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Improved Wetting For Improved Solubility and Dissolution of Candesartan Cilexetil, Comparative Study Of Surfactant And Modified Surfactant In Varying Ratios

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ABSTRACT : *Candesartan cilexetil is a poorly soluble antihypertensive agent with solubility limited bioavailability (15%). To initiate process of solubilization , it is very much necessary to displace the air at the surface and wet the drug surface with a non volatile solvent / surfactant ,with which drug is compatible . Solvents used here are surfactant (Tween 20) and modified surfactant (Transcutol) in different drug:solvent (1:1-1:9) ratio's for preparation of adsorbates. Adsorbates were then converted into free flowing powders as liquisolid compacts and compressed to form tablets. Liquisolid compacts were evaluated for improvement in saturation solubility and dissolution of candesartan cilexetil. All systems exhibited a promising advantage in terms of solubility and dissolution without affecting the drug structure as confirmed by IR and XRD. No considerable advantage in terms of solubility and dissolution was seen by increasing solvent ratio with drug.*
Key words –*Candesartan, dissolution enhancement.,improved wetting, liquisolid compacts, solubility enhancement*

I. INTRODUCTION

Various technologies are available for enhancing aqueous solubility and dissolution rate of poorly soluble drugs. To initiate process of solubilization , it is very much necessary to displace the air at the surface and wet the drug surface with a solvent or surfactant , with which drug is compatible . This technique is of "liquisolid compacts" is novel, easiest and one of the promising techniques for improving solubility of hydrophobic drugs. [1,2] Candesartan cilexetil is a poorly soluble antihypertensive agent with solubility limited bioavailability (15%).[3] Present research adopts the same principle to improve solubility and dissolution of candesartan cilexetil which involves surface wetting of candesartan cilexetil with non volatile solvents or surfactant by producing liquisolid compacts of drug. Liquid compacts are acceptably flowing and compressible forms of liquid medications. The term "liquisolid medication" implies oily liquid drugs and solutions or suspensions of water -insoluble solid drugs carried in suitable non volatile solvent systems. Using this new 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 reffered to as the carrier and coating materials. Various grades of cellulose, starch, lactose etc. may be used as the carrier, whereas very fine particle size silica powder may be used as the coating material. Liquisolid compacts are reported to be beneficial in enhancing, solubility [4], dissolution rate [5] and bioavailability [6] of poorly aqueous soluble drugs due to enhanced wetting properties.[7-17] Some literature reports use of liquisolid technology for sustaining release of drugs by using appropriate vehicle.[18,19]

Advantages of liquisolid products [20]

- Low cost than soft gelatin capsules
- Production is similar as that of conventional tablets
- Drug release can be modified using suitable formulation ingredients
- Capability for large scale industrial production
- Enhanced bioavailability as compared to conventional tablets.[21]

II.MATERIALS AND METHODS

Candesartan cilexetil was obtained as a gift sample from Alembic Ltd., Baroda. Transcutol was obtained as a gift sample from Gattefosse, India. All other solvents and chemicals used in this research were purchased from s.d.fine chemicals Ltd., Mumbai.

2.1Selection of surfactants

While choosing non volatile solvent, considering hydrophobic nature of drug, it was decided to use surfactants and modified surfactants for enhancing the solubility and dissolution rate of drug. Modified surfactant chosen was transcutol as drug showed a better solubility in the same as well as it is reported as a penetration enhancer for enhancing the bioavailability and tween 20 [22] was chosen as surfactant as it is recommended by Office of Generic Drugs in proposed dissolution medium for candesartan cilexetil.

2.2Preparation of liquisolid compacts

Several liquisolid compacts (denoted as LS-1 to LS-9) were prepared as follows: Candesartan Cilexetil was dispersed in liquid vehicle with different ratio's ranging from 1:1 to 1:9 (drug:liquid vehicle). A binary mixture of microcrystalline cellulose :silica (20:1) was then added to the mixture under continuous mixing in a mortar.Depending on the ratio of drug:liquid vehicle in formulation different liquid load factors(the liquid load factor Lf ,is the weight ratio of the liquid medication and carrier powder in the liquisolid formulations) were calculated by using the formula[23]

$$L=W/Q$$

Where, L=Liquid load factor, W=Weight of liquid medicament, Q=Weight of carrier material. The amounts of carrier and coating materials are enough to maintain acceptable flow and compression properties.

