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Dissolution Enhancement of Lovastatin by Liquisolid Compact Technique and Study of Effect of Carriers

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Abstract: Lovastatin is a poorly soluble, BCS class II drug belonging to the category of anti-hyperlipidemics having poor bioavailability (<5%).The present study is designed to enhance the dissolution rate and bioavailability of Lovastatin by Liquisolid compacts and to evaluate the effect of carriers on drug dissolution rates. Lovastatin Liquisolid tablets were prepared by using different carriers namely PEG-4000, PEG-6000, HPMC E-15, starch and microcrystalline cellulose. Aerosil was used as coating material. Propylene glycol was chosen as nonvolatile liquid vehicle and Polyplasdone as disintegrant. The mathematical model was applied precisely to calculate the amount of carrier and coating ratios. The prepared liquisolid systems were evaluated for their micromeritic and tabletting properities and they are found to be in the acceptable limits.Drug-polymer interaction studies like FTIR and DSC were performed and results showed that there were no possible interaction between drug and the excipients. It was found that Liquisolid tablets formulated with starch as carrier produced higher dissolution profile with acceptable tablet properties compared to conventional tablet. In conclusion, development of Lovastatin Liquisolid tablets is a good approach to enhance the dissolution rate.
Keywords: Lovastatin, Bioavailability, Carriers, Mathematical model, Dissolution rate

Introduction

Most of the therapeutic agents elicit systemic effects through the oral route as it holds more than a few advantages like its ease of ingestion, versatility and most importantly high patient compliance compared to many other routes[1]. But certain class II drugs [2] are expected to have a variable dissolution profile due to poor solubility, and these even in turn affect the absorption.

Different techniques are employed to enhance the dissolution of poorly soluble drugs like use of water-soluble salts and polymorphic forms, solid dispersions, reducing particle size to increase the surface area, pH adjustments, co-precipitation, polymeric modification, lyophilization, microencapsulation, inclusion of drug solutions or liquid drugs into soft gelatin capsules, solubilization in a surfactant system, Liquisolid compacts and manipulation of solid state of drug[3,4]. Among various techniques to achieve the better dissolution rates Liquisolid technology is one of the novel and most promising techniques for promoting drug dissolution [5]. Since last few years, the work is been carried on development of Liquisolid compacts to enhance dissolution rate and efficacy of poorly soluble drugs. The term "Liquisolid medication" implies oily liquid drugs and solutions or suspensions of water-insoluble solid drugs carried in suitable nonvolatile solvent systems . Using this formulation technique, a liquid medication may be converted into a dry looking, non-adherent, free flowing and compressible powder by a simple blending with selected powder excipients referred to as the carrier and coating materials.

Lovastatin((1*S*,3*R*,7*S*,8*S*,8a*R*)-8-{2-[(2*R*,4*R*)-4-hydroxy-6-oxooxan-2-yl]ethyl}-3,7dimethyl1,2,3, 7,8,8a-hexahydronaphthalen-1-yl (2*S*)-2-methylbutanoate) is a poorly soluble drug, used for lowering cholesterol (hypolipidemic agent) in those patients suffering with hypercholesterolemia. It's a prodrug and

inhibitor of 3-hydroxy-3methylglutaryl coenzyme A reductase (HMG-CoA reductase). It acts by inhibiting cholesterol synthesis and subsequently leads to up regulated production of hepatic low-density lipoprotein receptors[6]. It has a shorter half life of 1.1-1.7 hrs and bioavailability <5% , insoluble in water (0.4 µg/ml).

The goal of the present study was to enhance the dissolution rate of Lovastatin, a poorly soluble drug by Liquisolid compact technique and effect of carriers were studied. Finally the formulated and evaluated Liquisolid preparations were characterized for drug polymer interaction studies like DSC, FTIR and stability studies were conducted.

