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Research Article

ENHANCEMENT OF SOLUBILITY AND DISSOLUTION PROPERTIES OF LOVASTATIN BY LIQUISOLID TECHNIQUE

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ABSTRACT

Lovastatin is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal. The poor dissolution rate of water-insoluble drugs is still a major problem confronting the pharmaceutical industry. There are several techniques to enhance the dissolution of poorly soluble drugs. Among them, the technique of liquisolid compacts is a promising technique towards such a novel aim. In this study, the dissolution behaviour of Lovastatin from liquisolid compacts was investigated in simulated gastric fluid (SGF, pH1.2). To this end, several liquisolid tablets formulations containing various ratios of drug:Propylene glycol were prepared. The ratio of starch and microcrystalline cellulose (carrier) to silica (coating powder material) was kept constant in all formulations. The results showed that liquisolid compacts demonstrated significantly higher drug release rates than those of conventionally made directly compressed tablets. This was due to an increase in wetting properties and surface of drug available for dissolution.

Keywords: Liquisolid compacts, Lovastatin, Dissolution rate, propylene Glycol, surface adsorption.

INTRODUCTION

Synthesis of poorly water soluble drugs is gaining lot of importance nowadays. The poor dissolution rate of such water-insoluble drugs confronts a major obstacle in development of pharmaceutical dosage forms. The drugs which are poorly water soluble will be released at a slow rate owing to their limited solubility within gastrointestinal tract. The rate determining step in drug absorption is rate of drug dissolution. Enhancing the rate of dissolution or solubility of poorly water soluble drugs is a major challenge. Formulation methods are targeted at dissolution enhancement of poorly soluble drug substances. Different techniques used to enhance the dissolution of water insoluble drugs are particle size reduction, use of surfactant as solubilizing agent, drug complex with hydrophilic carrier, pro-drug approach, and formulation of drug as solid solution to improve the dissolution rate by decreasing the crystallinity. Among these the most promising method for promoting dissolution is the use of liquisolid compacts.

The term 'liquisolid systems' (LS) is a powdered form of liquid drug formulated by converting liquid lipophilic drug or drug suspension or solution of water-insoluble solid drug in suitable nonvolatile solvent systems, into dry looking, nonadherent, free-flowing, and readily compressible powdered mixtures by blending with selected carrier and coating materials.

Cellulose, starch, and lactose are used as the carrier materials, whereas silica powder is used as the coating material. The good flow and compression properties of LS may be attributed due to large surface area and fine particle size

of these carrier and coating materials. Hence LS compacts containing water-insoluble drugs expected to display enhanced dissolution characteristics and consequently improved oral bioavailability.[1]

Lovastatin is an inactive lactone, and hydrolyzed to the corresponding β-hydroxy acid form, which are a principal metabolite and an inhibitor of 3-hydroxy-3-methylglutaryl-Coenzyme A (HMG-CoA) reductase. Chemically identified as [1S-[1a(R*), 3a, 7b; 8b(2S*, 4S*), 8ab]] -1,2,3,7,8,8a- hexahydro-3, 7-dimethyl-8 -[2-(tetrahydro-4 -hydroxy-6-oxo-2H-pyran-2-yl ethyl]-1-naphthalenyl 2-methylbutanoate. The present investigation was an attempt to improve the dissolution rate of Lovaststin by liquisolid compacts.[2]

2. MATERIALS AND METHODS

2.1. Materials

Lovastatin was provided by Aurobindo Pharma Ltd, Hyderabad. Avicel pH 102 and Aerosol 200 was gift sample from Alpha med Pvt Ltd. Peg 400 and Propylene glycol was purchased from SD Fine Chemicals, Mumbai. Starch was purchased from High media laboratories, India and all other materials used in this study were of analytical and pharmaceutical grade.

Methods

1. Solubility studies

For the selection of best non volatile solvents solubility studies are used, in this procedure, pure drug was dissolved in two different non volatile solvents (propylene glycol and polyethylene glycol 400) and in 0.1 N HCl with 0.5% SLS (w/v) and distilled water. Excess amount of pure drug was added to the above solvents. From this obtained saturation solution were shaken on the rotary shaker for 48 hours at 25^0C under constant vibration. After 48 hours period the saturated solution were filtered through a filter paper, and analyzed by UV spectrophotometer.[3]

2. Calculation of loading factor (L_f)

Loading factors were calculated for different carriers, using various solvents. By using formula L_f = W/Q (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. If the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder.[4]

