Preparation and in-Vitro Characterisation of Lovastatin Liquisolid Self-Emulsified Drug Delivery System

Mokale Vinod*, Naik Jitendra, Wani Dharitri, Patil Jayesh, Yadava Sunil, and Verma Umakant

***Abstract*—**The main purpose of this work was to prepare self-emulsifying drug delivery system (SEDDS) for enhancement of dissolution rate for Lovastatin (LOV) poorly water soluble drug. SEDDS is the mixture of oils, surfactants, and co-surfactant, which are emulsified in aqueous media under condition of gentle agitation and digestive motility that would be encountered in the gastro-intestinal tract. Solubility study was performed in different excipients and on basis of solubility of LOV, pseudo-ternary phase diagram were constructed to identify the efficient self-emulsification region and drop size distribution of the resultant emulsion were determined by using motic microscope. After preliminary study, SEDDS formulations were prepared in caprylic acid (10%), cremophor RH40 (30%), and methanol (60%) by simple mixing. Furthermore, SEDDS was loaded onto liquisolid powders. Liquisoild powders were prepared using colloidal silicon, microcrystalline cellulose, and magnesium stearate as absorbent, diluent, lubricant respectively. The release rate of LOV from SEDDS was significantly higher than the conventional tablet. The prepared SEDDS was compared with the conventional tablet (Lostatin ®) by administering the prefilled hard gelatin capsule in USP dissolution apparatus I. The absorption of LOV from SEDDS from resulted in increase in dissolution compared with conventional tablet. Our studies illustrated the potential use of SEDDS for the delivery of hydrophobic, poor water soluble compounds, such as LOV by oral route. Liquisolid SEDDS LOV oral formulations were prepared that provide excellent drug solubility, dissolution, release rate and improved in-vitro release of LOV compare to marked product.

***Keywords*—** self-emulsifying drug delivery system, pseudo-ternary phase diagram, liquisolid, hydrophobic.

I. Introduction

LIPID-BASED formulations are highly water insoluble with low dissolution rate and low bioavailability has always been a challenge to the pharmaceutical technologist. Most of these highly water insoluble drugs, is not formulated properly, may lead to poor oral bioavailability on oral administration. Hence, it is a challenging task to formulate a suitable drug delivery system of highly poor water soluble drugs, (1) oral bioavailability of water insoluble drugs is now come under BCS (Biopharmaceutical system classification) class II (High Permeability, Low Solubility & class IV (Low Permeability, Low Solubility (2). There are many technique to improve the oral bioavailability like Micronization, Salt-Formation, Solvent deposition, Precipitation, Eutectic Mixtures, Solid Dispersion, Encapsulation with cyclodextrin, miocroemulsion, Self-emulsion drug delivery system (3,4).

Lipid-based formulations for enhancing the bioavailability of poorly water-soluble drugs there need to use of complex mixtures of triglycerides, partial glycerides, surfactants, co-surfactants/ co-solvents to solubilise drugs (5, 6). Depend on this composition self-emulsified drug delivery system is developed (7). Self-emulsified drug delivery system (SEDDS) is defined as, a mixture of oil(s), and surfactant(s), ideally isotropic, sometimes containing co-surfactant/co-solvent(s), which when introduced into aqueous phase under gentle agitation, spontaneously emulsifies to produce a fine oil-in-water dispersion .The size of the droplets produced by dilution of a SEDDS is in the range of 100 & 300 nm (8, 9).

However, SEDDS was traditionally prepared in the liquid state. So the liquid SEDDS are generally enclosed by hard or soft capsules to facilitate oral administration (10) but it produce some disadvantages, such as high production costs, low drug incompatibility and stability, drugs leakage and precipitation, capsule ageing. Then incorporation of liquid SEDDS into a solid dosage form by using absorbent is compelling and desirable, and it is called as liquid solid dosage form, some solid self-emulsifying (SE) dosage forms have been initially explored, such as SE tablet and pellets (11,12).

Dissolution of solid griseofulvin self-emulsified drug delivery system (SEDDS) it improve the drug dissolution rate with an increase in surface area (13). Goat fat and Tween 65 admixtures were used to formulate self-emulsifying tablets containing diclofenac (14). To prepare pellets, extrusion/spheronization technique has become popular in pharmaceutical industry because it is easily large-scale, and its products have many features, including spherical shape, narrow modal size distribution, good flow properties, low friability and uniform packing characteristics. The SE pellets combine both advantages of SEDDS and pellets, and the extrusion/spheronization technique has been introduced to prepare the SE pellets by (12).