These liquisolid compacts were then mixed with 5% (w/w) of sodium starch glycolate as disintegrants for a period of 10 minutes. The final mixture was compressed using a manual tabletting machine with 10 mm punch to achieve a tablet hardness of 5 kp.

Same procedure as that of preparation of liquisolid compacts with tween 20 was followed for preparation of liquisolid compacts using transcutol and were denoted as LStc 1 – LStc 9.

Table 1 Formulations with liquisolid technology

Sr.No.	Drug: vehicle	Formulation code	
		Tween 20	Transcutol
1	1:9	Lst1	Lstc1
2	1:8	Lst2	Lstc2
3	1:7	Lst3	Lstc3
4	1:6	Lst4	Lstc4
5	1:5	Lst5	Lstc5
6	1:4	Lst6	Lstc6
7	1:3	Lst7	Lstc7
8	1:2	Lst8	Lstc8
9	1:1	Lst9	Lstc9

2.3 Evaluation and characterization [24]

2.3.1 Saturation solubility testing

An amount of liquisolid compact powder equivalent to 10 mg of drug was added to 50 ml solvent in a volumetric flask. Flask was stoppered properly and vortexed for 2 minutes on a cyclomixer and then kept in rotary shaker for 48 hours at 37˚C. Resultant solutions were then filtered through whatmann filter paper,diluted suitably and absorbance was checked using UV spectrophotometer. Concentration in each solution was calculated**.** Solvents used for this study were water, 0.1 N HCl, and phosphate buffer pH 6.8.

2.3.2 Drug content

An amount of liquisolid compact equivalent to 8 mg of drug was taken and diluted to give a solution of 8 ppm. Absorbance of this solution was checked using a UV spectrophotometer and concentration was calculated.

2.3.3Dissolution testing

In vitro multimedia dissolution studies in different solvents such as water,0.1 N HCl,phosphate buffer pH 6.8 and OGD medium was carried out by using USP type II dissolution apparatus at 50 rpm at 37˚C ,with sampling points at 5 minutes, 10 minutes , 15 minutes, 20 minutes, 30 minutes, 45 minutes and 60 minutes. Each time 5 ml aliquot was withdrawn and replaced. Aliquotes were analysed by UV – spectrophotometer at 253 nm using respective blank.

2.3.4 Physicochemical characterization

Physicochemical characterization of given sample was done by FTIR by KBr pellet method and XRD patterns were collected by setting voltage and current at 40 kV and 20 mA respectively . All patterns were scanned over the range 0-60^o 2θ angle with a scan rate of 1.5^o/min.

III. RESULTS AND DISCUSSION

3.1 Preparation of liquisolid compacts

Liquisolid compacts were prepared by the method described in the previous section. Key formulation characteristics of liquisolid compacts with tween 20 as well as with transcutol are shown in table 2 and 3 respectively.

Table 2 Key formulation characteristics of liquisolid compacts of CC with tween 20

Liquisolid system	Drug concentration(%w/w) in liquid medication	Liquid load factor(L_f)	Unit dose weight(mg)	Weight with 5% SSG
Lst1	10	0.1363	666.6	699.93
Lst2	11.11	0.1355	603.3	633.3
Lst3	12.5	0.1415	516	541.8
Lst4	14.28	0.1460	439	460.95
Lst5	16.66	0.1486	371	389.55
Lst6	20	0.1420	321.6	337.68
Lst7	25	0.1430	255.6	268.38
Lst8	33.33	0.1448	189.6	198.75
Lst9	50	0.1454	126	132.3

It was seen that slightly higher amount of carrier material was required to convert liquisolid compacts with tween 20 in free flowing nature than that of liquisolid compacts with transcutol. Liquid loading factors were varying in range of 0.1393-0.1454 for ratio's of 1:9 - 1:1 for tween 20 with final weight of tablets varying between 699.93-132.3 mg respectively. For transcutol ,liquid loading factors were varying in range of 0.1560-0.1581for ratio's of 1:9 - 1:1 with final weight of tablets varying between 622.12-123.01 mg respectively.

