Research Article

Design and Evaluation of Solubility Enhancement of Poorly Soluble Drugs using Liquid Solid Compacts

***Neelamma Gajji[1], M.V.N.L. Chaitanya[2], Bellamkonda Satyavathi[1]**

1. Department of Pharmaceutics, Teja College of Pharmacy, Kodad, Nalgonda, Telagana, India.
2. Department of Pharmacognosy & Phytopharmacy, J.S.S. College of Pharmacy, Ooty, Tamilnadu, India.

ABSTRACT

Oral dosage form is the physical form of a dose of a chemical compound used as a drug or medication intended for administration or consumption by the oral route. The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. There are several methods used to increase the solubility of drugs, of those liquid-solid compact (LSC) technique is a new and promising addition towards such a novel aim, that the solubility of the insoluble drug moiety is increased by aid of non-volatile solvents and hence increasing the dissolution and bioavailability. LSC's when compared to all other standard methods used to improve the solubility, have more ability to enhance solubility. Liquisolid compacts were prepared by employing non-volatile solvents like-Polyethylene Glycol and Propylene Glycol, whereas microcrystalline cellulose (MCC) and Aerosil were used as carrier and coating materials, respectively. Disintegrants were used from 2% to 4% to ensure the immediate release of the drug and in turn achieve maximum peak plasma concentration. Magnesium Stearate acted as both glidant and lubricant added prior to compression of tablets. In-vitro drug release results showed that Liqui-solid compacts demonstrated significantly higher drug release rates in less time than those of conventionally made. This was due to an increase in wetting properties and surface of drug available for dissolution.

Keywords: Drug release, dissolution rate, fluvastatin, Liquisolid compacts, *in vitro* studies

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***Address for correspondence:**
Neelamma Gajji,
Assistant Professor,
Department of Pharmaceutics, Teja College of Pharmacy, Kodad, Nalgonda, Telagana, India.
E-mail: chaitanya.phyto@gmail.com

1. INTRODUCTION

Oral drug delivery is the oldest DDS and highly used route of drug delivery, despite of phenomenal advances in the inhalable, injectable, transdermal, nasal and other routes of administration. The unavoidable truth is that oral drug delivery remains well ahead of the pack as the preferred delivery route. The solubility behavior of a drug is one of the key determinants of its oral bioavailability. In recent years, the number of poorly soluble drug candidates has increased tremendously. The formulation of poorly soluble drugs for oral delivery presents a challenge to the formulation scientists. [1] The oral route remains the preferred route of drug administration due to its convenience, good patient compliance and low medicine production costs. In order for a drug to be absorbed into the systemic circulation following oral administration, the drug must be dissolved in the gastric fluids.

Bioavailability of poorly water-soluble drugs is limited by their solubility and dissolution rate. Several studies have been carried out to increase the dissolution rate of drugs by decreasing the particle size, by creating nano and micro particles. However, fine drug particles have a high tendency to agglomerate due to van-der Waals attraction or hydrophobicity. Here, agglomeration of the drug particles is prevented due to the binding of the drug to the carrier. However, due to the presence of the residual solvent in the drug formulation, it is disadvantageous to use toxic solvents. [2]

Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs. [3,4] The term liquisolid compacts as described by Spireas.,et al indicates that immediate or sustained release tablets or capsules that are prepared using the technique of "liquisolid systems" combined with inclusion of appropriate adjuvant required for tabletting or encapsulation such as lubricants and for rapid or sustained release action, such as disintegrants or binders, respectively. Liquisolid compacts prepared by using different solvents which dissolve the poorly soluble drug and give better bioavailability. It has been observed that the drug release superiority of liquisolid tablets is inversely proportional to the aqueous solubility of the contained drug. [5]

Liquisolid system is novel technique developed by Spireas et al; liquisolid systems involve conversion of liquid lipophilic drugs or 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. [6,7] In the case of water soluble drugs, the sustained release can be obtained. "Liquisolid systems" is formulated by converting liquid lipophilic drugs, or drug suspensions or solutions of water-insoluble solid drugs in suitable non-volatile solvent systems, into "dry" (i.e.,dry-looking),nonadherent, free-flowing and readily compressible powder admixtures by blending with selected carrier and coating materials. The steps involved in the preparation of liquid-solid systems are as shown in (**Fig. 1**).