In general, limited investigations have focused on the

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incorporation of liquid SEDDS into a liquisolid dosage form until now. Hereby, we intended to develop, prepare, in-vitro characterisation of liquisolid self-emulsified drug delivery system for the oral delivery of poorly water soluble drugs. Lovastatin (LOV) was selected as the model drug, LOV is a member of the drug class of statin, used for lowering cholesterol (hyperlipidemic agent) used in hypercholesterolemia which is practically insoluble in water and has poor oral bioavailability. In the study, we firstly prepared the liquid SEDDS containing LOV, solidified it with Colloidal silicon dioxide, microcrystalline cellulose, Magnesium stearate. Finally, the dissolution rate of LOV was studied for liquisolid SEDDS and the commercial conventional tablets.

II. Materials And Methods

LOV was gifted by Concord Biotech Limited, Ahemdabad, Coloidal Silicon dioxide and Micro-crystalline Cellulose was gifted by Ajanta Pharma Pvt. Ltd. Jalgaon. Cremophor RH40 BASF (Germany). All other chemicals used for analysis were of analytical grades.

A. Solubility Study

Screening of oils can be done by determining the equilibrium solubility of LOV in different oils and surfactants. An excess quantity of LOV was added to the 0.5 ml of excipients. Both the components were mixed in a vial for 5min 1 MLH Magnetic stirrer (Remi).The mixtures in vials were shaken at 25±1.0 ◦C for 48hr (19) using water bath shaker (Remi, Mumbai, India). The mixtures were centrifuged using 12C micro-centrifuge (Remi motors, Mumbai, India) at 5000 rpm. The supernant was separated and LOV was extracted in methanol. The drug content was analyzed using UV (15, 16) mini 1240 Shimadzu spectrophotometer at 239 nm.

B. Pseudo-ternary phase diagram study

Pseudo-ternary phase diagrams of oil, surfactant, co-surfactant and water were developed using titration method at 25±2 °C. Phase behaviour of systems was studied at various ratios of surfactant to co-surfactant (Km) viz. 1:0.5, 1:1 and 1:2, 1:3. Mixtures of surfactant and co-surfactant (at a specific Km) with oil were prepared at ratios (w/w) of 10:0, 9:1, 8:2, 7:3, 6:4, 5:5, 4:6, 3:7, 2:8, 1:9, 0:10. A small amount of water was added in vials; vortexed and allowed to equilibrate. Resulting mixtures were evaluated visually for transparency and flow properties. Endpoint of titration was the point, where mixture became turbid or phase separation was observed. At this point, amount of water, oil, surfactant and co-surfactant added was noted. Monophasic, clear, low viscous and non-birefringent systems were considered as microemulsion (ME) and shown as ME region. The Proper Ratio of one excipient to another in the SEDDS formulation was anaysed. The pseudo-ternary phase diagrams of the formulation composed of Caprylic acid (oil), Cremphor RH 40(Surfactant), Methanol (Co-surfactant).Pseudo ternary plot was constructed.

C. Preparation of self-emulsified system

Compositions of self-emulsified system (SES) formulations for 3 capsules each content 10(mg) of drug given in Table 1.Based on solubility and pseudo-ternary phase diagram studies, the formulation amount of LOV was dissolved initially with oil. Then Surfactant & co-surfactant are accurately weighed and added slowly to drug-oil mixture. The components were homogenized by gentle stirring by using magnetic stirrer (1MLH Remi). Finally, the mixture was kept at 250C.The formulation was equilibrated at ambient temperature for at least 48 hour, and examined for sign of turbidity or phase separation .

TABLE I
COMPOSITION OF SES

Sr. no.	Ingredient	Quantity(mg)
1	LOV	30
2	Caprylic acid	0.1
3	Cremophor RH40 (1)	0.3
4	Methanol (2)	0.6

D. Preparation of liquisolid dosage form

Compositions of liquisolid formulations for 3 capsule each 300(mg) Table 2. Powder blend was obtained by lipid (SES) with Colloidal silicon dioxide, Microcrystalline cellulose, Magnesium stearate used to produce liquisoild dosage form. Initially, the SES was mixed with colloidal silicon dioxide with mortar and pestle for 2 min. microcrystalline cellulose was added and mixed for 5 min. Finally Magnesium stearate was added. The resultant powder is dried by using hot air oven. Then accurately weighed 300mg of above powder and filled into capsule each content 10 (mg) drug.

