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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF EFAVIRENZ USING LIQUI SOLID COMPACT TECHNIQUE

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ABSTRACT

The objective of the present investigation is to formulate Liqui-Solid tablets of Efavirenz. In the present study Efavirenz immediate release tablets were prepared by using aid of non-volatile solvents like polyethylene glycol (PEG) and propylene glycol (PG), in which the poorly soluble drug is dissolved and thereby increasing its solubility and in turn dissolution rate. The tablets were formulated using direct compression technology by employing super disintegrants like cross povidone and sodium starch glycolate. The prepared liquid-solid compact tablets were evaluated for pre compression, post compression and *in-vitro* drug release. The *in-vitro* drug release pattern of liqui-solid tablets of Efavirenz was fitted in kinetic model which showed highest regression i.e. for zero order kinetics. Among all the formulations, LS-12 which is a combination of Propylene glycol, Ratio (R) =2 and cross povidone-4% was optimized based on desired immediate release time (10mins) followed by acceptable disintegration and drug release properties.

Key words: Efavirenz, Liqui-Solid tablets, Cross povidone, Sodium starch glycolate, *in-vitro* release, disintegration time.

INTRODUCTION

Immediate release preparations are primarily intended to achieve faster onset of action for drugs such as analgesics, anti-viral, antipyretics, and coronary vasodilators. Other advantages include enhanced oral bioavailability [1] through trans-mucosal delivery and pre-gastric absorption, convenience in drug administration to dysphasic patients, especially the elderly and bedridden, and pediatric patients [2,3]. As an estimated 40% of all newly developed drugs are poorly soluble or insoluble in water. In addition, up to 50% of orally administered drug compound suffer from formulation problems related to their low solubility and high lipophilicity[4,5]. The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of new and possibly, beneficial chemical entities donot reach the public merely because of the is poor oral bioavailability due to inadequate dissolution[6, 7]. Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The technique of Liquisolid compacts'' is a new and promising addition towards such a novel aim. The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract [8,9]. Liqui-solid system is novel technique developed by Spireas *et al* [10,11,12,13,14] liquisolid systems involves conversion of liquid lipophilic drug sor water insoluble solid drugs dissolved in non-volatile solvent and this liquid medication can be converted into free-flowing, non-adherent, dry looking, and readily compressible powders with the use of carrier and coating materials.

MATERIALS AND METHOD

Materials: Efavirenz was obtained as gift sample from Dr. Reddy's laboratories (Hyderabad, India). Sodium starch glycolate and Cross povidone were supplied by Aurabindo Pharmaceuticals (Hyderabad,

India). Microcrystalline cellulose and Aerosil was supplied by S.D. Fine Chemicals Pvt (India). All other chemicals used were of analytical grade.

Pre compression parameters:

1. Angle of repose: Angle of repose is defined as the maximum angle possible between the surface of a pile of the powder and the horizontal plane. The flow characteristics are measured by angle of repose.

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

Where h = height of pile, r = radius of the base of the pile = angle of repose.

Angle of repose below 25^0 indicates an excellent powder flow.

2. Bulk density: The bulk density of a powder is the ratio of the mass of an untapped powder sample and its volume including the part of the interparticulate void volume. It is expressed as gm/ml and calculated using the equation.

$$P = W/V_b$$

Where P = bulk density. W = mass of the powder blend. V_b = bulk volume of powder blend.

3. Tapped density: Tapped density is the ratio of mass of powder to the tapped volume. It is calculated using the following equation and expressed as gm/ml.

$$P_{b,\,max} = W/V_{50}$$

Where $P_{b,\,max}$ = tapped density, W = mass of the powder blend., V_{50} = volume of powder blend at 50 taps.