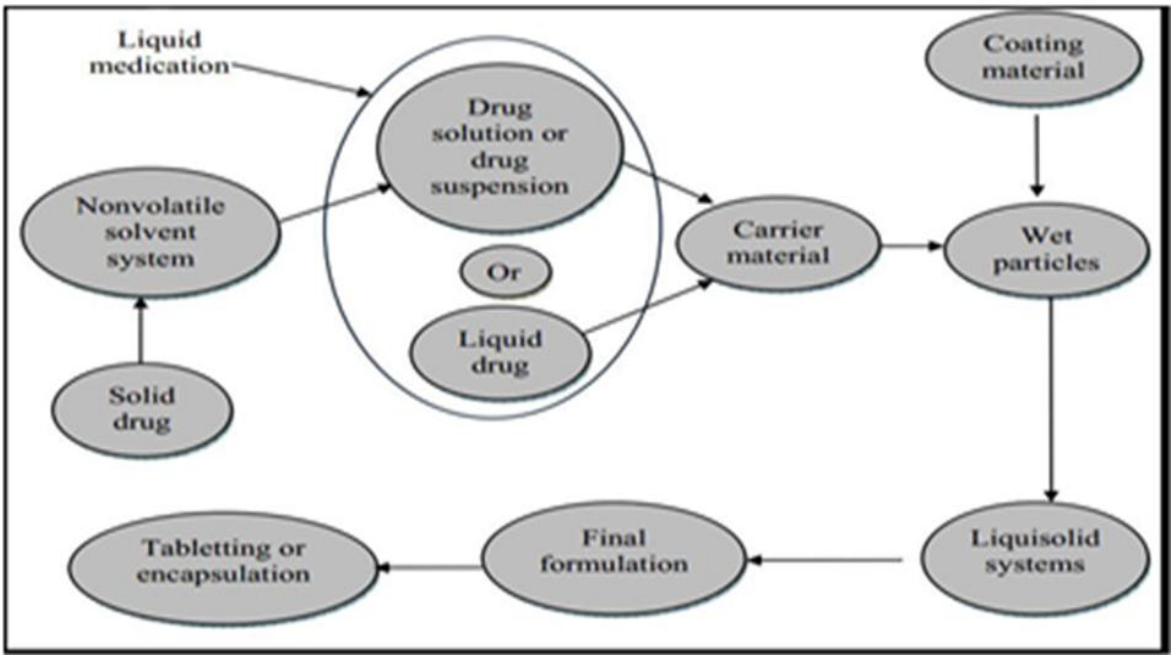

Figure 1: Steps Involved in the Preparation of Liquid Solid Systems

Mechanisms of Enhanced Drug release from Liquid-solid Systems includes an increased surface area of the drug available for release, an increased aqueous solubility of the drug, and an improved wet ability of the drug particles. Formation of a complex between the drug and excipients or any changes in crystallinity of the drug could be ruled out using DSC and XRPD measurements. [8] There are various applications of Liquisolid Techniques like Solubility and dissolution improvement, Flowability and Compressibility, Bioavailability Improvement. [9,10]

2. MATERIALS AND METHODS

2.1 Chemicals and reagents

The standard Fluvastatin (API) was purchased from Spectrum Pharma Labs. Hyderabad. Polyethylene Glycol, Propylene Glycol was purchased from Rankem Ltd. Microcrystalline Cellulose, Sodium starch glycollate, Magnesium Sterate were purchased from Colorcon. Aerosil was purchased from FMC Biopolymers. Cross

Povidone was purchased from Jaysons Pvt. Ltd.

2.2 Pre-formulation studies

Prior to the development of tablet dosage form, the pre-formulation studies were carried out to evaluate the drug substance analytically and determine its necessary characteristics and to establish its compatibility with different excipients. The various pre-formulation studies conducted were melting point for identification of purity of the drug, solubility studies with various solvents and Physicochemical parameters: the color, odor and taste of the drug were recorded using descriptive terminology and found to be white to off-white crystalline powder, tasteless and odorless.

2.3 Preparation of Powder tablet blends

Accurately weighed amount of Fluvastatin (40 mg) is weighed and added to a clean mortar, to this calculated amount of Propylene Glycol (R=2 and R=3), Microcrystalline cellulose i.e., carrier, Aerosil i.e., coating material, superdisintegrants (C.P/SSG/CCS) and Magnesium Stearate were added and were thoroughly triturated in a mortar with a glass pestle for about 10-15mins. Then the final powder blend is passed through sieve no. 60 to obtain a fine powder. Such prepared powder blends were further used to study pre-compression parameters (flow properties) like Angle of repose, bulk density, tapped density, Carr's consolidation index, Hausner's ratio were carried out.

2.4 Formulation of Fluvastatin Liqui-solid compact tablet (Preparation Method)

- The Drug was initially dispersed in the non-volatile solvent system (PG) termed as liquid vehicles with different drug: vehicle ratio. Then a mixture of carrier, coating and excipients was 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.
- To the above binary mixture disintegrants like sodium starch glycolate, cross povidone, cross carmellose sodium and other remaining additives are added according to their application and mixed for a period of 10 to 20 min in a mortar. Then the powder blend is passed through the sieve of numbers either 60 or 65 for assuming finer particles.
- Lastly Magnesium Stearate of accurately weighed quantity was added and preceded for punching. The final mixture was compressed using the tableting machine Cadmach Multisation (10) standard punching machine. The diameter of punch used was 12mm and was a concave type of punch. The hardness was adjusted manually and so was the die cavity. Standard hardness of about 7.5 kg/m2 was maintained throughout the punching process. Batch of 3 tablets for each formulation (n=3) was prepared and used for subsequent evaluation procedures.