Table 3 Key formulation characteristics of liquisolid compacts of CC with transcutol

Liquisolid system	Drug concentration(%w/w) in liquid medication	Liquid load factor(L_f)	Unit dose weight(mg)	Weight with 5% SSG
Lstc1	10	0.1560	592.5	622.12
Lstc2	11.11	0.1559	522	548.1
Lstc3	12.5	0.1626	457.5	480.37
Lstc4	14.28	0.1651	395.16	414.91
Lstc5	16.66	0.1565	354.66	372.39
Lstc6	20	0.1558	296.66	311.49
Lstc7	25	0.1576	235	246.75
Lstc8	33.33	0.1560	177.83	186.72
Lstc9	50	0.1581	117.16	123.01

3.2 Saturation solubility testing

Saturation solubility of all liquisolid compacts shown a drastic increase as compared to pure drug in all three above mentioned media. Saturation solubility of lst was found to vary in between 0.01-0.04 mg/ml in 0.1 N HCl, 0.03-0.1 mg/ml in Phosphate buffer pH 6.8 and 0.02-0.09 mg/ml in water against the solubility of 0.003 mg/ml of pure drug in all media.For Lstc , Saturation solubility was found to vary in between 0.056-0.063 mg/ml in 0.1 N HCl, 0. 58-0.6 mg/ml in Phosphate buffer pH 6.8 and 0.53-0.65 mg/ml in water.

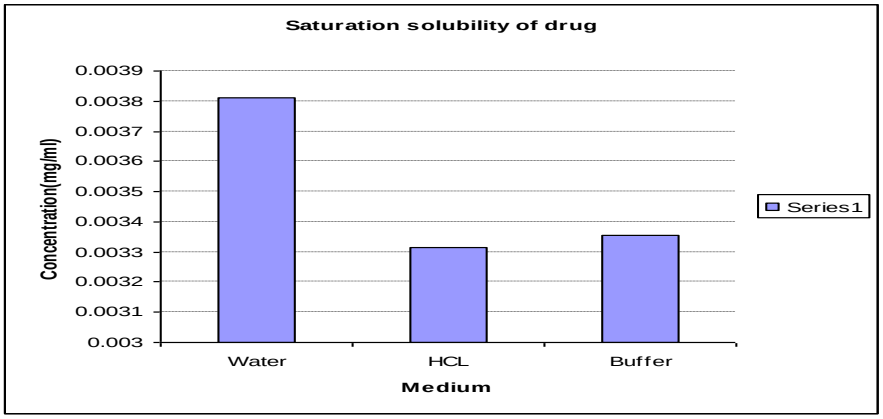

Figure 1 Saturation solubility of drug

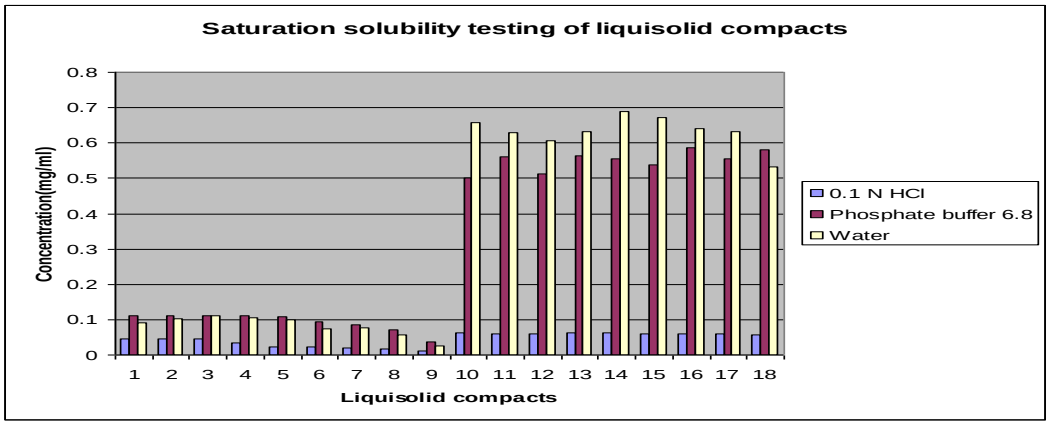

Figure 2 Saturation solubility testing of liquisolid compacts

3.3 Drug content

Drug content of all liquisolid compacts was found to be in the acceptable range of 98.3%-101.8%.