4. Carr's consolidation index:

It is defined as:

$$\text{Consolidation Index} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5. Hausner's ratio: It is defined as

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

Method: Formulation of EfavirenzLiqui-solid compact tablets:

1) The Drug was initiallydispersed in the non-volatile solvent systems (PEG-400& PG) termed as liquid vehicles with different drug : vehicle ratio.
2) Then a mixture of carrier, coating and excipients were added to the above liquid by continuous mixing in a mortar. These amounts of the carrier and excipients are enough to maintain acceptable flow and compression properties.
3) To the above binary mixture disintegrants like sodium starch glycolate, cross-povidone and other reaming additives are added according to their application and mixed for a period of 10 to 20min in a mortar.
4) Then the powder blend is passed through sieve of numbers either 60 or 65 for assuming finer particles.
5) Lastly Magnesium sterate of accurately weighed quantity was added and preceded for punching.
6) The final mixture was compressed using the tableting machine (Cadmach multi station) to achieve tablet hardness.
7) Characterize the final liquisolid granules for solubility, dissolution, flowability, compressibility.

Evaluation of tablets:

Tablet hardness: The Hardness of tablets was tested using Pfizer hardness tester.

Tablet thickness: A vernier caliper was used to determine thickness of 10 randomly selected tablets. Results are expressed as mean values.

Disintegration Time: The disintegration time was determined using disintegration test apparatus at 37^0C $\pm$ 2^0C. A tablet was placed in each of the six tubes of the apparatus and one disc was added to each tube. The time taken for complete disintegration of the tablet with no palpable mass in the apparatus was noted.

Drug content uniformity: Ten tablets were individually weighed and crushed. A quantity of powder equivalent to the mass of one tablet (600 mg) was extracted in 100 mL of pH 6.8 phosphate buffer. The solution was centrifuged at 3000 rpm for 15 min. The drug content was analyzed at 246 nm using a UV/ Visible spectroscopy after suitable dilution with pH 6.8 phosphate buffer.

Tablet friability: According to the BP specifications [14], 10 tablets were randomly selected and placed in the drum of a tablet friability test apparatus. The drum was adjusted to rotate 100 times in 4 min. The tablets were removed, dedusted and accurately weighed. The percent weight loss was calculated for all formulation and was reported.

Drug release studies: Drug release studies of Efavirenz liquid-solid compact tablets were performed, in triplicate, by using USP-Dissolution Tester Apparatus, type-II (Paddle) and the temperature is maintained at 37 ± 0.5 0C. The Paddles rotated at a speed of 50 rpm. The tablets were placed into 900 mL of phosphate buffer solutions (pH 6.8). Aliquots of 5mL were withdrawn from the dissolution apparatus at predetermined time intervals. The drug content was determined spectrophotometric ally at a wavelength of 246 nm, as mentioned before. At each time of withdrawal, 5mL of fresh medium was replaced into the dissolution flask.

RESULTS AND DISCUSSION

A standard concentration of Efavirenz was prepared in 6.8 pH phosphate buffer and the absorbances were measured at 246 nm. Efavirenz is showing good linearity with a correlation coefficient of 0.999. FTIR studies of the pure drug Efavirenz and formulations showed that there was no drug excepient interaction. Liquisolid compact tablets were formulated by using disintegrants such as sodium starch glycolate and cross povidone. The Pre Compression parameters for the powder blend was carried out and the result were shown in Table no.3 the angle of repose of all the formulations was found to be in the range of 27.40^0 - 31.44^0. The Bulk and Tapped density of powder blends were from 0.532-0.559gm/ml and 0.619-0.669gm/ml respectively. Carr's index calculated showed to vary from 13.50-17.78% and Hauser ratio ranged from 1.16-1.23. These values indicate that the powder blend exhibited good flow properties and were within the official limit. All the evaluated parameters result obtained from different formulations of tablet is shown in Table no.4. Hardness of various press coated tablet were in range of 7.1-8.0kg/cm^2 enabling good mechanical strength. The thickness observed was 6.1- 6.8mm. The friability of LSC tablet formulations were within the acceptable limits and ranged from 0.36-0.49%.

On immersion in pH 6.8 phosphate buffer at 37^0C ($\pm 2^0$C), the tablets disintegrated instantaneously. Table no.4 shows the results of the disintegration time. The best optimized formula (LS-12) showed a rapid disintegration of 1 Minute 23 seconds i.e., 83 seconds. The rest all formulations showed a Disintegration time (DT) of around 2 to 4 minutes respectively.