Table 1: Formulation Table of Fluvastatin*

S. No	Ingredients	LS-1 (C.P-2%)	LS-2 (C.P-4%)	LS-3 (SSG-2%)	LS-4 (SSG-4%)	LS-5 (CCS-2%)	LS-6 (CCS-4%)	LS-7 No.Dt.
1	Fluvastatin	40	40	40	40	40	40	40
2	Carrier (MCC)	217	217	217	217	217	217	217
3	Coating (Aerosil)	109	109	109	109	109	109	109
4	Disintegrant (C.P, SSG &CCS)	7	14	7	14	7	14	-
5	Magnesium Sterate	5	5	5	5	5	5	5
	Total Wt.	378	385	378	385	378	385	371

Note:*Formulations: - LS-1 to LS-7 is Propylene Glycol, Ratio:2 (R=2)

S. No	Ingredient	LS-8 (C.P-2%)	LS-9 (C.P-4%)	LS-10 (SSG-2%)	LS-11 (SSG-4%)	LS-12 (CCS-2%)	LS-13 (CCS-4%)	LS-14 No.Dt
1	Fluvastatin	40	40	40	40	40	40	40
2	Carrier (MCC)	275	275	275	275	275	275	275
3	Coating (Aerosil)	92	92	92	92	92	92	92
4	Disintegrant (C.P, SSG & CCS)	8	16	8	16	8	16	-
5	Magnesium Sterate	6	6	6	6	6	6	6
	Total Wt.	421	429	421	429	421	421	413

Note:*Formulations: - F-LS to LS-14 is Propylene Glycol, Ratio:3 (R=3)

2.5 Post compression parameters (Evaluation of tablet): After the formulation of Fluvastatin Liqui-solid compact tablet, they were subjected to post compression studies like Thickness, Hardness, Friability, Drug content uniformity, Disintegration Time, Dissolution study and pharmacokinetics studies were done do evaluate the cumulative drug release from the formulated tablets at different time Intervals were fitted to zero order kinetics, first order kinetics, Higuchi model and Korsmeyer –Peppas model to characterize mechanism of drug release.

3. RESULTS AND DISCUSSION

3.1 Pre-formulation studies

3.1.1. Physical Properties: For a drug substance to formulate into a dosage form, it is necessary to study the physicochemical properties of the bulk drug.

A. Colour: Off white colour

B. Melting Point: 194-197°

C. Solubility: Solubility of Fluvastatin was carried out in different solvents like-distilled water, PEG-400, PG, and Tween 80. Solubility of Fluvastatin was determined spectrophotometrically at 240nm. Fluvastatin is more soluble in PG.

3.2. Drug excipient compatibility:

Drug and excipient compatibility was confirmed by comparing spectra of FT-IR analysis of Pure drug with that of various excipients used in the formulation.

The compatibility studies were performed using IR spectrophotometer. The IR spectrum of pure drug and physical mixture of drug and excipients was studied. The characteristic absorption peaks of were obtained as above (**Table 2**) and as they are in official limits (±100 cm-1) the drug is compatible with excipients.

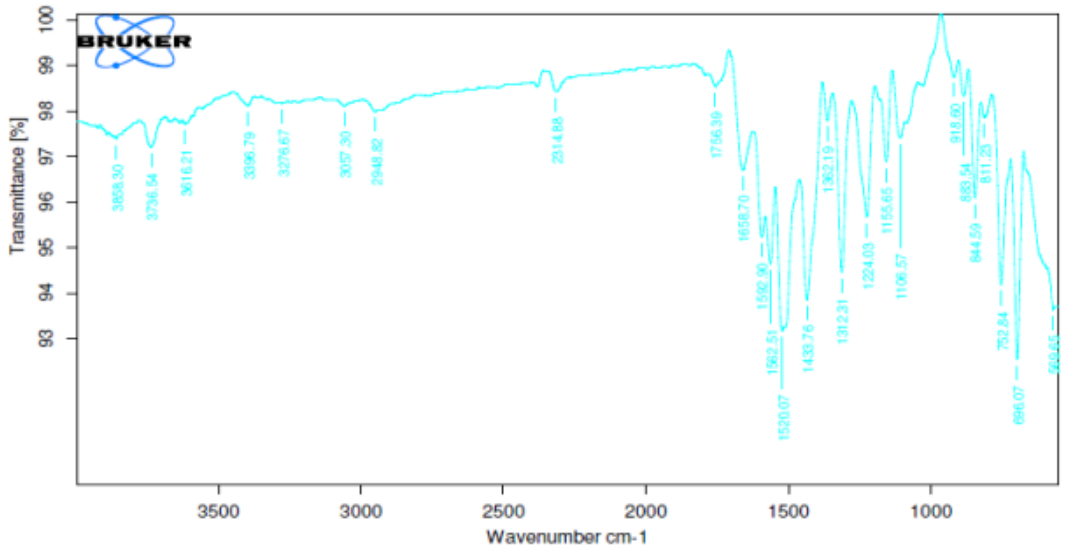

Figure 2: FT-IR Spectra of Pure Drug (Fluvastatin)