3.4 Multimedia dissolution studies

Multimedia dissolution studies was carried out in 0.1 N HCl, phosphate buffer pH 6.8 , water and OGD medium with procedure described in previous section. Maximum release at the end of one hour for Lst was found to be in between 9.12%-13.71% in 0.1 N HCl,8.55-25.34% in phosphate buffer pH 6.8,19.81-33.32% in water and more than 95% in OGD medium for drug to liquid vehicle ratio's of 1:1-1:9. For Lstc the dissolution values were varying in between between 6.93%-13.27% in 0.1 N HCl,13.37-36.99% in phosphate buffer pH 6.8,21.38-34.71% in water and more than 95% in OGD medium for drug to liquid vehicle ratio's of 1:1-1:9.All the results are shown in figure4,5,6 and 7 respectively. In all cases multimedia dissolution of liquisolid compacts was found to excel multimedia dissolution of pure drug as shown in figure 3.

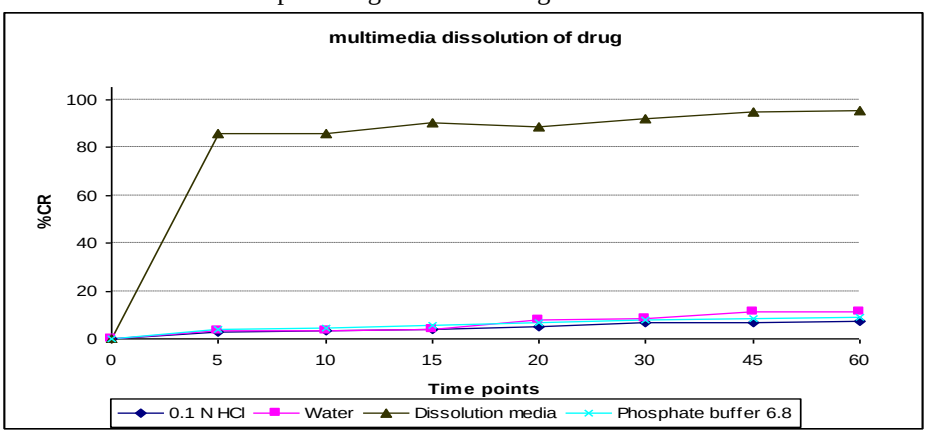

Figure 3 Multimedia dissolution of drug

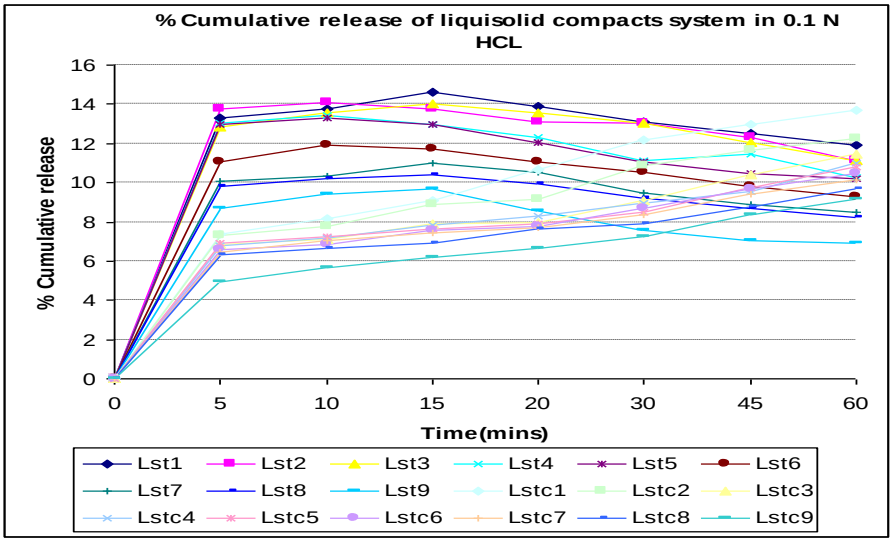

Figure 4 Percentage cumulative release of liquisolid system in 0.1 N HCl

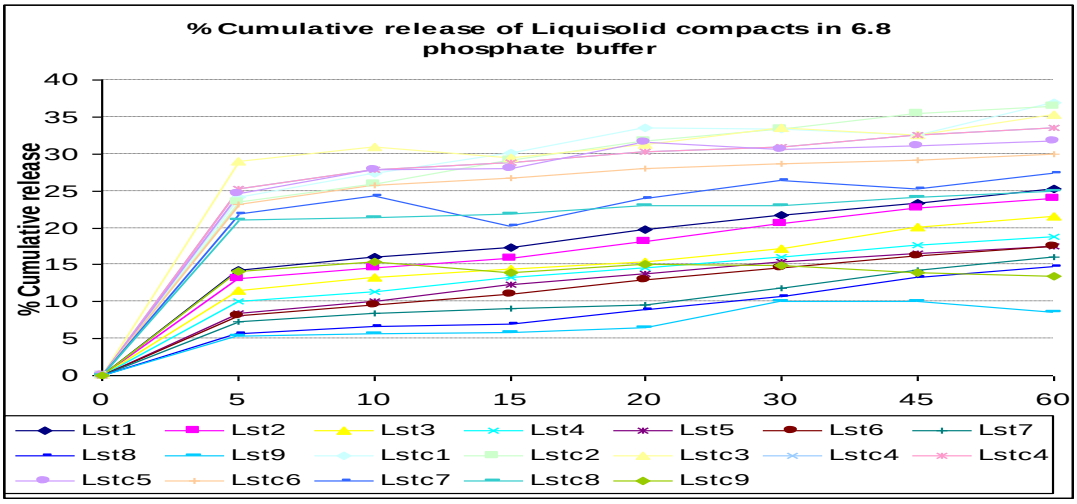

Figure 5 Percentage cumulative release of liquisolid system in phosphate buffer pH 6.8