PREPARATION OF LIQUISOLID TABLETS

Preparation of drug solution: For the preparation of liquisolid compacts of lovastatin, propylene glycol as non-volatile solvent chosen for dissolving the drug (lovastatin 20 mg). MCC as carrier and colloidal silica as the coating material was selected for the preparation of liquisolid compacts. Various ratios of carrier and coating materials were selected. According to solubility of Lovastatin desired quantities of drug and Propylene glycol were accurately weighed in a beaker and then stirred constantly, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Mixing: The mixing procedure was conducted in three stages. During the first stage, the system was blended at an approximate mixing rate of one rotation/sec for approximately one minute in order to evenly distribute the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min. The liquid powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off from mortar surfaces by means of aluminium spatula, and then the powder was compressed as tablets[7-9]. Similar formulations were prepared by using starch as carrier materials

The composition of Lovastatin liquisolid formulations is given in table no.1

Table 1: Composition of Lovastatin liquisolid formulations

Formulation	Drug:propylene glycol	R	Lf	MCC (mg)	Starch(mg)	Silica(mg)	Sodium starch glycolate(mg)
F1	1:3	5	0.4	200	-	40	10
F2	1:3	10	0.4	200	-	20	10
F3	1:3	15	0.4	200	-	13.33	10
F4	1:3	20	0.4	200	-	10	10
F5	1:4	5	0.4	200	-	40	10
F6	1:4	10	0.4	200	-	20	10
F7	1:4	15	0.4	200	-	13.33	10
F8	1:4	20	0.4	200	-	10	10
F9	1:3	5	0.5	-	200	40	10
F10	1:3	10	0.5	-	200	20	10
F11	1:3	15	0.5	-	200	13.33	10
F12	1:3	20	0.5	-	200	10	10
F13	1:4	2	0.5	-	200	40	10
F14	1:4	10	0.5	-	200	20	10
F15	1:4	15	0.5	-	200	13.33	10
F16	1:4	20	0.5	-	200	10	10

3. Flow properties of liquisolid system (Precompression parameters)

The flow properties of liquisolid system were estimated by determining the angle of repose, Carr's index and Hausner's ratio. The angle of repose was measured by the fixed funnel method. The bulk density and tapped densities were determined for the calculation of Hausner's ratio and Carr's index[5,6].

INVITRO EVALUATION OF LOVASTATIN LIQUISOLID TABLETS

Post compression parameters

Post compression parameters include, thickness , Weight variation, hardness, friability, disintegration time and drug content uniformity were conducted for prepared liquisolid tablets.

Dissolution test of Lovastatin liquisolid tablets

Drug release from Lovastatin liquisolid tablets was determined by using dissolution test Unit (USP type II (paddle)). The dissolution study was carried out in 900 ml of 0.1N Hcl with 0.5% SLS(w/v) as the dissolution medium at 37˚C ± 0.5˚C and 50 rpm.

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 20, 30, 45 and 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV-spectrophotometer. The concentration was calculated using standard calibration curve.[3]

Fourier transform infrared (FTIR) spectroscopy

The FTIR samples (Lovastatin, MCC, starch and liquisolid formulations) were recorded, using FT-IR system in the frequency range of 4000–400 cm^{-1} at 4 cm^{-1} resolution. In this technique samples were prepared in KBr disc (2 mg sample in 200 mg KBr).[3]

Stability studies

Stability studies were carried out according to ICH guidelines. The optimized formulation of liquisolid tablets were kept at different temperatures i.e., 30 ± 2^0 C and 40 ± 2^0C for 45 days. The parameters like physical characterization and % content of uniformity were evaluated for regular intervals of 15days.

RESULTS AND DISCUSSION

Solubility studies

The solubility of Lovastatin in Propylene glycol, PEG-400, 0.1 N HCl with 5% SLS and distilled water, was given in the table 2. The results shows that the Lovastatin has highest solubility in Propylene glycol then followed by PEG-400, 0.1 N HCl with 5% SLS and finally in distilled water.

Precompression studies of the liquisolid system

Powder flow is a complicated matter and is influenced by so many interrelated factors includes physical, mechanical as well as environmental factors[6]. Therefore, The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and

tapped), compressibility index and their values were shown in Table 3. The apparent bulk density and tapped bulk density values ranged from 0.279 to 0.335 and 0.350 to 0.421 respectively. The results of angle of repose and compressibility index (%) ranged from 18.54±1.6 to 38.55±1.3 and 16.3 to 22.3 respectively. The results of angle of repose (<40) and compressibility index (<23) indicates fair to passable flow properties of the powder mixture. Finally, formulations were proven to be acceptably flowing according to either the angle of repose, Carr's index and Hausner's ratio. Finally they were compressed into tablets and subjected for further evaluations.