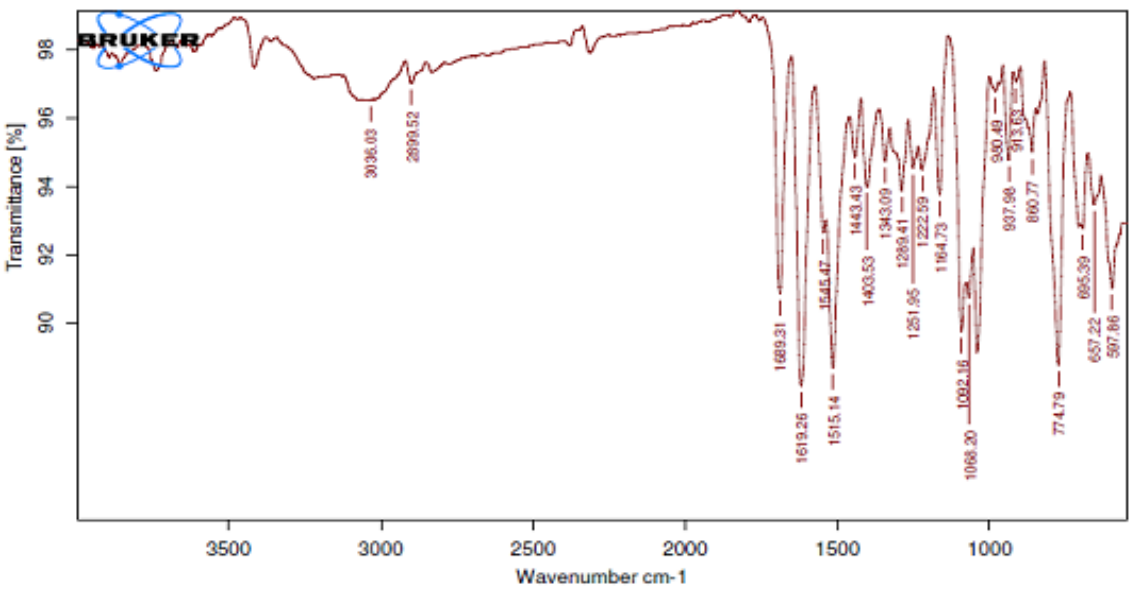

Figure 3: FT-IR Spectra of Optimized Formulation

Table 2: Characteristic peaks in FT-IR spectra of Fluvastatin

Wave number in cm^{-1}	Functional groups	Pure drug Fluvastatin
700-900	C-H Bending	755.96 cm^{-1}
1350-1480	C=C STRETCH	1432.91 cm^{-1}
1760-1550	C=O Stretching	1759.53 cm^{-1}
3010-2850	C-H STRETCH	3020.86 cm^{-1}
3500-3200	O-H Stretching	3318.84 cm^{-1}
3800-3300	N-H STRETCH	3689.41 cm^{-1}

3.3 Precompression Parameters:

Table 3: Precompression Parameters of Tablet Blend

Formulation	Angle of repose (θ)	Bulk density (gm/ml)	Tapped density (gm/ml)	Carr's index (%)	Hausner's ratio
LS 1	28.16°±0.88	0.533±0.03	0.621±0.32	14.17±0.86	1.26±0.04
LS 2	29.49°±1.15	0.537±0.01	0.632±0.36	15.03±0.84	1.19±0.02
LS 3	31.29°±0.66	0.541±0.03	0.658±0.39	17.78±0.90	1.21±0.04
LS 4	28.12°±0.32	0.532±0.03	0.619±0.34	14.05±0.71	1.19±0.07
LS 5	29.28°±0.32	0.539±0.08	0.645±0.37	16.43±1.46	1.12±0.05
LS 6	30.31°±1.73	0.555±0.02	0.661±0.33	17.44±1.26	1.29±0.08
LS 7	27.50°±0.65	0.553±0.08	0.622±0.38	13.50±1.23	1.26±0.12
LS 8	28.22°±0.95	0.538±0.02	0.624±0.31	14.93±0.78	1.19±0.03
LS 9	29.28°±0.32	0.554±0.10	0.633±0.38	13.89±1.22	1.18±0.12
LS 10	31.29°±0.66	0.537±0.01	0.626±0.46	15.13±0.81	1.28±0.02
LS 11	29.28°±0.32	0.554±0.08	0.620±0.28	14.50±1.19	1.18±0.12
LS 12	27.40°±0.65	0.552±0.08	0.656±0.37	13.56±1.2	1.22±0.12
LS 13	31.44°±0.14	0.549±0.07	0.655±0.29	17.76±0.92	1.13±0.04
LS 14	31.14°±0.14	0.543±0.07	0.644±0.29	17.7±0.92	1.24±0.04

Data are represented as mean S.D. (n=3)

The flow properties of different outer coating material formulation are shown in the (**Table 3**). The results for angle of repose (θ) obtained was found to vary from 27.400 - 31.440 which indicates the powder blend has fairly good flow property and can be used for direct compression.

The Bulk and Tapped density of outer coating material blend were from 0.532-0.555gm/ml and 0.619-0.661gm/ml respectively. Carr's index calculated showed to vary from 13.50-17.78% indicating that the blend has a good flow property, whereas Hausner's ratio analyzed is in 1.12-1.29 range representing a good flow.