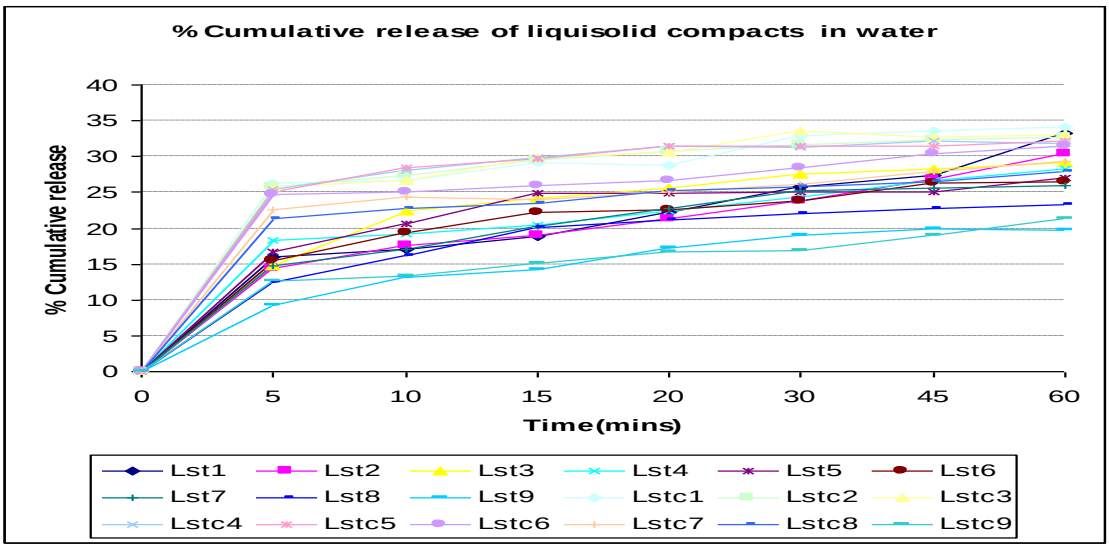

Figure 6 Percentage cumulative release of liquisolid system in water

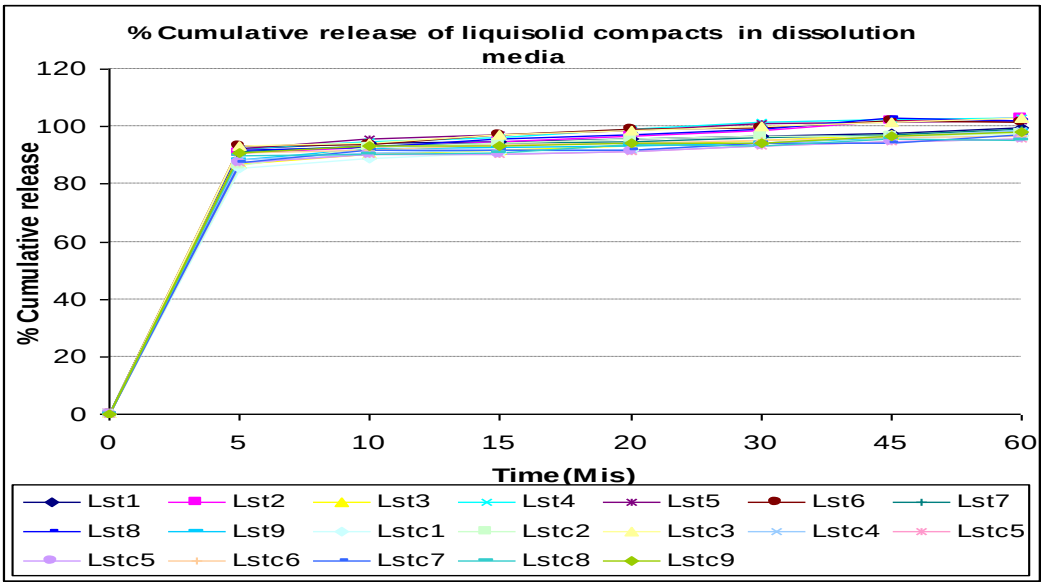

Figure 7 Percentage cumulative release of liquisolid system in OGD media

3.5 Physicochemical characterization

3.5.1 XRD Analysis

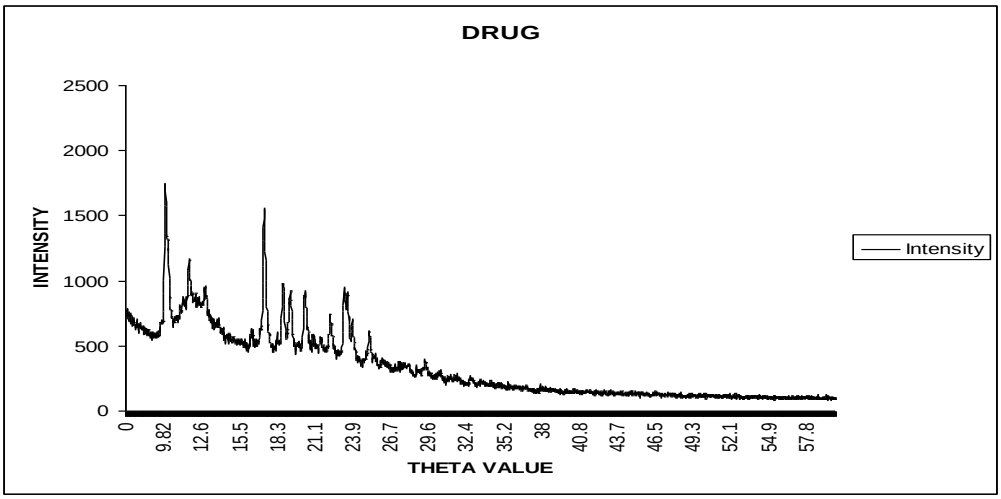

Figure 8 XRD spectra of pure drug

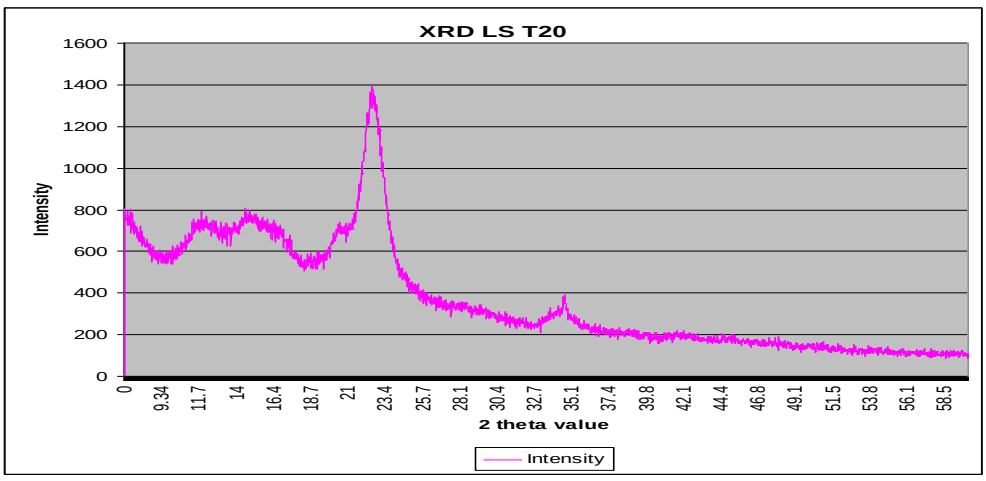

Figure 9 XRD spectra of Lst1