Materials and Methods:

Materials:

Lovastatin was provided by MSN Laboratories, Hyderabad, India. Carriers like PEG 4000, PEG6000, HPMC-E15, and solvents like PEG-400, PEG-200 and propylene glycol were provided by Srichandra chemicals, Hyderabad, India. All other chemicals used were of analytical grade.

Solubility Studies

Solubility studies of Lovastatin were carried out in propylene glycol, PEG-200, PEG-400, distilled water and 0.1N HCl buffer. Saturated solutions[7] were prepared by adding surplus amount of drug to the vehicles (10ml) and subjected to constant shaking for 48h at 25^0C. Then after this time period the solutions were filtered through a 0.45µm Millipore whatmann filter, diluted and analyzed by UV-spectrophotometer (Elico Ltd.SL 210) at a wavelength of 238nm.

Application of the Mathematical Model for Designing the Liquisolid Systems

In this study propylene glycol was used as liquid vehicle; PEG-4000, PEG-6000, HPMC E-15, MCC and starch were used as the carriers. Aerosil was used as coating material to improve the flow property due to its size, shape and also due to glidant property[8]. To attain and to calculate the appropriate quantities of excipients required for good flowability and compressibility of Liquisolid compacts, the mathematical model of Liquisolid systems was employed. This mathematical model was based on new powders properties like the flowable liquid retention potential (Φ-value) and compressible liquid retention potential (Ψ-number). According to the new theories (Spireas & Aulton)[9,10] particles which possess porous surface with high absorption properties may be used as the carrier material like starch and lactose. As increasing moisture content of carriers results in decreased powder flowability, So as to maintain the powder flowability coating material is required to cover the surface[11]. Depending on the excipients ratio (R) or the carrier: coating ratio of the powder system used, where

Eq.1. R =amount of carrier (Q)/amount of coating (q**)**

R represents the ratio between the weights of carrier (Q) and coating (q) materials of the formulation. An acceptably flowing and compressible Liquisolid system can be prepared only if a maximum liquid on the carrier material is not exceeded or within the limit; such a distinctive amount of liquid is termed the liquid load factor (L_f) and defined as the ratio of the weight of liquid medication (W) over the weight of the carrier powder (Q) in the system, which should be possessed by an acceptably flowing and compressible Liquisolid system. i.e.

Eq.2. $$L_f = W/Q$$

Spireas et al. used the flowable liquid retention potentials (Φ -values) of powder excipients to calculate the required ingredient quantities, Hence, the powder excipients ratios R and liquid load factors L_f of the formulations are related as follows:

Eq.3. $$L_f = \Phi + \Phi\,(1/R)$$

So in order to calculate the required weights of the excipients used, first, from equation (3), Φ and Φ are constants, therefore, according to the ratio of the carrier/ coating materials (R), L_f was calculated from the linear relationship of L_f versus 1/R. Next, according to the used liquid vehicle concentration, different weights of the liquid drug solution (W) will be used. So, by knowing both L_f and W, the appropriate quantities of carrier (Q) and coating (q) powder materials necessary to convert a given amount of liquid medication (W) into an acceptably flowing and compressible Liquisolid system, could be calculated from equations (1) and (2)

Methods:

Preparation of Liquisolid Compacts and Conventional Tablet

Preparation of drug solution

Liquisolid compacts of Lovastatin denoted as LS-1 to LS-9 were prepared by choosing a non-volatile solvent for dissolving the drug. From the results of solubility studies propylene glycol is chosen as the liquid vehicle due to higher solubility profile of the Lovastatin, PEG-6000 as carrier and Aerosil as the coating material were selected. With consideration to solubility of Lovastatin desired quantities of drug and propylene glycol (1:0.5, 1:1, 1:2, 1:3 & 1:4) 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 best concentration of calculated quantity of PEG 6000 carrier contained in a mortar, then replace the PEG 6000 with other carriers like PEG-4000, HPMC E15, starch & MCC and the effect of the carriers is said to be noted.