3.4 Post Compression Parameters:

Table 4: Post Compression Parameters

Formulation	Weight. Variation	Hardness (Kg/cm²)	Thickness (mm)	Friability (%)	Drug content (%)	Disintegration time (Minutes)
LS 1	341±0.03	6.3 ±0.19	6.2± 0.24	0.24	97.95±0.88	3 mins 15secs
LS 2	345±0.25	6.4±0.20	6.4 ± 0.02	0.25	100.3±0.83	2 mins 48secs
LS 3	333±0.22	6.5±0.04	6.4 ± 0.07	0.20	98.73±0.87	3 mins 23secs
LS 4	336±0.18	6.5 ±0.11	6.4 ± 0.05	0.19	100.81±0.64	3 mins
LS 5	342±0.26	6.8 ±0.11	6.2 ± 0.02	0.19	99.84±0.58	3 mins 25secs
LS 6	356±0.32	5.7 ±0.18	6.6 ± 0.07	0.15	99.99±0.8	3 mins 41secs
LS 7	342±0.26	6.2±0.16	6.5 ± 0.07	0.21	99.88±0.42	2 mins 55secs
LS 8	372±0.19	6.1±0.32	6.3 ± 0.05	0.32	99.90±0.5	2 mins 28secs
LS 9	380±0.37	6.3±0.26	6.4 ± 0.24	0.39	98.85±0.69	3 mins 37secs
LS 10	389±0.22	6.4±0.15	6.6± 0.02	0.28	99.98±0.62	4 mins 24secs
LS 11	380±0.31	7.1±0.16	6.5 ± 0.07	0.32	98.89±0.42	2 mins 38secs
LS 12	384±0.12	6.2±0.32	6.8 ± 0.05	0.27	100.25±0.5	2 mins 20secs
LS 13	381±0.04	6.2±0.26	6.7 ± 0.02	0.35	99.79±0.69	1 mins 53secs
LS 14	394±0.26	6.4±0.15	6.6 ± 0.07	0.36	98.17±0.62	4 mins 24secs
M P	100±0.15	5.8 ±0.22	6.6 ± 0.05	0.39	96.80±0.03	3 mins 53secs

Data are represented as mean S.D. (n=3)

All the evaluated parameters result obtained from different formulations of tablet are shown in (**Table 4**). Hardness of various press coated tablet were in the range of 5.7-7.1kg/cm² enabling good mechanical strength. The thickness observed was 6.2- 6.7mm. The friability of LSC tablet formulations was within the acceptable limits and ranged from 0.15-0.39%.

On immersion in pH 6.8 phosphate buffer at 370C (±20C), the tablets disintegrated instantaneously. (**Table 4**) shows the results of the disintegration time. The best optimized formula (LS-12) showed a rapid disintegration of 1 Minute 24 seconds i.e., 84 seconds. The rest all formulations showed a disintegration time (DT) of around 2 to 4 minutes respectively.

The *in-vitro* release studies were compared according to the percentage of disintegrants (CP,SSG and CCS) used ie 2% and 4% to that of without disintegrant and solvents ratio(R) starting from **R=2** and then **R=3** with **PG** respectively are as follows.

3.4 *In-vitro* Drug Release Studies

Table 5: *In-vitro* Drug Release Studies Data

Time in Mins.	LS-1	LS-2	LS-3	LS-4	LS-5	LS-6	LS-7	LS-8	LS-9	LS-10	LS-11	LS-12	LS-13	LS-14	M.P.
0	0	0	0	0	0	0	0	0	0	0	0	0	0	0	0
5	59.82	61.64	56.72	57.60	46.68	48.82	58.82	49.82	59.82	48.67	79.74	88.74	65.85	83.42	40.60
10	73.93	73.93	67.61	71.30	59.25	59.38	69.38	69.38	70.38	60.68	97.87	99.96	79.38	92.55	55.50
15	81.49	84.82	75.87	85.52	70.82	68.39	78.39	72.39	81.39	71.25	-	-	86.40	100.1	64.28
20	93.95	93.78	84.82	90.27	79.71	76.36	86.63	83.36	92.36	80.42	-	-	92.73	-	78.24
25	99.87	100.98	95.75	99.39	86.67	87.62	99.62	91.62	99.82	85.81	-	-	99.31	-	79.90

30	-	-	99.68	-	91.28	93.70	-	98.92	-	90.67	-	-	-	-	88.97
40	-	-	-	-	96.87	100.39	-	-	-	97.25	-	-	-	-	90.22
50	-	-	-	-	101.94	-	-	-	-	100.23	-	-	-	-	95.86
60	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100.2