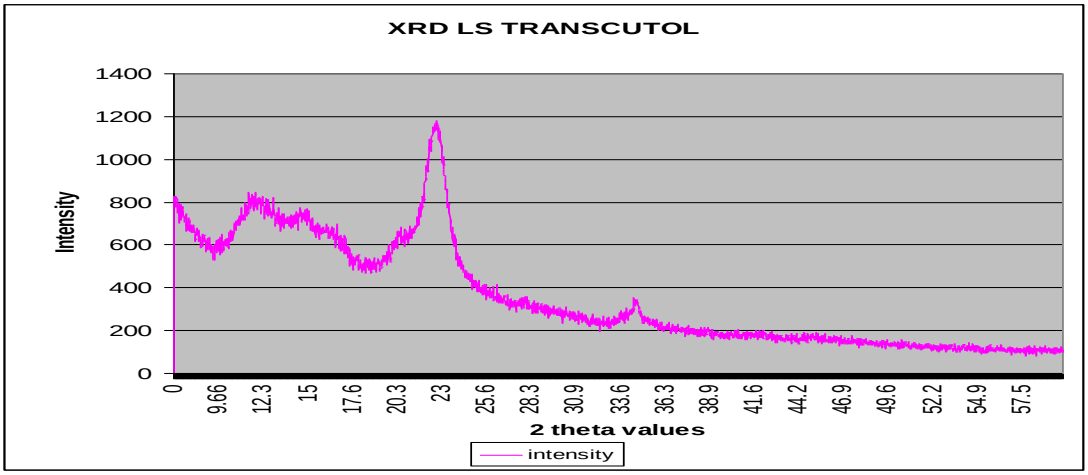

Figure 10 XRD spectra of LStc1

Change in crystallinity of drug was observed from XRD spectra which shows absence of characteristic peak at 2θ angle 9.8 as well as shown in Figures 8,9 and 10 respectively. FTIR spectra also shows reduced intensity of characteristic band due to carbonyl stretching in crystalline state but not complete absence of it. Results are shown in Figures 11,12 and 13 respectively.