In vitro evaluation of liquisolid compacts

All the liquisolid tablets were evaluated for their post compression parameters. In weight variation test, all the liquisolid tablets had acceptable pharmacopoeial limit for the tablets of not more than 7.5% of the average weight. The mean hardness of each liquisolid formula was determined and proving that all the liquisolid tablet formulae had acceptable hardness. The high compressibility and compactness of microcrystalline cellulose can be explained by the nature of the microcrystalline cellulose particles themselves which are held together by hydrogen bonds.

All the Lovastatin liquisolid tablets had acceptable friability. Since all the prepared formulae met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and shipment. The disintegration time for all the liquisolid tablets was found to be within the pharmacopoeial limits. The drug content uniformity for all the liquisolid formulations was found to be in the limits of 93.1±0.4 to 99.36±0.61. All the results of postcompression parameters were shown in table no.4.

Invitro drug release studies of liquisolid compacts

The percent of Lovastatin released from liquisolid compacts containing varying amounts of carrier and coating materials (from F1 to F16) was found to vary from 2.05±0.22 to 90.34± 0.58 in 10 min (Figure 1,2, 3 and 4). This indicates the fast release of drug is observed from above formulations. The optimized formulation F16 showed the 90.34 ± 0.58 drug release in 10 min where as the marketed tablets (control) showed 23.2±0.76 in 10 min (Figure 5). Thus the formulation F16 was considered better among other formulations to produce fast release of the Lovastatin. The percent drug release in 10 min (Q_{10}), initial dissolution rate (IDR) for optimized formulation were 90.34±0.58, 9.034%/min. These were very much higher compared to marketed tablet (23.2±0.76%, 2.32%/min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 3.89±0.03. The DE was found to be 85.32 and it is increased by 4 times with optimized liquisolid formulations compared to marketed tablets (Table 9). Overall increase in the dissolution performance of the optimized formulations described in terms of dissolution parameters (IDR, DE, RDR) compared to marketed tablets could be due to the lesser disintegration time and increased wetting properties and surface area available for drug dissolution.

The most important observation is that Propylene glycol containing formulations had higher drug dissolution rate than the direct compressed tablet. In case of liquisolid tablets, the surface of drug available for dissolution is related to its specific molecular surface which by any means, is much greater than that of the Lovastatin particles delivered by the plain, directly compressed tablets. Therefore, the hypothesis that the significantly increased surface of the molecularly dispersed Lovastatin in the liquisolid tablets may be chiefly responsible for their observed higher and consistent drug dissolution rates appears to be fundamentally valid[15]. All the results were shown in table no. 5-10.

Fourier transform infrared (FTIR) spectroscopy studies

The FTIR studies were done for pure drug and the optimized liquisolid formulations (F16). The results were showed that there is no interaction between the drug and excipients. Results were shown in table no.11

Stability studies

Stability studies for the optimized tablets were carried out at a temperature of 40±2^{o} C and 30±2^{o}C for a period of 45 days. Tablets were evaluated for physical appearance, assay. An average drug content of the tablets was 99.82% w/w and 99.5% w/w. Tablets have not shown any significant change during storage. Hence it was concluded that the optimized tablets have good stability during their shelf life.

Table 2: Solubility studies of Lovastatin in various solvents

S. No.	Solvent	Solubility(mg/ml)
1.	Propylene glycol	16.33
2.	Poly ethylene glycol-400	9.72
3.	0.1 N HCl with 5% SLS (w/v)	6.35
4.	Distilled water	0.0004

Table 3: Evaluation of pre compression parameters of liquisolid compacts.

Formulation	Angle of repose	Bulk density (gm/cc^3)	Tapped density (gm/cc^3)	Carr's index (%)	Hausner's ratio
F1	18.54±1.6	0.291±0.21	0.358±0.44	18.7±0.36	1.23±0.02
F2	23.35±1.2	0.292±0.32	0.353±0.32	17.2±0.6	1.20±0.01
F3	27.12±1.1	0.320±0.47	0.389±0.35	17.73±0.43	1.21±0.01
F4	34.23±1.0	0.325±0.34	0.403±0.28	19.35±0.33	1.24±0.01
F5	37.56±1.6	0.325±0.3	0.378±0.23	16.3±0.42	1.16±0.02
F6	38.31±1.9	0.312±0.2	0.387±0.41	19.3±0.22	1.24±0.02
F7	38.5±1.3	0.323±0.31	0.402±0.33	19.6±0.3	1.24±0.01
F8	32.82±1.1	0.302±0.4	0.403±0.28	16.8±0.23	1.20±0.01
F9	35.84±1.2	0.310±0.34	0.403±0.42	21±0.43	1.26±0.02
F10	34.87±1.6	0.324±0.23	0.401±0.25	19.2±0.42	1.23±0.02
F11	28.37±1.0	0.322±0.31	0.397±0.43	18.8± 0.34	1.23±0.02
F12	26.54±1.8	0.279±0.61	0.352±0.27	20.7±0.26	1.26±0.02
F13	30.12±1.1	0.301±0.34	0.387±0.32	22.2±0.32	1.28±0.02
F14	34.22±1.5	0.323±0.36	0.421±0.35	19.4±0.45	1.30±0.01
F15	35.25±1.2	0.320±0.38	0.412±0.32	22.3±0.43	1.28±0.01
F16	34.23±1.1	0.318±0.32	0.350±0.62	18.4± 0.51	1.10±0.03