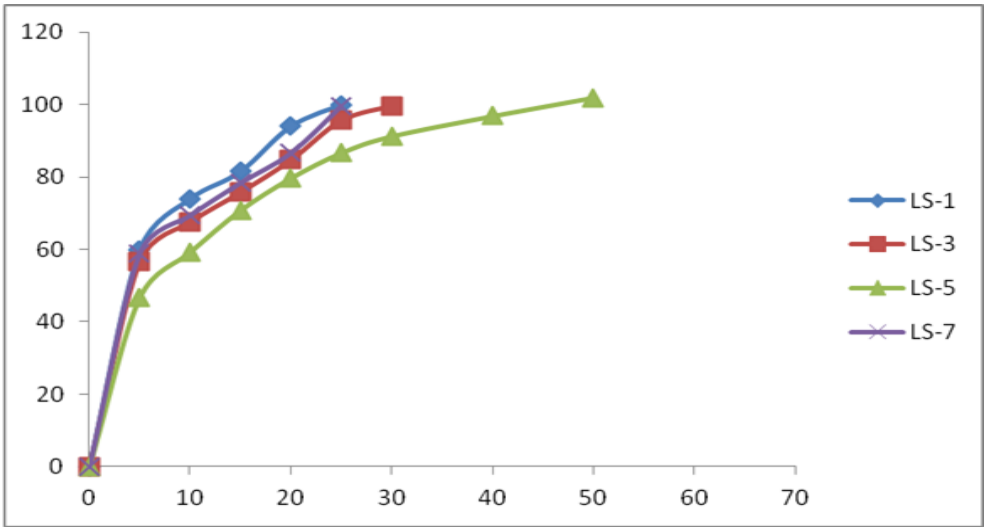

Figure 4: Comparative Dissolution Profile for LS-1, LS-3, LS-5 and LS-7

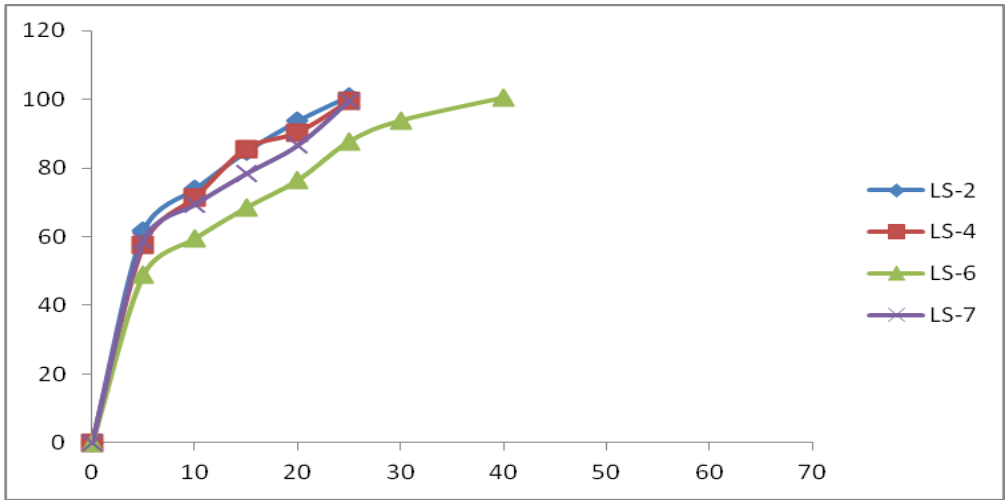

Figure 5: Comparative dissolution profile for LS-2, LS-4, LS-6 and LS-7

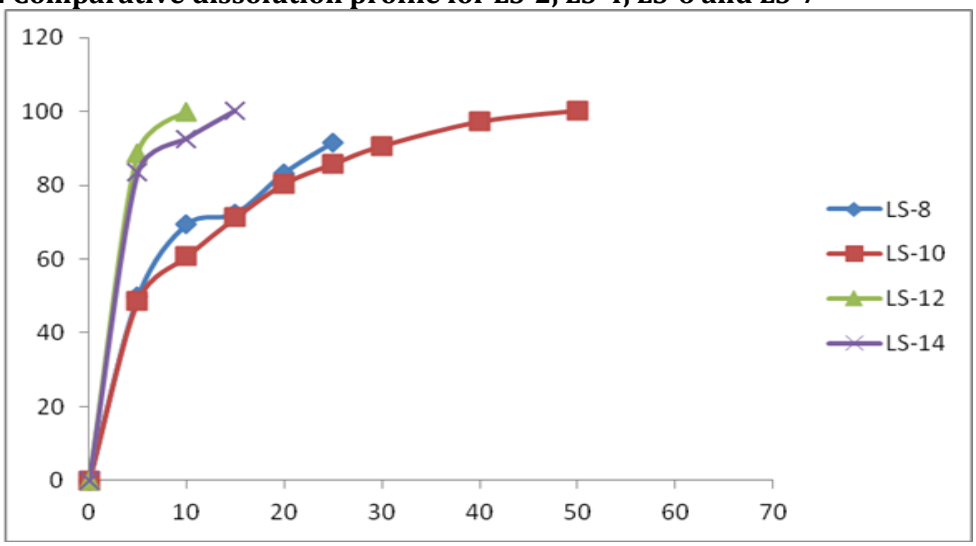

Figure 6: Comparative Dissolution Profile for LS-8, LS-10, LS-12 and LS-14

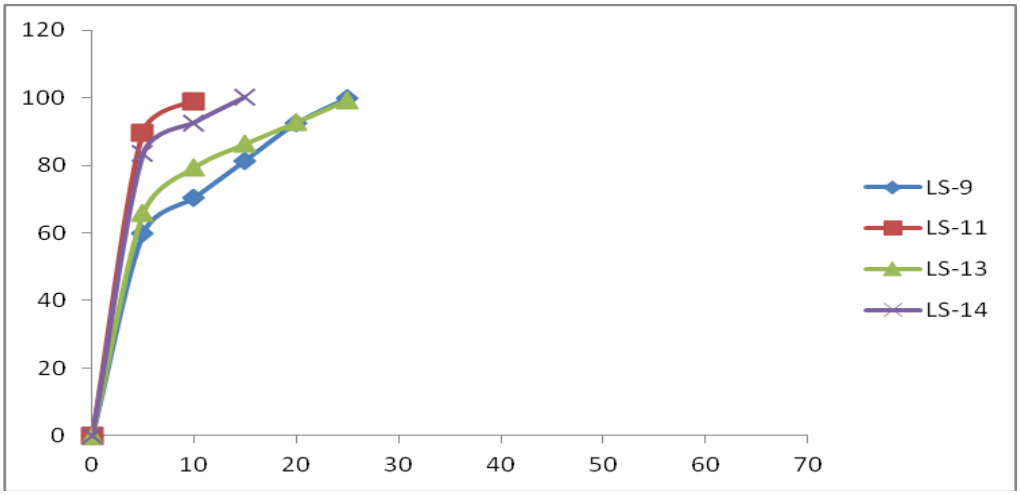

Figure 7: Comparative Dissolution Profile for LS-9, LS-11, LS-13 and LS-10

Table 6: Comparative Dissolution Profile for Optimized Formula (LS-12) and Conventional (Marketed) Formulation:

