99.01
Mean	55.03	71.67	79.17	89.98	94.86	96.49
Minimum	52.05	70.06	77.12	88.10	92.12	93.21
Maximum	59.10	74.09	82.09	92.04	97.10	99.01

Table.14.Invitro Dissolution Studies of Efavirenz (Trail 5)

Unit no.	Cumulative drug release					
	5 Minutes	10 Minutes	15 Minutes	30 Minutes	45 Minutes	60 Minutes
1	70.05	86.06	90.09	98.10	99.02	99.01
2	82.16	89.10	93.10	97.90	100.06	99.05
3	82.25	92.11	96.66	98.12	100.10	101.10
4	86.54	87.14	91.77	100.03	98.80	101.11
5	73.09	88.60	91.30	97.85	100.07	100.21
6	80.91	90.06	91.20	97.05	99.10	101.31
Mean	79.16	88.84	92.35	98.17	99.52	100.29
Minimum	70.05	86.06	90.09	97.05	98.80	99.01
Maximum	86.54	92.11	96.66	100.03	100.10	101.31

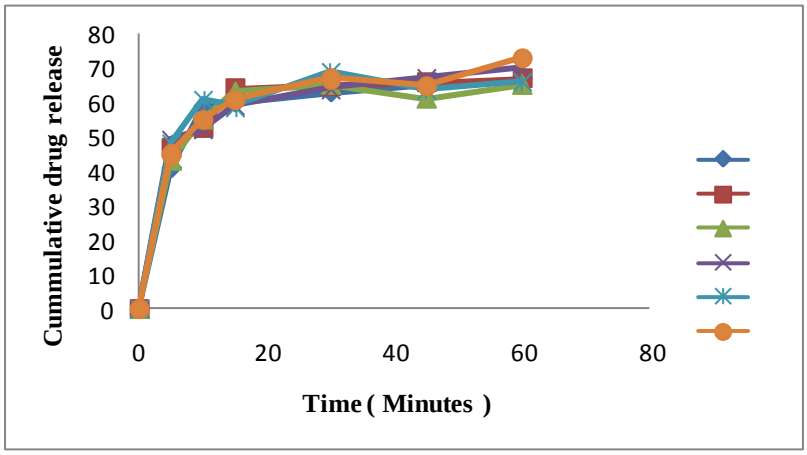


Fig.1 .Invitro Dissolution Studies of Efavirenz (Trail 2)

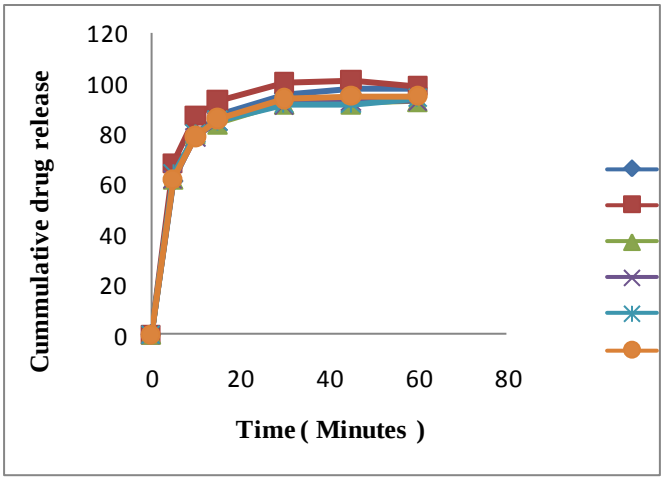


Fig.2.Invitro Dissolution Studies of Efavirenz (Trail 3)

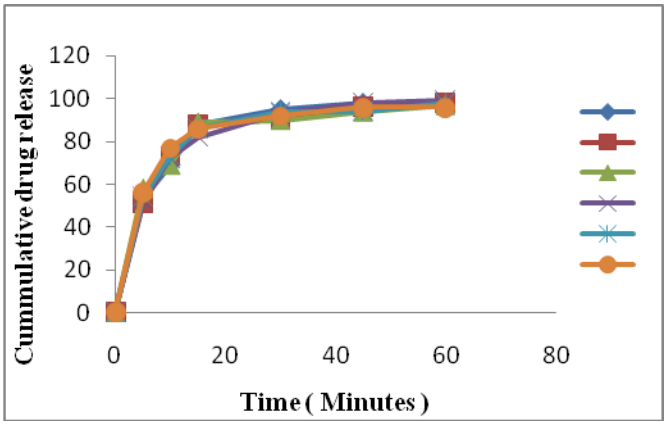


Fig.3.Invitro Dissolution Studies of Efavirenz (Trail 4 - Turret 20 Rpm)