Mixing and Compression

The mixing procedure includes three stages. In the first stage, the liquid medication is said to be evenly distributed into the powdered drug at mixing rate of one rotation/sec for one minute. In the second stage, calculated quantities of carrier and coating material was added to the system and mixed 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 the mortar surfaces by means spatula, then finally Liquisolid formulation is said to be compressed. Similar formulations are prepared by using HPMC-E15, PEG 4000, MCC and starch as carrier materials (Table.1).

Table.1 Formulation of Lovastatin Liquisolid compacts(LS-1 to LS-9)

LS	LOVASTATIN (mg)	R	Lf	PG	PEG 6000 (mg)	PEG 4000 (mg)	HPMCE15 (mg)	MCC (mg)	STARCH (mg)	LACTOSE (mg)	DISINTEGRANT (mg)	AEROSIL (mg)	UNIT DOSE (mg)
LS-1	20	20	0.02	10	447	-	-	-	-	70	30	22.38	600
LS-2	20	20	0.04	20	438	-	-	-	-	70	30	21.9	600
LS-3	20	20	0.09	40	419	-	-	-	-	70	30	20.95	600
LS-4	20	20	0.15	60	400	-	-	-	-	70	30	20	600
LS-5	20	20	0.18	80	428	-	-	-	-	70	30	21.4	650
LS-6	20	20	0.15	60	-	400	-	-	-	70	30	20	600
LS-7	20	20	0.15	60	-	-	400	-	-	70	30	20	600
LS-8	20	20	0.15	60	-	-	-	400	-	70	30	20	600
LS-9	20	20	0.15	60	-	-	-	-	400	70	30	20	600

A conventional formulation of Lovastatin was directly compressed into cylindrical tablets, each containing 20 mg drug. In addition, tablet contained the following powder excipients like starch, lactose and Polyplasdone.

Pre Compression Studies of Prepared Liquisolid Compacts

The powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density and compressibility index[12]. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following for

$$\mathbf{Tan\ \theta = h/r} \qquad (4)$$

In which, θ is angle of repose, h is height of the cone and r is radius of the cone base.

The tapping method was used to determine the tapped density, bulk density and percent compressibility index. The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formulas:

$$\mathbf{Carr's\ Index = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100} \qquad (5)$$

In which, ρ_b is bulk density and ρ_{tap} is tapped density.

Drug-Polymer Interaction Studies

DSC studies were carried out on pure drug, polymer and optimized formulation of Lovastatin and the thermograms were obtained using DSC (Perkin-Elmer, Shelton, USA). The analysis were performed under nitrogen (nitrogen flow rate 50 ml/min) in order to get rid of oxidative and pyrrolytic effects at a standard heating rate of 15ºC/min over a temperature range of 0ºC-500ºC. Further the infrared spectra studies of Lovastatin and optimized formulations recorded between 400 and 4000 cm^{-1} on FTIR spectrometer (Perkin Elmer FTIR, Perkin Elmer Inst. USA) to detect the drug-excipient interactions using KBr disk method.

Post Compression Characterization

The prepared tablets were studied for their physical properties like weight variation, hardness, friability, and disintegration test and drug content uniformity. For estimating weight variation, 20 tablets from each formulation were randomly selected and average weight was determined. Then individual tablets were weighed and was compared with average weight using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan). The strength of tablet is expressed by measuring hardness (Kg/cm^2). The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined in by Roche friabilator (Electro lab, Mumbai, India) Preweighed samples of tablets was placed in the friabilator and subjected to 100 revolutions i.e, for 4 min at 25 rpm. The tablets were dedusted and reweighed.

Disintegration test

The disintegration test was carried out using disintegration test apparatus (USP Electrolab DT) as specified in the Indian Pharmacopoeia[13] and the results for all the batches of Lovastatin Liquisolid compacts are shown in Table.3.