TABLE II
COMPOSITION OF LIQUISOLID DOSAGE FORM

Sr. no.	Ingredient	Quantity (mg)
1	Self-emulsifying system (SES)	1(mL)
2	Colloidal silicon dioxide	250
3	Microcrystalline cellulose	611
4	Magnesium Stearate	9

E. Droplet size analysis

Self-emulsified system (SES) about 1 (ml) diluted with water 100 (ml) in volumetric flask and gently mixed by inverting the flask. The droplet size distribution and emulsion were determined by using motic microscope.

Droplet size of reconstituted microemulsion

Solid SEDDS (300mg) prepared were dispersed with 100 (ml) of distilled water) in volumetric flack and gently mixed by inverting the flask. Filter the solution through whatman filter paper. The droplet size distribution and emulsion were determined by using motic microscope (BBM Series).

F. FT-IR

LOV samples were analysed by infrared spectroscopy (spectrophotometer FT-IR model Shimadzu) to characterize the probable structural modification produced. The samples were prepared by the KBr pellet technique under hydraulic pressure of 150 kg/cm2 with 1 % sample for analysis in the 4000 and 400 cm-1 region.

G. Differential scanning calorimetry determination

Samples of 2–8 mg of the individual substances and 1:1 physical mixture of LOV and additives were accurately weighed, encapsulated and hermetically sealed in flat bottomed aluminium pan with crimped on lid. The pans were positioned on sample pan holder of a DSC (Shimadzu DSC50). The samples were heated in an atmosphere of nitrogen over a temperature range from 50 to 3000C with a constant heating rate of 100C/min. Thermo grams were obtained by the DSC analyzer program and recorded at constant chart speed of 1 inch/min. The thermo gram, transition temperature range, the onset of peak transition and the maximum peak of transition were recorded.

H. Drug content

Assay of weight amount of formulation were carried out to determine the drug content. The weighed samples were dissolved in 10ml methanol and stirred by vortex mixer. The solutions were filtered using whatman filter paper. The content was estimated spectrophotometrically (UV) at 239 nm using standard curve.

I. In-vitro dissolution study

The in-vitro dissolution study of each selected SEDDS formulation of LOV was determined on USP dissolution apparatus I (Electrolab). The flask is cylindric with hemisperical bottom contained 900 mL of 0.1 N HCl41 maintained at 37 ± 0.5°C and paddle speed set at 75 rpm. The capsule is place in basket. The basket is immersed in the dissolution medium. A 5 mL sample was withdrawn at 5, 10, 15, 20, 30, 45, and 60 min respectively. The withdrawn sample was replenished with 5 mL of fresh media. The withdrawn samples were analyzed for LOV content by measuring the absorbance at 239 nm using UV mini 1240 Shimadzu spectrophotometer. The content of LOV was calculated from the standard curve [OD = 0.0737 × Conc. + 0.011 (r = 0.9996; P < 0.001)]. The in-vitro dissolution profiles were calculated.

III. Results And Discussion:

A. Solubility Study

One important consideration when formulating a self-emulsifying formulation is avoiding precipitation of the drug on dilution in the gut lumen in vivo. Therefore, the components used in the system should have high solubilization capacity for the drug, ensuring the solubilization of the drug in the resultant dispersion. The solubility of LOV in various oils and surfactant given in Table 3 and 4. LOV had maximum solubility in Capryric acid and Cremophor RH40 as compared to other lipid vehicles and surfactants. The co-surfactants Methanol showed highest capacity to dissolve the LOV.

TABLE III
SOLUBILITY IN OILS

Sr. No.	Samples	Concentration
1	Caproic acid	83.82±6.83
2	Caprylic acid	88.52±4.57
3	Castor oil	1.15±0.84
4	Cottonseed oil	1.39±0.05
5	Oleic acid	23.9±3.3
6	Olive oil	44.7±0.9
7	Sap oil	68.04±.06
8	Soyabean oil	77.02±1.58
9	Sunflower oil	81.86 ±1.52

TABLE IV
SOLUBILITY IN SURFACTANT

Sr. No.	Surfactant	Concentration
1	Tween 80	30.6±87
2	Cremophor RH40	52.5±60

B. Pseudo-ternary phase diagram study

Self-microemulsifying systems form fine oil-water emulsions with only gentle agitation, upon their introduction into aqueous media. Surfactant and cosurfactant get preferentially adsorbed at the interface, reducing the interfacial energy as well as providing a mechanical barrier to coalescence. The decrease in the free energy required for the emulsion formation consequently improves the thermodynamic stability of the microemulsion formulation. Therefore, the selection of oil and surfactant, and the mixing ratio of oil to S/CoS, play an important role in the formation of the microemulsion. The construction of Pseudo-ternary phase diagram makes it easy to find out the concentration range of components for the existence range of SEDDS. Pseudo-ternary plot was constructed by using Caprylic acid, Cremophore RH40 and Methanol as presented in the Figs. Formation of microemulsion systems was observed at room temperature. Phase behavior investigation of this system demonstrated the suitable approach to determining an optimum oil, surfactant and co-surfactant ratio with which transparent microemulsion system was formed. Figures 1, 2, 3 and 4 show ternary phase diagrams for Cremophor RH40-Methanol-caprylic acid. The size of microemulsion region was compared; larger the size, greater is the self microemulsification efficiency. From Fig 3,