CONCLUSION

On comparing the best/optimized formula i.e., LS-12 with conventional formulation, it was clearly observed that the drug was released immediately, 99.96% within 10mins by best formulation, whereas it is 99.57% for the 60th min by conventional formulation. So, the % of drug release was instantaneous in LSC tablet than the conventional tablet.

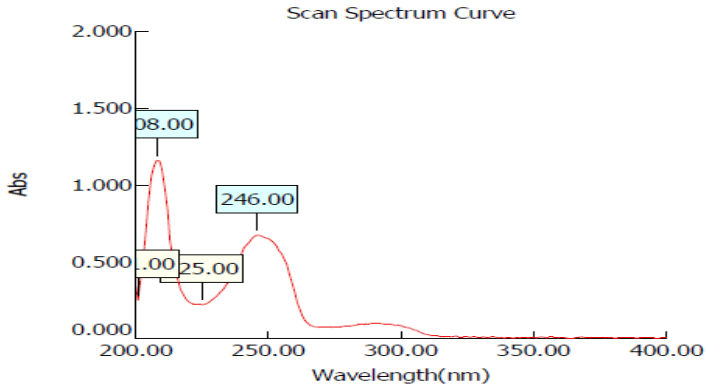

Fig.1- λ-maxof Efavirenz (in 6.8 pH buffer)

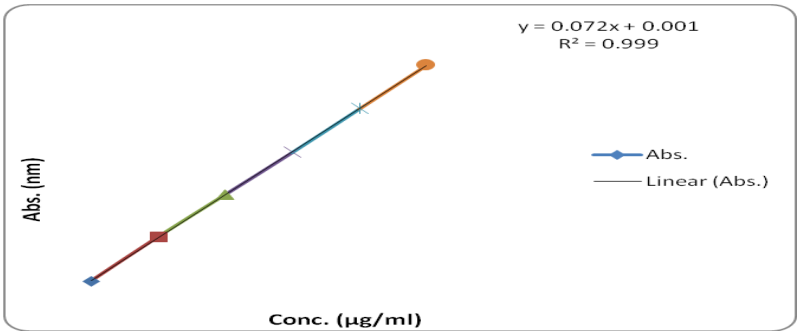

Fig.2 Calibration curve of Efavirenz(in 6.8 pH buffer)