Table-3 Physical properties of Lovastatin tablets. All values represent mean standard deviation,n = 20.*All values represent mean standard deviation n = 6;All values represent mean standard deviation, n = ± 3**

LS	Weight variation*	Friability(%)	Hardness**(kg/cm^2)	Disintegration time (sec)
LS-1	599±0.12	0.61	4.3±1.14	54±0.65
LS-2	601±0.34	0.567	3.9±0.34	48±1.10
LS-3	599±0.25	0.674	3.2±0.22	45±1.34
LS-4	598±0.14	0.68	3.5±1.30	42±0.42
LS-5	653±0.21	0.59	4.1±0.43	61±1.42
LS-6	599±0.25	0.56	3.6±0.42	57±1.30
LS-7	600±0.02	0.6	3.6±1.22	52±0.23
LS-8	602±0.11	0.598	3.8±1.02	49±0.57
LS-9	602±0.23	0.624	3.6±0.54	40±0.11

Determination of Drug Content

For estimation of drug content, ten tablets were crushed, and the sample of powder equivalent to 100 mg of drug was dissolved in suitable quantity of 0.1N HCl buffer Solution containing 1% sodium lauryl sulphate then the solution is filtered and diluted and drug content determined by UV-Visible spectrophotometer (Elico Ltd.SL 210) at 238 nm. The drug concentration was calculated from the calibration curve.

In-Vitro Dissolution Studies

Dissolution studies were carried out in USP Type II apparatus(Electrolab DT TDT 08L) at 50rpm in 900ml of 0.1N HCl containing 1% of Sodium laurlyl sulphate (SLS), and the temperature is maintained at 37 ± 0.5ºC**.** 5ml aliquot was withdrawn at the specified time intervals (5, 10, 15, 20, 25, 30, 45 and 60 min) and replaced with fresh dissolution media, and then these samples were filtered through whatmann filter paper and analyzed spectrophotometrically at 238nm. Dissolution studies were performed in triplica.

Calculation of Dissolution Parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 5 minutes (Q_5) was calculated. Initial dissolution rate (IDR) was calculated as percentage of drug dissolved over the first 5 minutes. Dissolution efficiency (DE) was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 5 minutes [14].

Stability studies

Stability studies of Liquisolid tablets were conducted as per specifications of FDA and ICH guidelines. The study was performed under accelerated stability conditions at 40˚C ± 2˚C/75% RH ± 5% RH for three months. The stored tablets were evaluated for Assay, hardness, disintegration time and dissolution rate.

Results and Discussion:

Solubility Studies

The solubility of Lovastatin in Propylene glycol, PEG-200, PEG-400, distilled water & 0.1NHCl is given in Table.2 the table shows that the Lovastatin has highest solubility in Propylene glycol.

Table.2 Solubility of Lovastatin in various liquid vehicles

Liquid vehicle	Solubility(% w/w)
Propylene glycol	12.84
PEG-200	6.646
PEG-400	5.415
Distilled water	0.703
0.1N HCl	0.168

Pre Compression Parameters

The powder mixtures of different formulations were evaluated for angle of repose, bulk density (apparent and tapped), and compressibility index. The apparent bulk density and tapped bulk density values ranged from 0.283±0.43 to 0.342±0.21and 0.356±0.46 to 0.398±0.23 respectively. The results of angle of repose and compressibility index (%) ranged from 26.12±1.15 to 32.24±1.21 and 17.091 to 22.650 respectively.