it is evident that ratio (1:2) Cremophor RH40-Methanol-caprylic acid system has larger microemulsification region. Therefore, due to larger microemulsification area and greater capacity for oil incorporation, which is desirable to improve drug loading Cremophor RH40-Methanol-caprylic acid system was selected for further studies. In conclusion, the study helped to identify microemulsion formation area, effect of ratio of surfactant to co-surfactant on it and maximum oil incorporation. It also helped to determine a suitable Km (1:2) and concentration range of various components for formation of SEDDS.

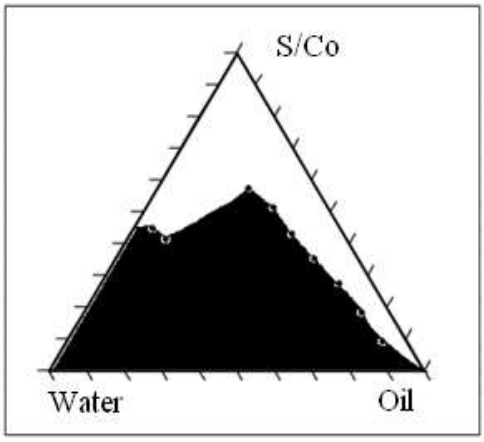

Fig 1 Ratio 1:0.5, Cremophor RH40-Methanol- caprylic acid

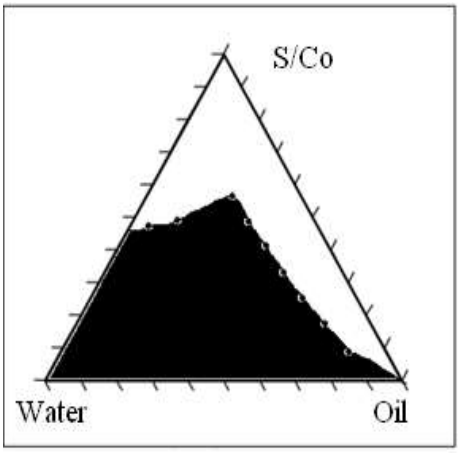

Fig 2 Ratio 1:1, Cremophor RH40-Methanol-caprylic acid

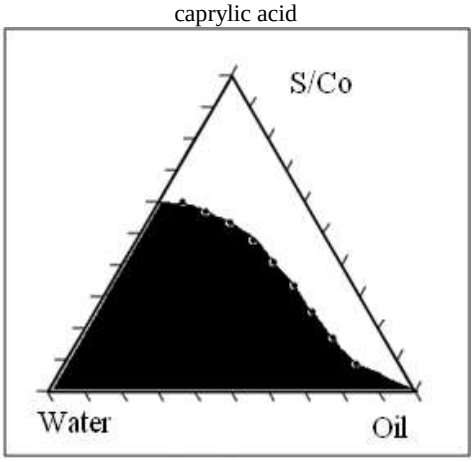

Fig 3 Ratio 1:2, Cremophor RH40-Methanol-caprylic acid

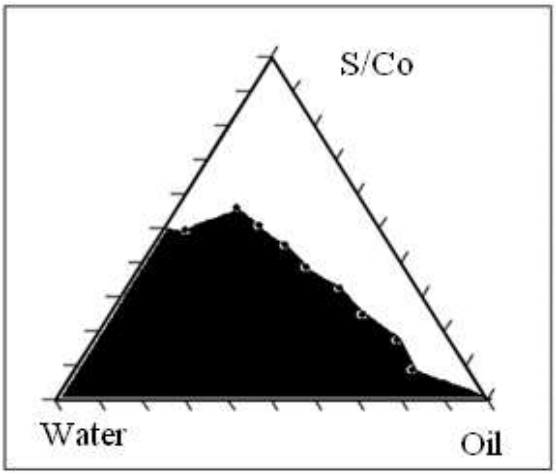

Fig 4 Ratio 1:3, Cremophor RH40-Methanol-caprylic ac

C. Preparation of Self-emulsified System

Based on solubility study oil, surfactant, co-surfactant was selected. By the pseudo-ternary phase diagram study the microemulsion region and proportion of oil, surfactant, and co-surfactant were determined and then prepared the Self-emulsified system. The prepared SES was clear and no phase separation.