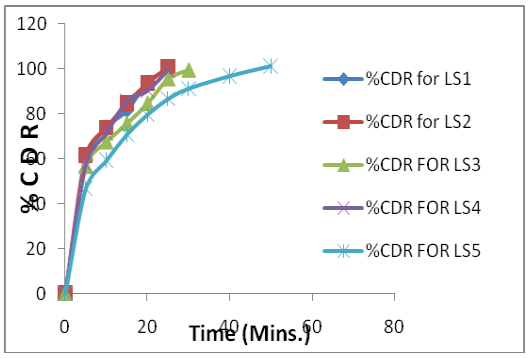

Fig.3: %CDR FOR BATCHES LS-1 TO LS-5

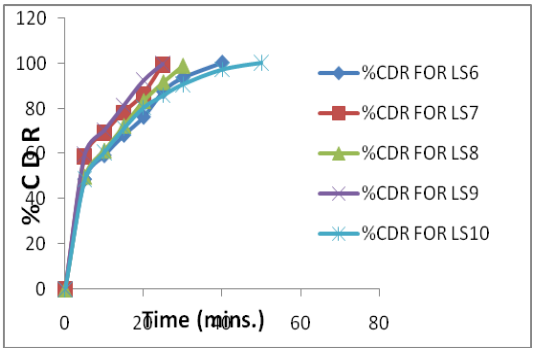

Fig.4: %CDR FOR BATCHES LS-5 TO LS-10

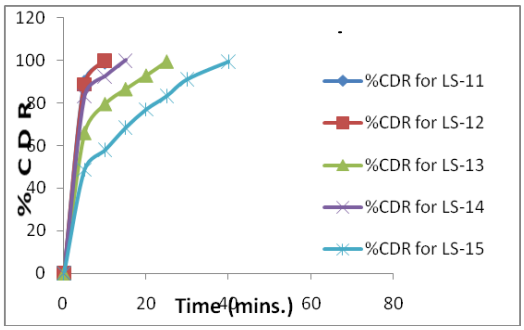

Fig 5: %CDR FOR BATCHES LS-11 TO LS-15

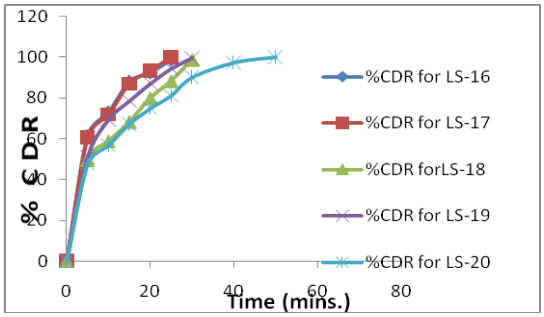

Fig. 6: %CDR FOR BATCHES LS-15 TO LS-20

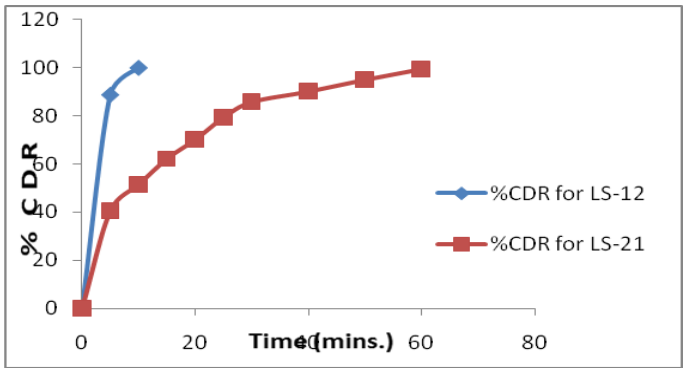

Fig. 7: %CDR Comparison for Best Formulation (LS-12) and Conventional Formulation (LS-21)

Table No.1: Formulation table for EfavirenzLiqui-solid compact tablets

S. No	Ingredients	LS-1 (C.P-2%)	LS-2 (C.P-4%)	LS-3 (SSG-2%)	LS-4 (SSG-4%)	LS-5 No.Dt	LS-6 (C.P-2%)	LS-7 (C.P-4%)	LS-8 (SSG-2%)	LS- 9 (SSG-4%)	LS-10 No.Dt.
1	Efavirenz	50	50	50	50	50	50	50	50	50	50
2	Carrier (MCC)	382	382	382	382	382	478	478	478	478	478
3	Coating (Aerosil)	191	191	191	191	191	160	160	160	160	160

4	Disintegrnt (C.P and SSG)	12.5	25	12.5	25	-	14	28	14	22	-
5	Magnesium Sterate	9.5	10	10	10	10	11	11	11	11	11
	Total Wt.	645	658	645	658	633	713	727	713	727	700

Note:*Formulations: - LS-1 to LS-5 is Polyethylene Glycol, Ratio: 2 (R=2) and LS-6 to LS-10 is Polyethylene Glycol, Ratio: 3 (R=3)

Table No.2:Formulation table for EfavirenzLiqui-solid compact tablets (contd.)