Drug-Polymer Interaction Studies

DSC studies were performed to understand the nature of the drug in the formulated tablets. Thermograms obtained for pure drug, starch, and optimized formulation were shown in Fig.1. The DSC of Lovastatin showed endothermic peaks equivalent to its melting point at 172.21^{0}C. Whereas thermograms of the optimized formulations did not show any significant shift in the endothermic peaks. The FTIR spectrum in Fig.2 of above mentioned excipients (starch) and optimized formulation were compared to that of pure

Lovastatin. The IR spectra of pure Lovastatin and optimized formulation of Liquisolid compact, exhibit peak at 1298 cm^{-1} ,1050 cm^{-1} is due to lactone and ester C-O-C bending vibration stretching, peaks at 1430 cm^{-1} is due to methyl and methylene bending, and peaks at 2364.3 cm^{-1} , 2930cm^{-1} is due methyl and methylene C-H stretching, though additional peaks were observed with optimized formulation which could be due to the presence of polymers[15,16]. Thus, conforms the structure of drug Lovastatin.

Figure.1 DSC studies of Pure drug(c), Starch(b) and Optimized formulation(a)

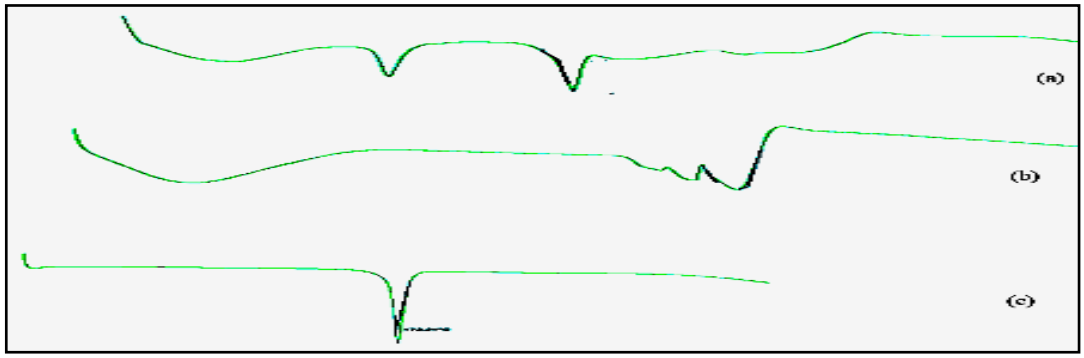
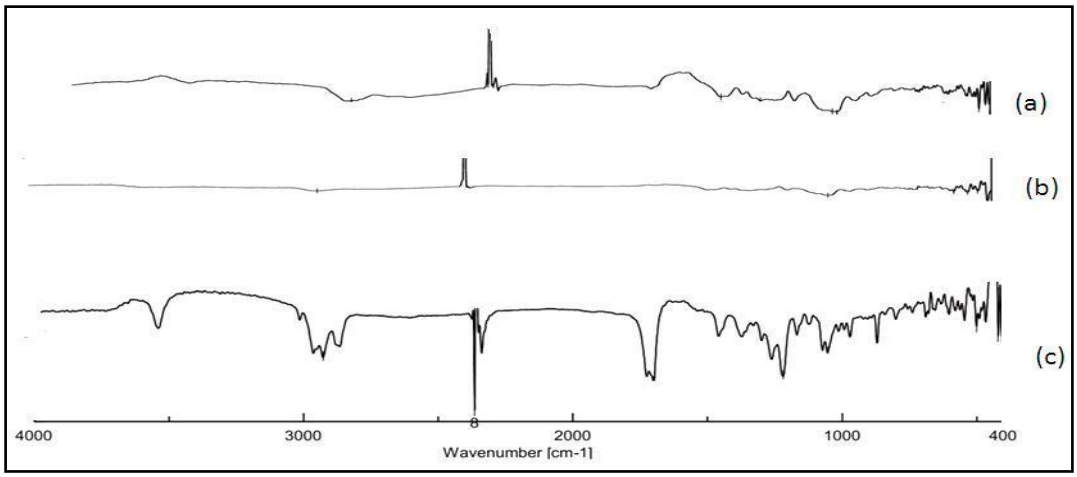


Figure.2 FTIR Studies of Pure drug (c), Starch(b), Optimized formulation(a)