D. Preparation of liquisolid dosage form

SES is than formulated into liquisoild dosage form by using coloidal silicon as absorbent, microcrystalline cellulose as diluent, Magnesium sterate as lubricant.That powder was filled in hard gellatin capsule.

E. Emulsion droplet size

Drop size after microemulsification was the most important property of SEDDS. Drop size effect on drug absorption may include enhanced the dissolution & improve release rate. An increase in the ratio of the oil phase (Caprylic acid) resulted in a proportional increase in particle size, because of the simultaneous decrease in the S/CoS proportion. Increasing the S/CoS ratio led to a decrease in mean droplet size. It is well known that the addition of surfactants to the microemulsion systems causes the interfacial film to stabilize and condense, while the addition of co-surfactant causes the film to expand; thus, the relative proportion of surfactant to co-surfactant has varied effects on the droplet size. Result is given in Fig.5. The Reconstituted microemulsion was release from SEDDS when exposed to aqueous media given in Fig.6. The microemulsion from SEDDS had shown a similar droplet size, average between 1-20um.

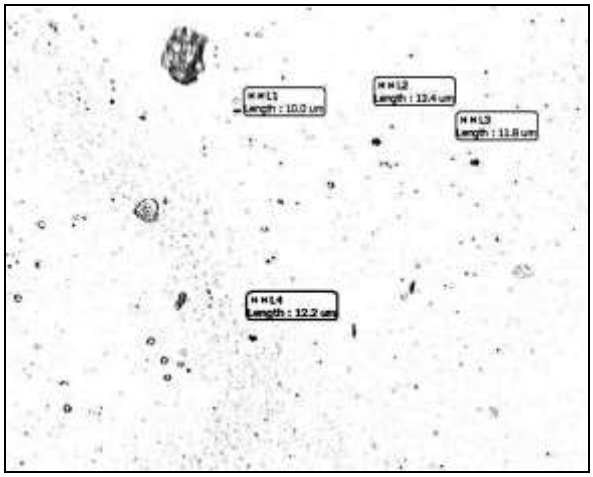

Fig 5 Droplet size of SES

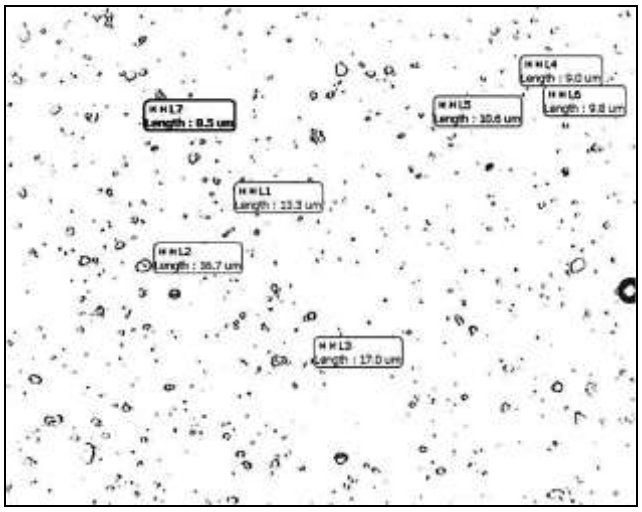

Fig 6 Droplet size of SEDDS

F. FTIR spectra

The FT-IR spectra of LOV and SEDDS are shown in Fig.7. with comparison. LOV is containing the lactone ring. It gives characteristic peak at 1725.6, 1698.1 cm-1. Physical mixing of LOV with surfactant and co-surfactant showed no major changes in position of the characteristic peaks of drug which indicate compatibility of surfactant and co-surfactant with drug.