Data represents Mean ± S.D (n=3)

Table 4: Evaluation of post compression parameters of liquisolid compacts.

Formulation code	Weight variation (mg)	Thickness (mm)	Hardness (kg/cm^2)	Friability (%)	Disintegration time(sec)	Content of uniformity (%)
F1	325.3±2.15	4.9±0.015	3.8±0.015	0.045±0.04	123±2.8	93.9±0.65
F2	306.5±1.75	4.51±0.01	3.38±0.07	0.19±0.06	160±5	94.35±0.5
F3	301.2±1.92	4.81±0.01	3.02±0.06	0.3±0.090	170±4	93.7±0.20
F4	299.75±0.5	4.53±0.05	4.0±0.064	0.15±0.030	115±5	93.76±0.3
F5	347.7±1.1	4.93±0.05	3.36±0.15	0.19±0.03	115±5	95.1±1.31
F6	328.6±0.7	4.80±0.01	3.2±0.1	0.20±0.32	99.3±5.03	94.7±0.30
F7	319.9±1.9	4.6±0.01	3.41±0.18	0.28±0.64	90±5	95.4±0.85
F8	300.6±0.1	4.55±0.02	4.06±0.11	0.29±0.04	120±2	97.06±0.6
F9	325.7±1.9	4.6±0.005	4.13±0.20	0.22±0.026	130±5	93.1±0.4
F10	306.5±1.3	4.4±0.02	3.5±0.1	0.32±0.040	154±4.5	94.6±1.05
F11	301.2±1.1	4.82±0.11	3.53±0.05	0.30±0.07	138.3±5	94.4±1.35
F12	302.5±1.2	4.95±0.05	3.39±0.16	0.28±0.064	154.3±3.5	92.0±0.71
F13	346±0.15	4.7±0.07	3.8±0.25	0.27±0.06	138.3±2.8	99.36±0.6
F14	328.6±1.05	4.5±0.12	3.2±0.16	0.26±0.04	140±5	98.56±0.9
F15	319.9±0.12	4.5±0.19	3.7±0.35	0.21±0.01	144±3.5	95.56±0.9
F16	300.7±0.12	4.8±0.01	3.4±0.1	0.34±0.02	141±3.6	98.33±0.5

Data represents Mean ± S.D (n=3)

Table 5: Dissolution profiles of formulations containing 1:3 Ratio of drug and solvent mixture drug solution by using Starch as carrier. Data represents Mean ± S. D (n=3)

TIME (min)	CUMULATIVE % DRUG RELEASE			
	F1	F2	F3	F4
5	2.05±0.22	3.22±0.25	13.63±0.45	16.98±0.65
10	2.54±0.85	8.68±0.16	21.36±0.82	22.24±1.52
20	3.51±1.04	11.81±1.43	28.12±1.73	38.61±0.45
30	4.51±0.42	22.74±1.32	33.91±0.51	47.63±1.37
45	5.85±0.65	27.85±2.21	50.33±0.73	65.60±1.38
60	6.96±0.65	37.54±0.58	53.12±0.04	68.10±0.15