Post Compression Parameters

The physical properties of Lovastatin are given in Table-3. In weight variation test, the pharmacopoeial limit for the tablets is not more than 5% of the average weight (USP). The hardness of the tablets was found to be in the range of 3.2±0.23 to 4.3±0.56 kg/cm^2. The Liquisolid tablets should be subjected to low compression force such that rapid tablet disintegration and drug dissolution are maintained at the same time. Another measure of tablets strength is friability. The percentage friability for all formulations was below 1%, indicating that the friability is within the prescribed limits such that they are expected to withstand fracturing and attrition during normal handling, packaging and transporting processes[17, 18].The tablets were found to contain 97.4±1.54 99.8±0.60 % of the labeled amount indicating uniformity of drug content.

In-Vitro Dissolution Study

The cumulative mean percent of Lovastatin released from Liquisolid compacts containing varying amounts of carrier and coating materials (from LS1 to LS9) was found to be varied from 15.14 ± 0.28 to 101.93 ± 0.34 in first 5min. The optimized formulation LS9 showed drug release of 101.93 ± 0.34 in first 5min, where as the Conventional tablets showed 29.5±0.11 in 5min. In Fig.3 a graph is plot between the Liquisolid formulations (LS-1to LS-5) & conventional tablet showing enhancement in the dissolution rate, whereas Fig.4 shows the effect of carriers on the dissolution rate (LS-4, LS-6 to LS-9) with respect to conventional tablet.

The initial dissolution rate (IDR) for optimized formulation and conventional formulation were 20.38%/min and 5.9%/min respectively. The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR).The RDR and DE was found to be 3.45±0.02 and 76.86 for optimized formulation(LS9)(Tab-4).This results were very much higher compared to conventional tablets. Hence, overall increase in the dissolution rate of all the optimized formulations described

in terms of dissolution parameters with respect to conventional tablet possibly due to improved disintegration time (40 ±0.11 sec) solubility/wetting of drug.

Figure.3. Comparision of drug release profiles of various Liquisolid formulation (LS-1 to LS-5) with respect to conventional formulation

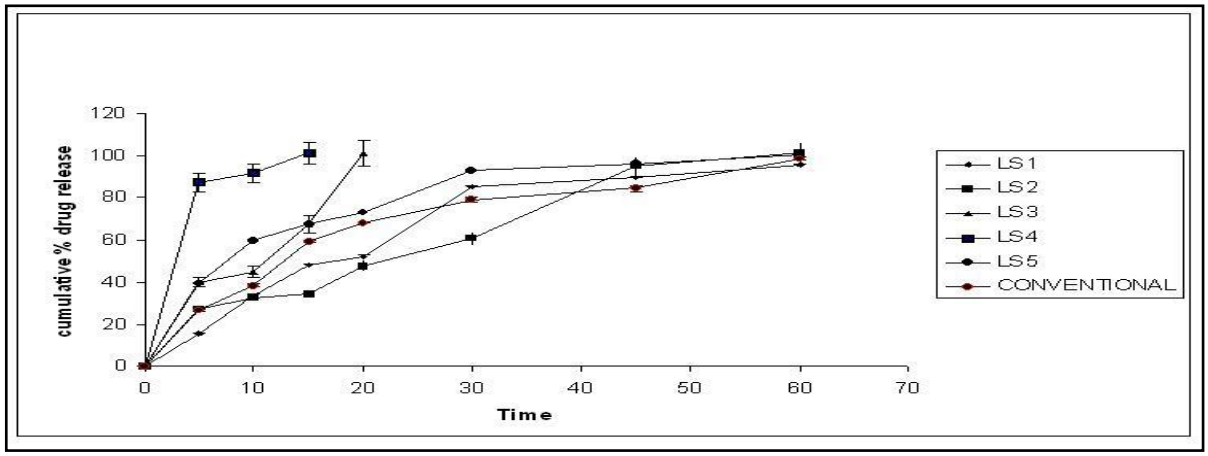


Figure.4. Effect of carriers on various Liquisolid formulations with respect to conventional formulation