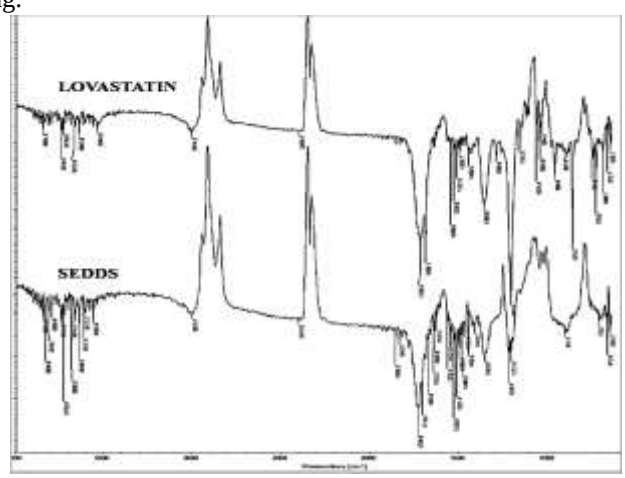

Fig 7 FT-IR Spectra of Self Emulsified Drug Delivery System

G. Differential scanning calorimetry

DSC enables the quantitative detection of all processes in which energy is required or produced (i.e., endothermic or exothermic phase transformations). The physical state of LOV in the liquisolid SEDDS was investigated since it would have an important influence on the in-vitro release characteristics. DSC curves of pure LOV, the liquid SEDDS of LOV and the solid SEDDS of LOV are shown in Fig. 8, 9, and 10 respectively. Pure LOV showed sharp endothermic peak at temperature 172.750C which corresponding to drug melting point. The appearance of sharp endothermic peak is due to its crystalline nature. The liquid SEDDS of LOV showed two exothermic peaks, and one endothermic peak. No obvious peaks for LOV and lipid were found in the liquisolid SEDDS of LOV. In DSC thermo gram, LOV give endotherm at 172.750C.This endotherm does not change after physical mixing with surfactant and co-surfactant indicates that the absence of any interaction between drug and selected vehicles.

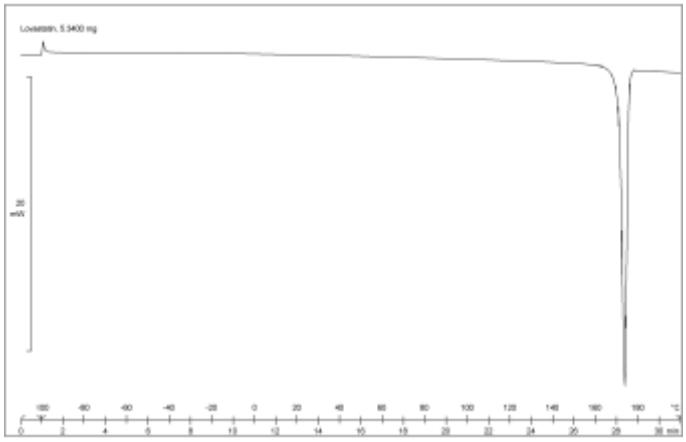

Fig 8 DSC Spectra of LOV

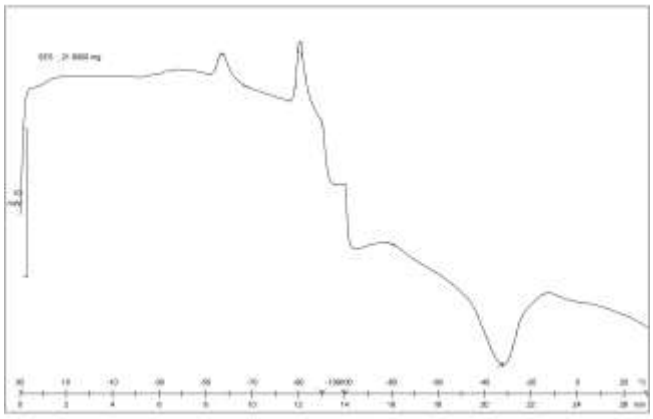

Fig 9 DSC spectra for SES

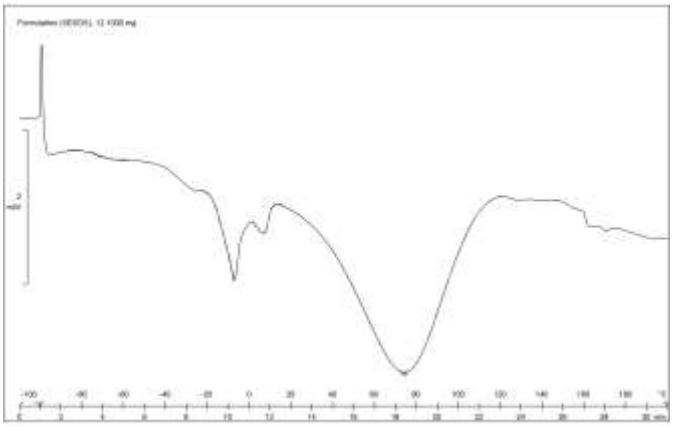

Fig 10 DSC spectra for SEDDS formulation

H. Drug content

Irrespective of ratios of oil and surfactant used, the drug content in liquisolid SEDDS was found in the range of 85.41–98.34%, indicating uniform dispersion of drug in formulations.