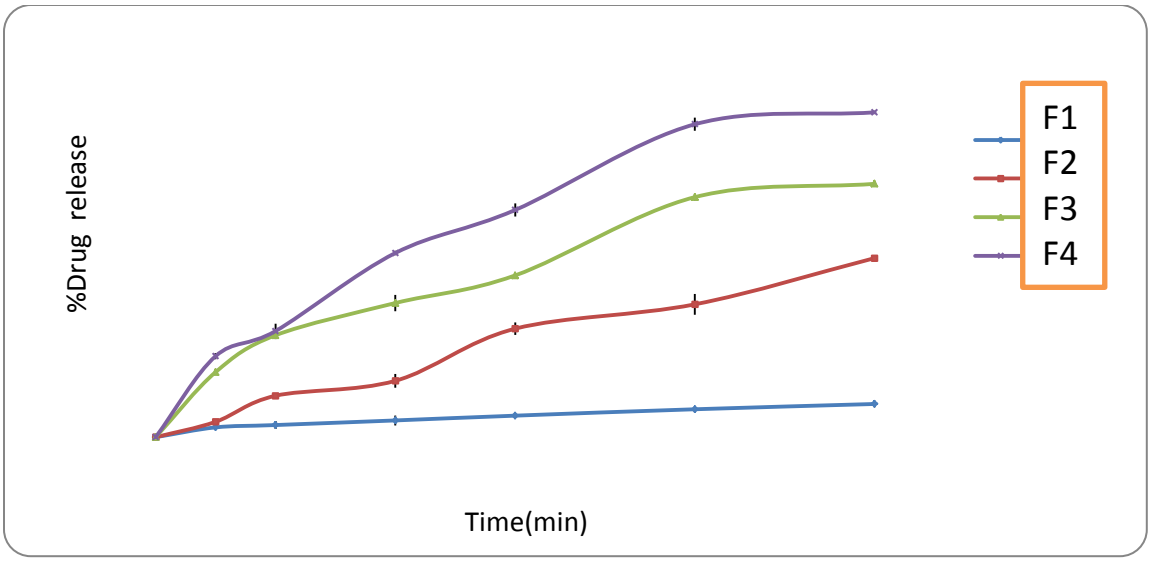


Fig. 1: Dissolution profiles of formulations containing 1:3 Ratio of drug and solvent mixture drug solution by using Starch as carrier. Data represents Mean± S. D (n=3)

Table 6: Dissolution profiles of formulations containing 1:4 Ratio of drug and solvent mixture drug solution by using Starch as carrier.

TIME (min)	CUMULATIVE % DRUG RELEASE			
	F5	F6	F7	F8
5	11.39±1.11	12.4±0.61	17.23±0.40	26.46±0.61
10	19.77±0.31	20.72±0.25	21.51±0.72	37.02±0.61
20	32.07±0.82	34.77±0.60	39.84±0.54	51.96±0.50
30	40.63±0.44	44.28±1.06	47.03±0.86	62.01±0.60
45	44.96±0.04	51.81±0.46	54.81±0.60	73.36±0.61
60	49.83±0.40	64..88±0.31	66.72±1.86	74.65±0.45

Data represents Mean ± S. D (n=3)

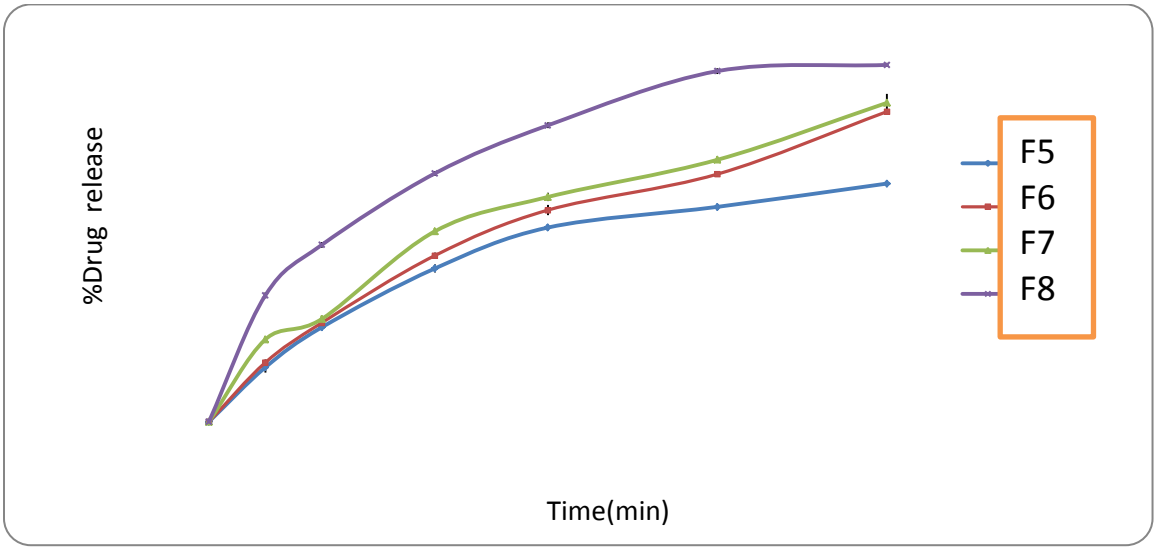


Fig. 2: Dissolution profiles of formulations containing 1:4 Ratio of drug and solvent mixture drug solution by using Starch as carrier. Data represents Mean ± S. D (n=3)

Table 7: Dissolution profiles of formulations containing 1:3 Ratio of drug and solvent mixture drug solution by using micro crystalline cellulose as carrier.