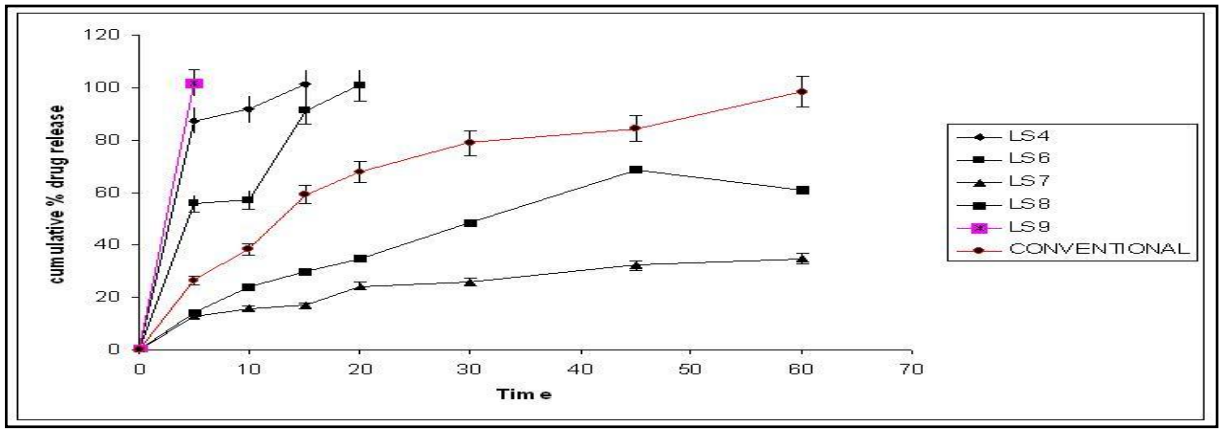


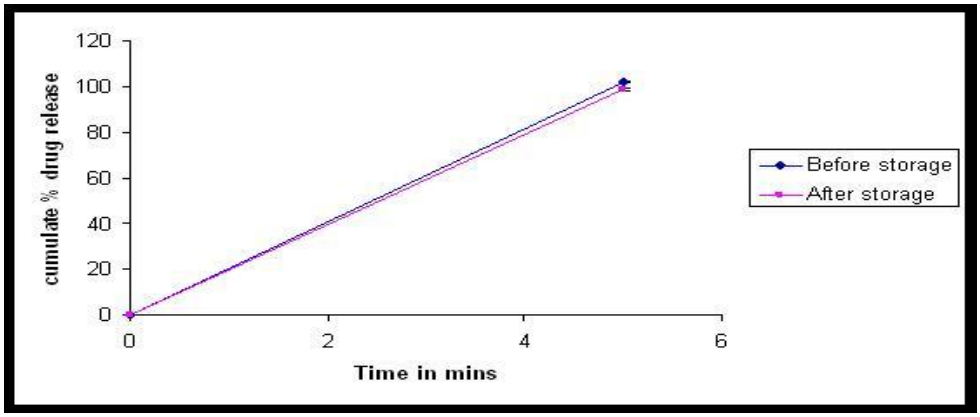
Table-4 Dissolution Parameters of optimized and conventional Lovastatin formulations.Q_5-percent drug release in 5 minutes, IDR-initial dissolution rate, DE-dissolution efficiency and *RDR* relative dissolution rate. * All values represent mean ± standard deviation, n=3.