I. In-vitro drug release

Dissolution may better mimic conditions in the stomach following oral administration of SEDDS pre-concentrate. In case of Self-nanoemulsifying granules of ezetimide shows 3 fold increase in dissolution rate compared to plain ezetimide, (16) The optimized formulation of coenzyme Q10 self-nanoemulsified tablet dissolution profile showed that 80-90% drug release took place in 45 minute(11). SEDDS containing Ketoprofen was formulated as sustained release dosage form and found that drug released was increased. Drug release from the formulation increased with increasing amount of cosurfactant (17). Enhanced bioavailability upto 1.88 of silymarin by self-microemulsifying drug delivery system (18). An antimalarial drug Halofantrine was prepared as SEDDS and SMEDDS and resulted in 8 fold improvement in absolute oral bioavailability relative to previous data of the solid (19) Self-microemulsifying drug delivery system (SMEDDS) of simavastin was developed to enhance its oral bioavailability 1.5 fold compared to conventional tablet. This study illustrated the potential use of SMEDDS for the delivery of hydrophobic compounds (20).

Dissolution studies were performed for Liquisolid SEDDS of LOV, and the conventional tablet (Lostatin ®). The release of LOV from these dosage forms was evaluated in 0.1N HCl; the release percentage of LOV from the SEDDS form was significantly higher than that of LOV from the conventional tablet (Fig. 11, 12). It could suggest that LOV dissolved perfectly in SEDDS form could be released due to the small droplet size, which permits a faster rate of drug release into aqueous phase, faster than conventional tablet, including insolubilized LOV, and it could affect the bioavailability. Liquisolid self-emulsifying of LOV shows 1.44 fold increases in dissolution rate compared to plain LOV. The spontaneous formulation of an emulsion upon drug release in the GI tract advantageously presents the drug in a solubilized form, and the small droplet size provides a large interfacial surface area for drug absorption (21).

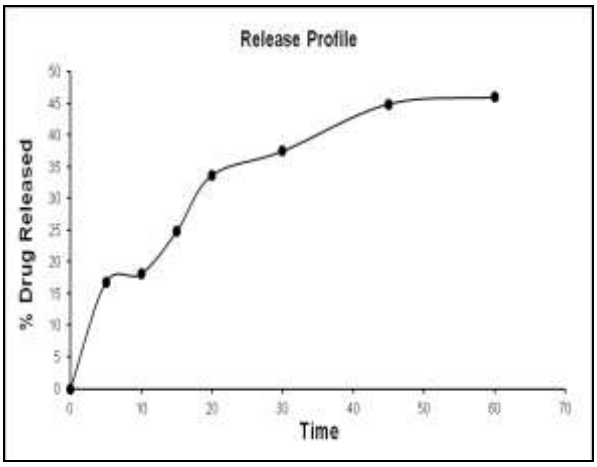

Fig 11 Release profile of Conventional LOV Tablet

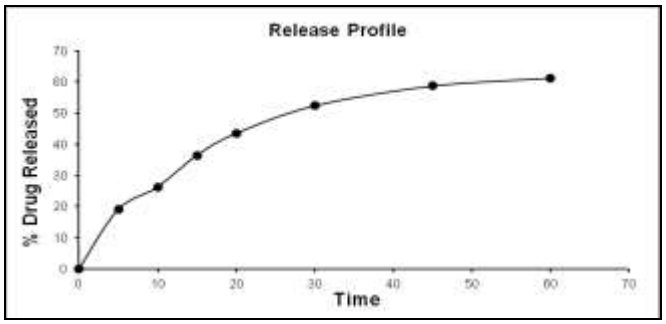

Fig 12 Release profile of LOV Liquisolid SEDDS

IV. CONCLUSION

A liquisolid self-microemulsifying drug delivery system (SEDDS) containing LOV was designed and developed for oral administration. Based on the solubility and phase diagram study, the system consisting of caprylic acid, cremophor RH40, methanol with fixed amount of LOV were employed to formulate SEDD formulations. Further it is formulated in liquisolid powder by using colloidal silicon, microcrystalline cellulose, and magnesium stearate as absorbent, diluents, lubricant respectively. The screened formulations were found suitable for LOV- loaded liquisolid self-microemulsifying drug delivery systems on the basis of assessed parameters. FT-IR and DSC studies indicated no interaction between drug, oil and surfactants. SEDDS drop size which ranged between 1-20 µm upon dilutions with aqueous media. LOV dissolved perfectly in SEDDS form could be released due to the small droplet size, which permits a faster rate of drug release into aqueous phase than conventional tablet (Lostatin ®). From the given study we can conclude that, by formulation of LOV into liquisolid SEDDS results in increase solubility, dissolution and release rate. This study result that we can increase the solubility, dissolution and release rate of poorly water soluble and hydrophobic drug like LOV.