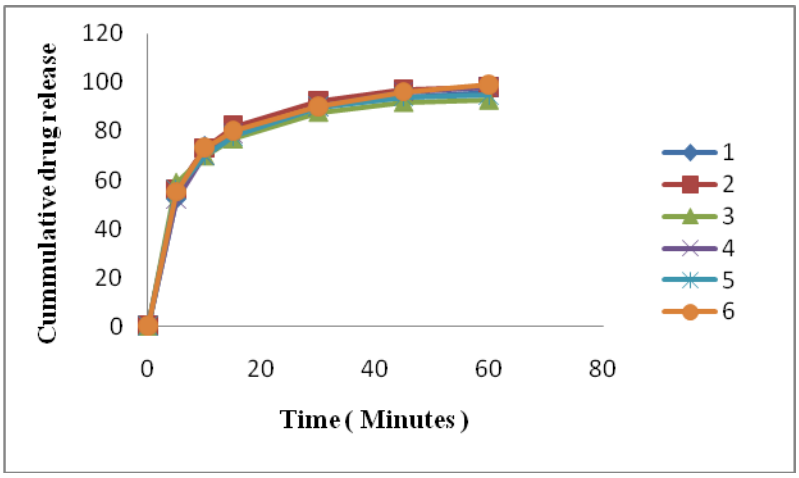


Fig.4.Invitro Dissolution Studies of Efavirenz (Trail 4 - Turret 25 Rpm)

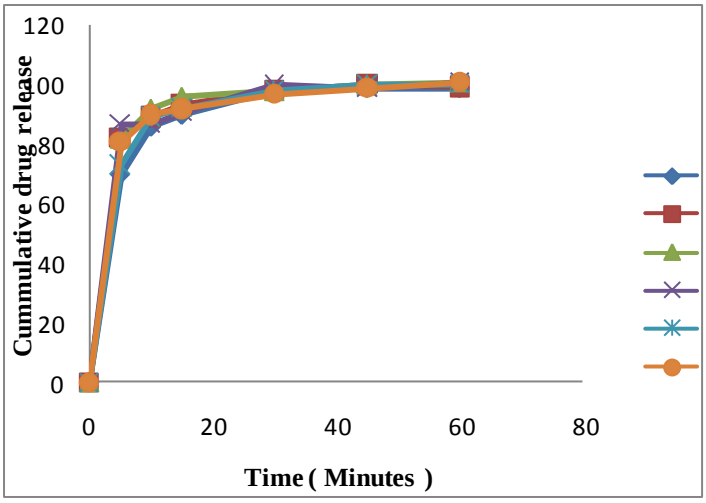


Fig.5.Invitro Dissolution Studies of Efavirenz (Trail 5)

DISCUSSION

Pre-Compression Characteristics

Pre compression tests are performed on the tablets for Bulk Density, Tapped Density, Compressibility Index, Particle Size Analysis, Solubility, Flow Ability, Moisture Content, Assay and Angle of Repose. Parameters are found to be good and recorded in the table2.

Post-Compression Characteristics

- The physical properties of granules were studied performing loss in drying, bulk density, tapped density Carr's index and Hausner's ratio which are recorded in the table 3. Trail 1 the flow properties of the powder is poor, the flow properties of the powder is found to be fair by increasing the kneading time and by increase in fluid uptake.
- Particle size distribution for all the trail batches is been performed and found to be normal. The results for the trails are represented in the table 4.
- In the table 5 the trails 1 and 5 were represented where trail 1 shows the results of various timing for optimisation and the trail 5 which shows the best dry mixing time.
- In the table 6 the trails 1 and 5 were represented where trail 1 shows the results of various timing for optimisation and the trail 5 which shows the best rapid adsorption time.
- In the table 7 the trails 1 and 5 were represented where trail 1 shows the results of various timing for optimisation and the trail 5 which shows the best lubrication time.
- The table 8 shows compression of the tablets is done at different turret speeds of 20 rpm, 25 rpm, and 30 rpm in the trail 4.When the compression is done at 30 rpm turret speed the weight variation is seen thus the turret speed of 20 – 25 rpm is set as the optimum turret speed for compression of the tablet. The trail 5 results have shown the best results.
- The table 9 shows the minimum and maximum values at different hardness for various parameters. Hardness studies were performed to check the minimum and the maximum limits of the various parameters like average weight, weight uniformity, thickness, hardness, disintegration time and friability. The hardness studies are carried out at 18-22 kp, 22-25 kp, 25 – 29 kp.