TIME (min)	CUMULATIVE % DRUG RELEASE			
	F9	F10	F11	F12
5	2.39±0.55	2.7±0.6	9.37±1.03	15.11±0.17
10	2.65±0.76	15.2±1.75	16.69±1.3	36.89±0.50
20	4.31±1.21	16.4±1.31	23.17±2.03	37.86±0.93
30	21.73±1.45	25.56±1.85	30.69±1.11	38.25±0.73
45	37.87±1.96	46.07±1.29	46.97±2.56	50.83±0.96
60	51.71±0.71	57.71±1.85	62.8±1.8	68.82±0.55

Data represents Mean ± S. D (n=3)

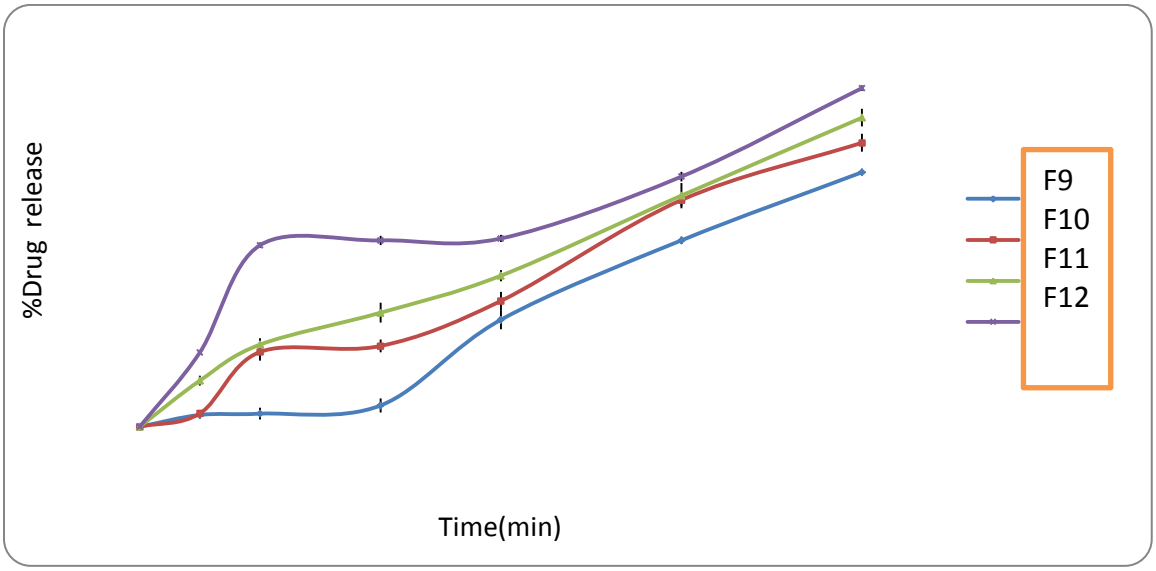


Fig. 3: Dissolution profiles of formulations containing 1:3 Ratio of drug and solvent mixture drug solution by using micro crystalline cellulose as carrier. Data represents Mean ± S. D (n=3)

Table 8: Dissolution profiles of formulations containing 1:4 Ratio of drug and solvent mixture drug solution by using micro crystalline cellulose as carrier.

TIME (min)	CUMULATIVE % DRUG RELEASE			
	F13	F14	F15	F16
5	30.24±0.74	31.48±0.42	41.78±1.31	49.20±0.78
10	38.99±1.1	50.01±0.11	69.3±0.89	90.34±0.58
20	61.27±1.01	65.51±0.54	87.65±2.2	92.04±0.18
30	72.48±1.77	85.90±0.94	90.6±1.39	94.25±0.76
45	86.65±1.16	87.66±0.20	92.53±0.45	96.44±0.58
60	90.71±0.55	92.02±0.32	93±0.1	98.04±0.24

Data represents Mean ± S. D (n=3)