OPTIMIZED FORMULATION	(Q5)*	IDR(%/min)	DE	RDR
LS4	87.5±0.34	17.5	51.5	2.96±0.03
LS6	57.2±0.22	11.44	32.16	1.93±0.03
LS7	12.8±1.2	2.56	8.34	0.43±0.11
LS8	14.11±0.23	2.82	8.73	0.47±0.14
LS9	101.93±1.34	20.38	76.86	3.45±0.02
CONVENTIONAL	29.5±0.11	5.9	16.95	----

Stability studies

Stability studies of Liquisolid tablets showed that there were no major difference in the assay (99±0.23%) hardness (3.6±0.46 kg/cm2) and disintegration time (40 ± 0.54 s) after storing the formulations for three months under accelerated storage conditions. The dissolution profile(Fig.5) of before & after storage Lovastatin Liquisolid compacts showed that there was no significant difference on drug release (P> 0.05).Thus, the prepared Liquisolid formulations are found to be stable.

Figure.5 Stability studies of optimized (LS-9) Liquisolid formulation



Discussion

In the present study Lovastatin Liquisolid tablets were prepared by using Propylene glycol as a non-volatile liquid vehicle. PEG-4000, PEG-6000, Microcrystalline cellulose, HPMC-E15, Starch were used as carrier materials and Aerosil as coating material in different ratios and they were evaluated for different pre and post compression parameters and drug release studies to find the optimized formulation that shows enhanced and fast dissolution rate.

From the solubility studies the results revealed that, the solubility of drug was highest in propylene glycol then followed by PEG-200, PEG-400, distilled water and poor in 0.1N HCl, which indicates the propylene glycol was better liquid vehicle. The results of angle of repose (<40) and Carr's index (<22) indicates fair to passable flow properties of the powder mixture. DSC and FTIR showed that there was no interaction between the drug and excipients. These was conformed from the results (presence of principal peaks) of IR spectral analysis of pure drug and optimized formulation, polymers, where as in DSC studies thermograms of the optimized formulation did not show any significant shift in the endothermic peak, indicating that there was no physical change in drug in the Liquisolid compacts.

The prepared tablets were studied for their physical properties like weight variation, hardness, friability, disintegration time and uniformity of drug content and they were said to be complied with pharmacopoeial limits. The average percentage deviation of all tablet formulations was found to be within the above mentioned limit and hence all formulations (LS-1 to LS-9) passed the uniformity of weight as per official requirements (India Pharmacopoeia 1996). From the physical characterization of all tablet formulations (LS-1 to LS-9) were uniform in hardness, friability and drug content uniformity and disintegration time was lower in case of LS-9. From the in vitro drug release studies, formulations LS-4 & LS-9 were considered better among other formulations (Liquisolid systems). From the calculations of DE and RDR, LS-9 formulation showed better improvement in dissolution and hence it is considered as optimized formulation. From these we can conclude that by changing the carrier in the same formulation the dissolution efficiency varies. Among all the carriers starch was found have better drug release followed by PEG-6000, PEG-4000 and it was poor in case of MCC and HPMCE-15. Overall increase in the dissolution performance of the optimized formulation was described in terms of dissolution parameters (IDR, DE, RDR) and compared with conventional tablet (CT). The improvement may be due to increased wetting properties, solubility and increased surface area of drug particles[19] in case of Liquisolid compacts. Stability studies confirmed that there were no considerable changes in assay, hardness, disintegration time & dissolution rate of prepared Liquisolid , hence they are found to be stable.

Conclusion

The observations showed that there was a poor dissolution rate in case of conventional formulation. Improvement of aqueous solubility in such a case is valuable goal to improve therapeutic efficacy. Thus, Lovastatin tablets formulated by using Liquisolid technique showed better enhancement in the dissolution rate and solubility of the drug [20].

From the in-vitro drug release studies the optimized formulation LS-9 showed fast drug release when compared to the conventional tablet. The dissolution efficiency of optimized Liquisolid formulations was found

to increase by 4.53 times when compared to conventional tablet. In conclusion, the Liquisolid compacts technique can be a promising alternative for the formulation of water-insoluble drugs, such as Lovastatin into immediate release tablets. Hence the further efficacy of prepared Liquisolid systems must be assessed by performing phamacokinetic studies in human.

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