Dissolution Studies

The dissolution is found to be in the lower limit in the trail 2 since the drug release is less than 75 % in 45 minutes, to overcome that the mesh sizes are changed in the multi mill in the trail 3.Dissolution is carried out in 900 ml 2% SLS in purified water USP apparatus II, paddle with 50 rpm.The release of the drug efavirenz is more than the 75% in the trail 3, 4 and 5.Trail 5 has showed the optimum dissolution values.

CONCLUSION

After compilation of the data generated during the formulation of efavirenz tablets 600mg USP studies and results shows that the critical parameters identified at developmental stages of formulation were reproducing. However the following changes are recommended in various stages of manufacturing process for executing the Test batch / Pilot scale batches.

- Dry mixing, pre lubrication, lubrication times are to be optimised.
- Kneading time increased to overcome the sticking problem.
- Change of mesh and sieves to overcome the dissolution problem.
- Turret speed is optimised to 20 – 25 rpm.

REFERENCES

1. Herbert.A.Liberman,Leon Lachmann, Joseph B.Schwartz., Pharmaceutical dosage forms, tablets, vol I, 2nd edition, revised and expanded,New York**,** Basel : M. Dekker, c1989, 106-160.
2. Heather J. Ribaudo, Ph.D., Cecilia M. Shikuma, M.D., Triple-Nucleoside Regimens versus Efavirenz-Containing Regimens for the Initial Treatment of HIV-1 Infection, JAIDS Journal of Acquired Immune Deficiency Syndromes: 2001 Volume 28, Issue 4,399.
3. Gerber, John G MD; Rosenkranz, Susan L PhD Effect of Efavirenz on the Pharmacokinetics of Simvastatin, Atorvastatin, and Pravastatin: Results of AIDS Clinical Trials Group 5108 Study, JAIDS Journal of Acquired Immune Deficiency Syndromes: 2005 Volume 39, Issue 3,307-312.
4. Chen CM, Dhananjaya A, Michael RI, Jeffrey LC. Comparison of moisture-activated dry granulation processes with conventional granulation methods for sematilide hydrochloride tablets. Drug DevInd Pharm, 1990, 16(3):379-94. Available from: URL:http:// informahealthcare.com/doi/abs/ 10.3109/0363904900911
5. Carstensen JTEffect of moisture on the stability of solid dosage forms. Drug DevInd Pharm 1998, 14(14):1927-69.
6. Christensen LH, Johansen HE, Schaefer T. Moisture-activated dry granulation in a high shear mixer. Drug DevInd Pharm 2009, 20(14):2195-2213.
7. Aniruddha MR, Joseph BS. The effects of formulation factors on the moist granulation technique for controlled-release tablets. Drug DevInd Pharm 2001, 27(9):893-8.
8. Aniruddha MR , Joseph BS. Evaluation and comparison of a moist granulation technique to conventional methods. Drug DevInd Pharm 2000, 26(8):885-89.
9. Ullah et al., Pharm. Technol.(1987).11(9), 48–54.
10. Ullahetal.,*Pharm.* Technol. (2009).33(11), 62–70.
11. Starr, Stuart E. Efavirenz liquid formulation in human immunodeficiency virus-infected children, The new England journal of medicine, 1999 vol 40,Issue 2,418.

12. Raymond, C. Rowe., Paul, J. Sheskey., Paul, J. Weller., Handbook of pharmaceutical excipients, sixth edition. Pharmaceutical Press, Aug.62009, 134-206.
13. SiriratLikanonsakul., TippawanRattanatham., SirilukFeangvad., SumonmalUttayamakul., WisitPrasithsirikul.,"Enhancing dissolution of Efavirenz", 2009 patentsonline.com.
14. Saitoh A., Sarles E., Capparelli E., Aweeka F., Kovacs A., Burchett, S.K., Wiznia A., Nachman S., Fenton T., Spector, S.A., "CYP2B6 genetic variants are associated with efavirenzpharmacokinetics and clinical response in HIV-1-infected children", American journal of medication, 2007, vol.3, 213-221.
15. Harrigan P.R., "The derivatives of Efavirenz", The Journal of Infectious Diseases, 1998, 67-73.
16. Edmund Capparelli., D Kabamba., T Cressey., D Burger., "efavirenz Exposure with WHO Pediatric Weight Band Dosing--Enhanced Therapeutic Concentrations Predicted Based on Extensive International Pharmacokinetic Experience", British journal of medication, 2008, 65-88.
17. DenizGökengin.,TansuYamazhan., "Bioequivalent formulation of efavirenz", British journal of medication, 2002, 60-65.
18. Carl, A. Busacca., Mike Cerreta., Yong Dong., Magnus, C. Eriksson., Vittorio Farina., "Development of a Pilot-Plant Process for a efavirenz Analogue HIV NNRT Inhibitor", American Chemical Society, 2008 ,12 (4), 603–613.