S	Ingredients	LS-	LS-	LS-	LS-	LS-	LS-16	LS-17	LS-18	LS-19	LS-20	Conv
1	Efavirenz	50	50	50	50	50	50	50	50	50	50	50
2	Carrier (MCC)	290	290	290	290	290	368	368	368	368	368	111
3	Coating (Aerosil)	145	145	145	145	145	123	123	123	123	123	36
4	Disintegnt (C.P and SSG)	10	20	10	20	-	11	22	11	22	-	2
5	Magnesium Sterate	8	8	8	8	8	9	9	9	9	9	1
	Total Wt.	503	513	503	513	492	561	572	561	572	549	200

Note:*Formulations: - LS-11 to LS-15 is Propylene Glycol, Ratio:2 (R=2) ; LS-16 to LS-20 is Propylene Glycol, Ratio:3 (R=3) and LS-21 is Conventional Tablet

Table.No.3. Results showing Flow properties of tablet blend. (SD= n±3**)**

Formulation	Angle of repose	Bulk density	Tapped density	Carr's index	Hausner's
LS 1	28.16 ^{o} ±0.88	0.533±0.03	0.621±0.32	14.17±0.86	1.16±0.04
LS 2	29.49 ^{o} ±1.15	0.537±0.01	0.632±0.36	15.03±0.84	1.18±0.02
LS 3	31.29 ^{o} ±0.66	0.541±0.03	0.658±0.39	17.78±0.90	1.22±0.04
LS 4	28.12 ^{o} ±0.32	0.532±0.03	0.619±0.34	14.05±0.71	1.16±0.07
LS 5	29.28 ^{o} ±0.32	0.539±0.08	0.645±0.37	16.43±1.46	1.22±0.05
LS 6	30.31 ^{o} ±1.73	0.555±0.02	0.661±0.33	17.44±1.26	1.21±0.08
LS 7	27.50 ^{o} ±0.65	0.553±0.08	0.622±0.38	13.50±1.23	1.16±0.12
LS 8	28.22 ^{o} ±0.95	0.538±0.02	0.643±0.31	14.93±0.78	1.17±0.03
LS 9	29.28 ^{o}±0.32	0.554±0.10	0.624±0.38	13.50±1.22	1.16±0.12
LS 10	31.29 ^{o}±0.66	0.537±0.01	0.633±0.46	15.13±0.81	1.18±0.02
LS 11	29.28 ^{o}±0.32	0.554±0.08	0.626±0.28	13.40±1.19	1.17±0.12
LS 12	27.40 ^{o}±0.65	0.552±0.08	0.620±0.37	13.50±1.2	1.16±0.12
LS 13	31.44 ^{o}±0.14	0.543±0.07	0.656±0.29	17.76±0.92	1.23±0.04
LS 14	31.14 ^{o}±0.14	0.541±0.07	0.655±0.29	17.77±0.92	1.22±0.04
LS 15	28.22 ^{o}±0.95	0.534±0.02	0.644±0.36	14.88±0.75	1.17±0.03
LS 16	30.31 ^{o}±1.73	0.559±0.02	0.669±0.31	17.43±1.23	1.21±0.08
LS 17	28.12 ^{o} ±0.32	0.532±0.03	0.619±0.34	14.05±0.71	1.16±0.07
LS 18	29.28 ^{o} ±0.32	0.539±0.08	0.645±0.37	16.43±1.46	1.22±0.05

LS 19	30.31° ±1.73	0.555±0.02	0.661±0.33	17.44±1.26	1.21±0.08
LS 20	27.50° ±0.65	0.553±0.08	0.622±0.38	13.52±1.23	1.16±0.12
LS 21	30.22° ±0.95	0.548±0.02	0.653±0.31	14.93±0.78	1.18±0.03

Table.No.4. Results Showing Postcompression parameter's (SD= n±3)