Time in Mins.	LS-12	M.P
0	0	0
5	87.74	40.60
10	99.96	55.50
15	-	64.28
20	-	78.24
25	-	79.90
30	-	88.97
40	-	90.22
50	-	95.86
60	-	100.21

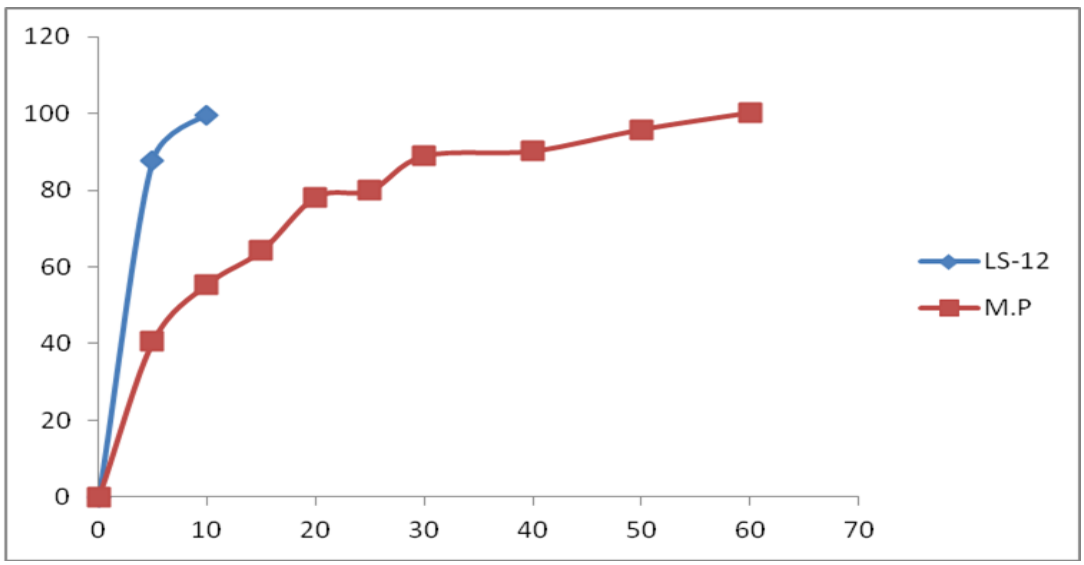

Figure 8: Comparative Dissolution Profile for Optimized Formula (LS-12) and conventional (marketed) formulation

On comparing the best/optimized formula i.e., LS-12 with the conventional formulation, it was clearly observed that the drug was released immediately, 99.96% within 10mins by best formulation, whereas it is 100.21% for the 60th min by

conventional formulation. So, the % of drug release was instantaneous in LS-12 tablet than the conventional tablet.

3.5 Kinetics Analysis for LS-12:

The percentage of drug release was 99.96% within 10mins in the conventional formulation LS-12. The kinetic studies were carried to ensure the rate of drug release. Showing the results of kinetic data LS-12 in (**Table 7**).