REFERENCES

[1] Lipinski, C.A. Poor aqueous solubility—an industry wide problem in drug discovery. Am. Pharm. Rev. 2002; 5: 82–85.

[2] Stegemanna S, Leveillerb F. When poor solubility becomes an issue: from early stage to proof of concept. European Journal Pharmaceutical Science. 2007; 31: 249-261.

[3] Aungst, B.J., et al. Novel formulation strategies for improving oral bioavailability of drugs with poor membrane permeation or presystemic metabolism. J. Pharm. Sci. 1993; 82: 979–986.

[4] M.J. Lawrence, G.D. Rees, et al. Microemulsion-based media as novel drug delivery system, Adv. Drug Deliv. Rev. 2000; 45: 89–121.

[5] C.W. Pouton. Lipid formulations for oral administration of drugs: nonemulsifying, self-emulsifying and 'self-microemulsifying' drug delivery systems, Eur. J. Pharm. Sci. 2000;11: S93–S98.

[6] C.W. Pouton. Formulation of self-emulsifying drug delivery systems, Adv. Drug Deliv. Rev. 1997; 25: 47–58.

[7] David J. Hauss. Oral Lipid-Based Formulations enhancing the bioavailability of poor water soluble drugs. USA Drugs and the pharmaceutical sciences. . 2007; 107: 149-177.

[8] Vladimir P. Torchilin. Multifunctional Nanocarriers. Advanced Drug Delivery Reviews. 2006; 58: 1532-1555.

[9] A.J. Humberstone, W.N. Charman. Lipid-based vehicles for the oral delivery poorly water soluble drugs, Adv. Drug Deliv. Rev., 1997; 25: 103–128.

[10] Cilexetil Jill b. Shukla et al. Formulation and evaluation of self-micro emulsifying system of candesartan International Journal of Pharmacy and Pharmaceutical Sciences. 2010; 2: 0975-1491.

[11] S. Nazzal and M.A. Khan. Controlled release of a self-emulsifying formulation from a tablet dosage form: Stability assessment and optimization of some processing parameters. International Journal of Pharmaceutics 2006; 315: 110 -12.

[12] Zhiyuan Wang et al. Solid self-emulsifying nitrendipine pellets: Preparation and in vitro/in vivo evaluation International Journal of Pharmaceutics. 2010; 383: 1–6.

[13] Vikas Agarwal et al. Dissolution and powder flow characterization of solid self-emulsified drug delivery system (SEDDS). International Journal of Pharmaceutics. 2009; 366: 44–52.

[14] A.A. Attama, et al. The use of Solid Self-Emulsifying Systems in the delivery of diclofenac. International Journal of Pharmaceutics. 2003; 262: 23–28.

[15] Sandeep Kumar Singh et al. Development and characterization of a lovastatinloaded self-microemulsifying drug delivery system. Pharmaceutical Development and Technology, 2010; 15(5): 469–483.

[16] R.P. Dixit, M.S. Nagarsenker. Self-nanoemulsifying granules of ezetimibe: Design, optimization and evaluation, European journal of pharmaceutical sciences 2008; 35: 183-192.

[17] Pradeep Patil, Prasad Joshi, and Anant Paradkar. Effect of Formulation Variables on Preparation and Evaluation of Gelled Self-emulsifying Drug Delivery System (SEDDS) of Ketoprofen, AAPS PharmSciTech. 2004; 42: 1-8.

[18] Wei Wu, Yang Wang, Li Que. Enhanced bioavailability of Silymarin by self-microemulsifying drug delivery system. European Journal of Pharmaceutics and Biopharmaceutics. 2006;63: 288–294.

[19] Shui-Mei Khoo a, Andrew J. Humberstone. Formulation design and bioavailability assessment of lipidic self-emulsifying formulations of Halofantrine. International Journal of Pharmaceutics. 1998; 167: 155–164.

[20] Bok Ki Kanga, et al. Development of self-microemulsifying drug delivery systems (SMEDDS) for oral bioavailability enhancement of Simvastatin in beagle dog. International Journal of Pharmaceutics. 2004; 274: 65–73.

[21] Charman, S.A et al. Self-emulsifying drug delivery systems: formulation and biopharmaceutical evaluation of an investigational lipophilic compound. Pharm. Res. 1992; 9: 87–93