			Friability(%)	Drug content	Disintegration time
LS 1	7.4 ±0.19	6.2 ± 0.24	0.40	98.95±0.88	3 mins 21 secs
LS 2	7.2±0.21	6.4 ± 0.02	0.37	100.1±0.83	2 mins 46 secs
LS 3	7.4±0.04	6.5 ± 0.07	0.39	99.73±0.87	3 mins 13 secs
LS 4	7.6 ±0.11	6.3 ± 0.05	0.38	100.8±0.64	3mins
LS 5	7.7 ±0.11	6.4 ± 0.02	0.39	99.4±0.58	3 mins 35 secs
LS 6	6.9 ±0.18	6.1 ± 0.07	0.38	99.99±0.8	3 mins 40 secs
LS 7	7.0 ±0.16	6.4 ± 0.07	0.42	99.8±0.42	2 mins 52 secs
LS 8	7.3±0.32	6.6 ± 0.05	0.41	99.9±0.5	2 mins 25 secs
LS 9	7.2±0.26	6.5 ± 0.24	0.40	98.84±0.69	3 mins 32 secs
LS 10	7.5±0.15	6.7 ± 0.02	0.39	99.98±0.62	4 mins 14 secs
LS 11	8.0 ±0.16	6.6 ± 0.07	0.40	98.8±0.42	2 mins 20 secs
LS 12	7.1±0.32	6.1 ± 0.05	0.36	100.2±0.5	1 min 23 secs
LS 13	7.2±0.26	6.6 ± 0.02	0.40	99.74±0.69	2 mins 48 secs
LS 14	7.5±0.15	6.7 ± 0.07	0.42	98.18±0.62	2 mins 10 secs
LS 15	7.6 ±0.11	6.5 ± 0.07	0.46	99.4±0.58	3mins 22 secs
LS 16	7.4 ±0.18	6.8 ± 0.05	0.47	101.5±0.8	3 mins 15 secs
LS 17	7.2±0.15	6.5 ± 0.24	0.43	98.74±0.69	3 mins 02 secs
LS 18	7.7 ±0.11	6.7 ± 0.02	0.44	97.98±0.62	2 mins 51 secs
LS 19	7.8 ±0.18	6.4 ± 0.07	0.45	98.4±0.58	2 mins 18 secs
LS 20	7.9 ±0.11	6.6 ± 0.07	0.48	98.88±0.62	4 mins 10 secs
LS 21	7.6 ±0.18	6.7 ± 0.05	0.49	99.71±0.58	3 mins 33 secs

Table.no.5. *In-vitro* drug release studies data of batches LS-1 to LS-10

Time in Mins.	LS-1	LS-2	LS-3	LS-4	LS-5	LS-6	LS-7	LS-8	LS-9	LS-10
0	0	0	0	0	0	0	0	0	0	0
5	59.36	61.6	56.72	57.6	46.6	48.82	58.8	49.82	59.82	48.67
10	73.93	73.9	67.61	71.3	59.2	59.38	69.3	61.38	70.38	60.68
15	81.49	84.8	75.87	85.5	70.8	68.39	78.3	72.39	81.39	71.25
20	93.95	93.7	84.82	90.2	79.7	76.36	86.3	83.36	92.36	80.42
25	99.87	100.	95.75	99.3	86.6	87.62	99.6	91.62	99.82	85.81
30	-	-	99.68	-	91.2	93.70	-	98.90	-	90.67
40	-	-	-	-	96.8	100.3	-	-	-	97.25
50	-	-	-	-	101.	-	-	-	-	100.23
60	-	-	-	-	-	-	-	-	-	-

Table.no.6. *In-vitro* drug release studies data of batches LS-11 to LS-21

Time in Mins.	LS-11	LS-12	LS-13	LS-14	LS-15	LS-16	LS-17	LS-18	LS-19	LS-20	LS-21
0	0	0	0	0	0	0	0	0	0	0	0
5	89.74	88.74	65.85	83.42	48.67	61.30	60.67	49.67	50.89	47.67	40.60
10	98.87	99.96	79.38	92.55	57.88	72.81	71.81	58.88	69.36	56.88	51.50
15	-	-	86.40	100.1	68.38	87.87	86.87	68.38	78.47	67.38	62.28
20	-	-	92.73	-	76.99	92.30	93.30	79.99	86.96	74.99	70.24
25	-	-	99.31	-	83.31	98.57	99.94	88.31	94.26	81.31	79.50
30	-	-	-	-	91.18	-	-	98.91	99.51	90.18	85.87
40	-	-	-	-	99.45	-	-	-	-	97.45	90.22
50	-	-	-	-	-	-	-	-	-	100.1	95.14
60	-	-	-	-	-	-	-	-	-	-	99.57

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