Table 7: Drug Release Data of LS-12

Time	%CDR	% ARA	Log%ARA
0	0	100	2
5	87.74	12.26	1.08849
10	99.96	0.04	-1.39794

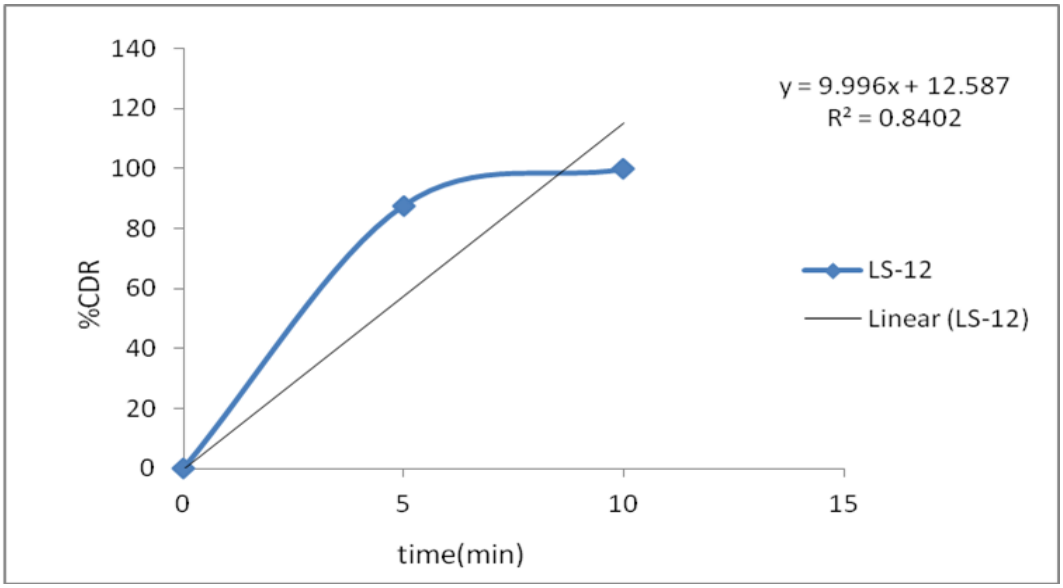

Figure 9: Zero Order Plot of LS -12

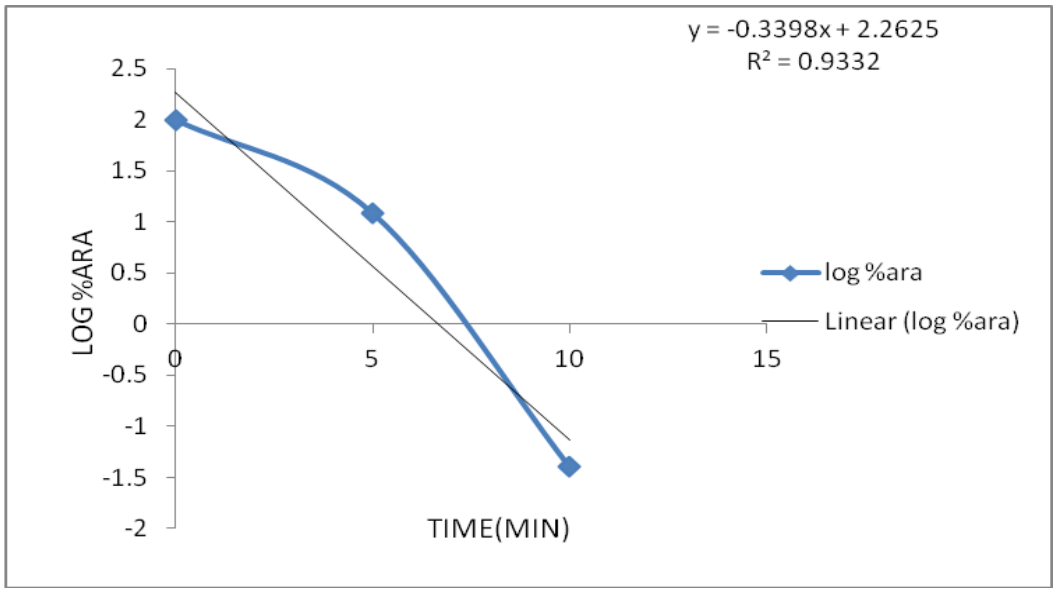

Figure 10: First Order Plot for LS-12

Table 8: Drug Release Kinetics Data of LS-12

S.No	Zero order	First order
CODE	R^2	R^2
LS-12	0.8402	0.9332

The drug release from the tablets was explained by the using mathematical model equations such as zero order, first order methods. Based on the regression values it was concluded that the optimized formulation LS-12, followed First order release where the regression value was found to be 0.933.

3.6 Stability Studies:

Table 9: Stability Studies of LS-12

S.no	Trial No.	1st Day (%)	30th Day (%)	60th Day (%)	90th Day (%)
1.	I	99.03	98.69	99.91	99.96
2.	II	98.28	99.65	99.58	99.97
3.	III	99.39	99.24	99.35	99.95
4.	Mean (X)	99.42	99.71	99.42	99.96

The stability studies were done as per ICH guidelines and the results compared to the optimized formulation. There was not much difference in the *in-vitro* release rates.

4. SUMMARY

The present work involves the formulation development, optimization and in-vitro evaluation of immediate release tablets by Liqui-Solid compacts technique. Since Fluvastatin is BCS Class-II drug, LSC technique was opted to increase its solubility and dissolution rate, in turn bioavailability of the same. As the drug is moisture & heat sensitivity and to minimize critical process parameters, direct compression method was selected for the formulation of tablets.

Under pre-formulation studies API characterization and drug-excipient compatibility studies were carried out. The API characterization showed compliance with the drug characteristics. The disintegrants and other excipients were selected based on the satisfying results produced during drug- excipient compatibility studies to develop the final formulation.

The final suitable formulation (LS-12) was achieved fruitfully by the direct compression technique using Propylene glycol ratio (R=3) and Cross carmellose sodium as disintegrant which exhibited an rapid disintegration time (1.24mins), percentage drug content per tablet (100.35%) and in vitro drug release (99.96%).

5. CONCLUSION

Considering the results of batches containing Propylene glycol and Cross carmellose sodium as disintegrant it can be concluded that the formulation LS-12 was meeting the higher in-vitro correlation limits and in less instance of time, when subjected to comparison with marketed formulation which was a positive result, proving LSC tablet was better than the normal conventional tablet. It was also observed that direct compression was the best suitable method used for producing immediate release tablets of Fluvastatin.

The stability studies were conducted and results subjected that the LS-12 formulation was stable even after three months of time

Based on all the above considerations, these formulas will be subjected to bioavailability studies and if it complies to all the requirement of those studies the same formula will be commercialized.

Further improvement in these formulations can be achieved by implementing different non-volatile solvents and more further using disintegrants of comparatively higher grades and more porous ones.

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