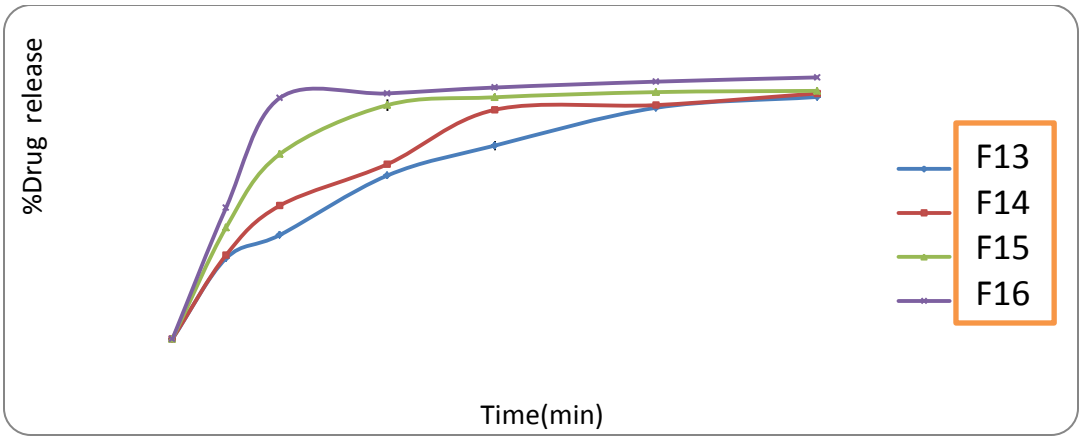


Fig. 4: Dissolution profiles of formulations containing 1:4 drug solution Ratio of drug and solvent mixture by using micro crystalline cellulose as carrier. Data represents Mean ± S. D (n=3)

Table 9: Dissolution profile of direct compressed tablet (DCT), marketed (AZTATIN®) and F16

TIME (min)	CUMULATIVE % DRUG RELEASE		
	DCT	AZTATIN®	F16
5	1.97±0.65	10.3±1.01	49.20±0.78
10	2.43±0.78	23.2±0.76	90.34±0.58
20	3.47±1.2	30.13±0.52	92.04±0.18
30	4.39±0.87	37.8±1.17	94.25±0.76
45	5.79±1.43	41.02±1.3	96.44±0.58
60	6.5±0.52	48.01±0.47	98.04±0.24

Data represents Mean ± S. D (n=3)

Table 10: Dissolution parameters (D.R, D.E and R.D.R) of optimized formulation (F16), Marketed formulation and directly compressed tablets

Formulation	Q_{10}	D.R (µg/min)	Initial Dissolution Rate (%/min)	D.E	R.D.R
Optimized (F16)	90.34±0.58	451.7	9.34	85.32	3.89±0.03
Marketed tablet (AZTATIN®)	23.2±0.76	116	2.32	20.2	
DCT	2.43±0.78	12.15	0.24	3.83	

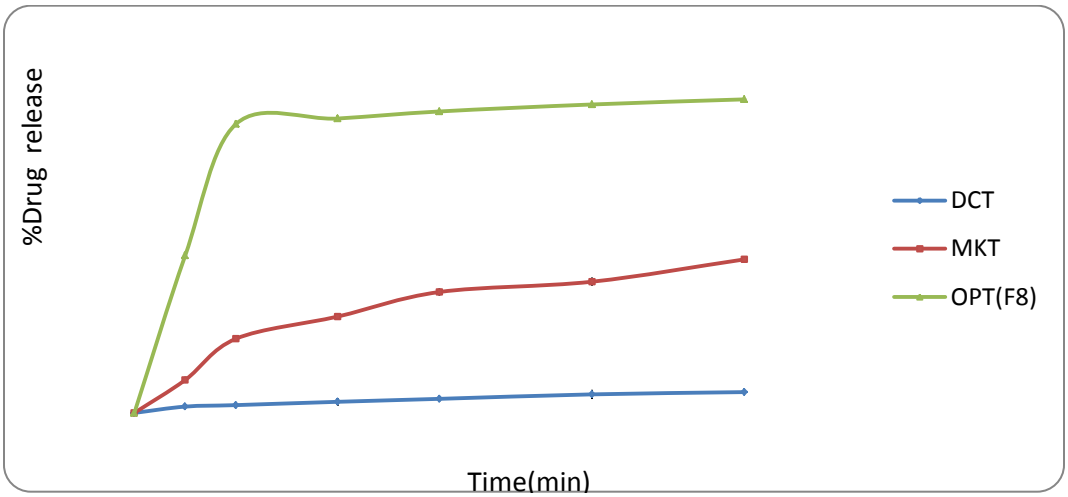
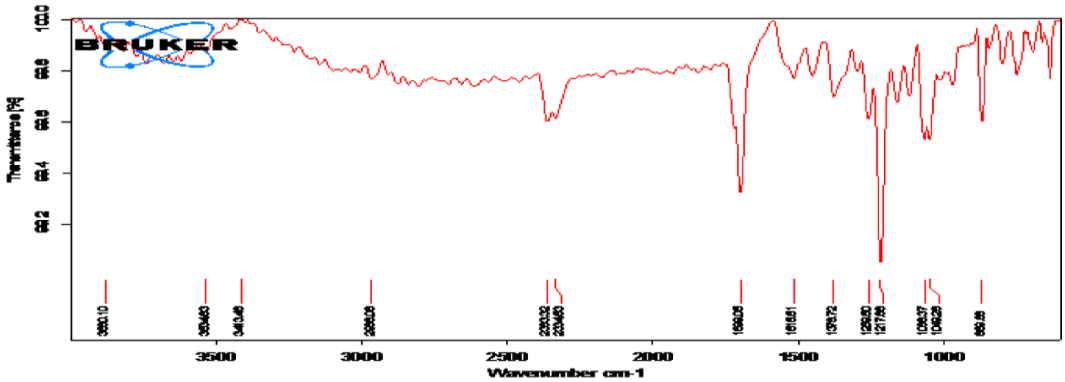


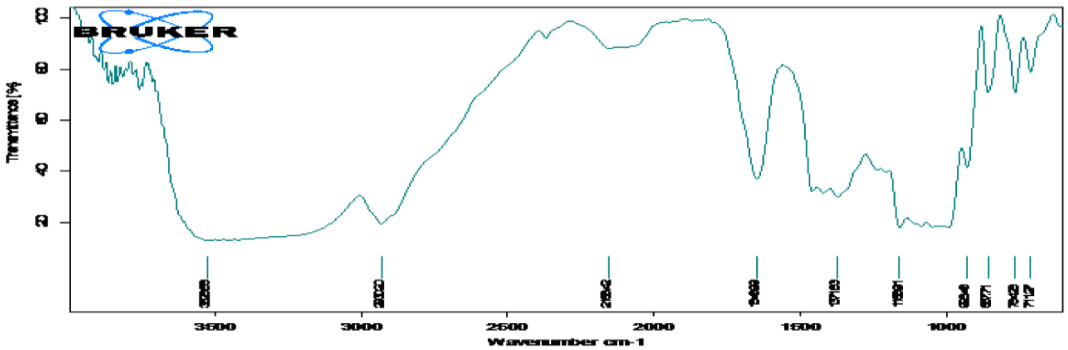
Fig. 5: Dissolution profiles of Direct compressed tablet (DCT), marketed (AZTATIN) and F16. Data represents mean ± S. D (n=3)

Table 11: FTIR vibrations in Lovastatin drug

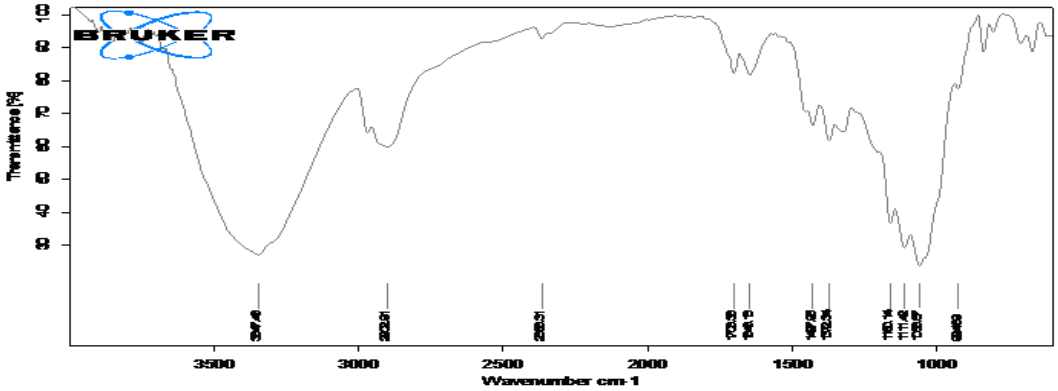
3534 cm^{-1} & 3413 cm^{-1}	Alcohol O-H stretching
3016 cm^{-1}	Olefinic C-H stretching
2966 cm^{-1}	Methyl C-H asymmetric stretching
2363, 2334 cm^{-1}	Alkynes -c-c-
1699 cm^{-1}	Lactone and ester carbonyl stretch
1212 cm^{-1}	Ester C-O-C asymmetric bend
1066 cm^{-1}	Lactone C-C symmetric bend
1049 cm^{-1}	Ester C-O-C symmetric bend
869 cm^{-1}	Trisubstituted olefinic C-H



FTIR of Lovastatin



FTIR of Formulation containing starch as carrier



FTIR of Formulation containing microcrystalline cellulose as carrier

CONCLUSION

From the above results, it was concluded that, Lovastatin liquisolid tablets showed higher dissolution profiles than the directly compressed tablet and marketed formulation (AZTATIN). A clear relationship was found in between the invitro drug release, amount of solvent and type of carrier used. It was found that the rate of drug release was increased with increased ratio of solvent with respect to drug incorporated. The burst release of drug was observed with microcrystalline cellulose but it was hindered incase of starch. Finally, Liquisolid technique can be used as a promising approach to improve the solubility and dissolution of Lovastatin, a poorly insoluble drug.

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