3.5.2 IR Analysis

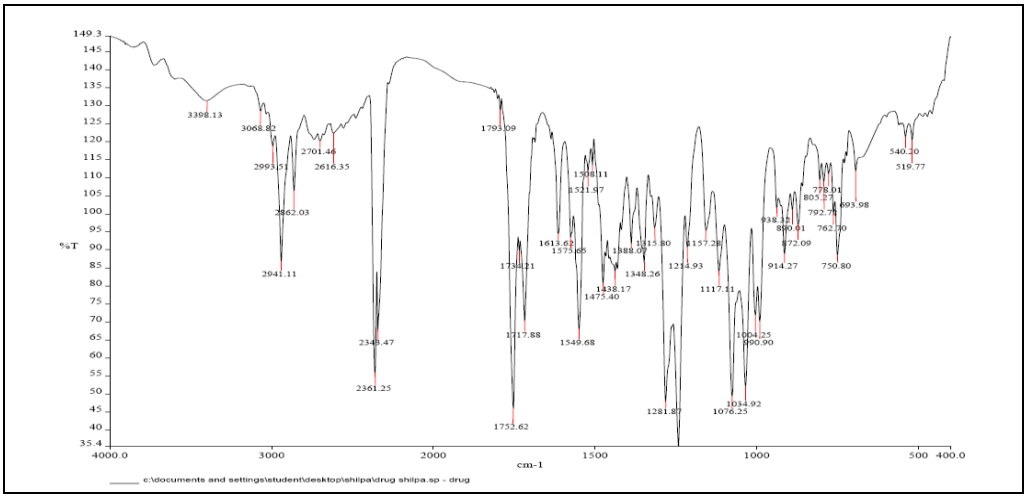

Figure 11 FTIR spectra of pure drug

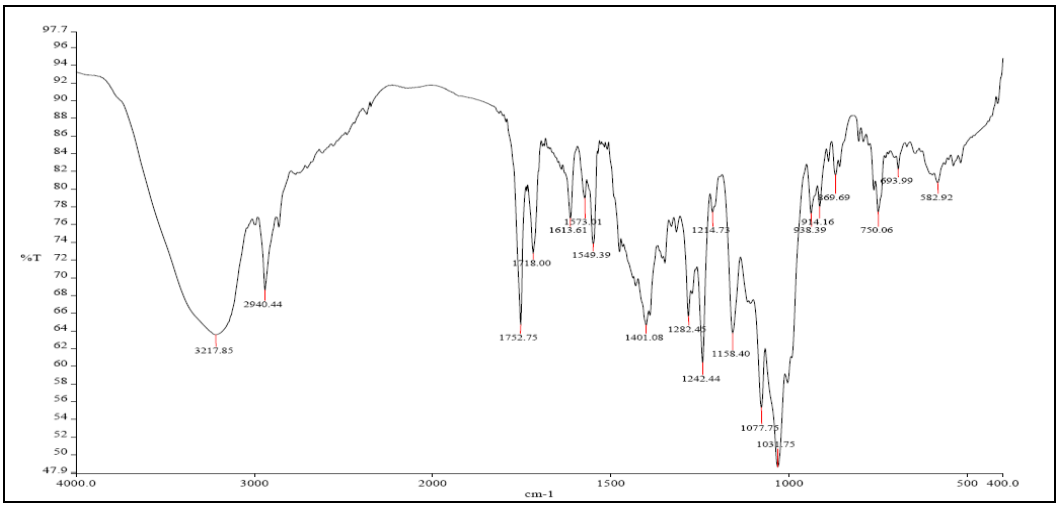

Figure 12 FTIR spectra of Lst1

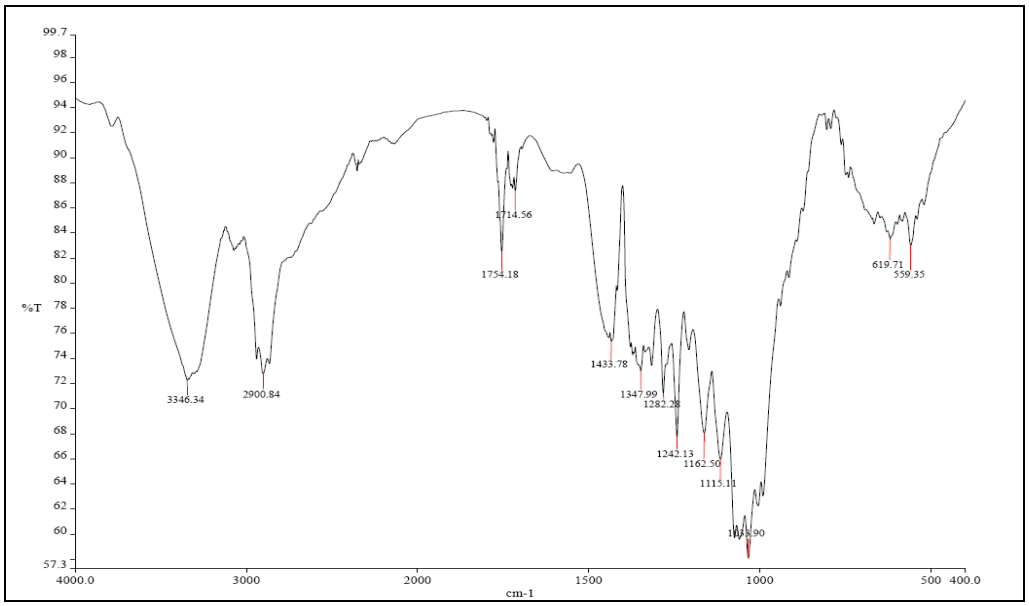

Figure 13 FTIR spectra of Lstc1

IV. CONCLUSION

Improved wetting by use of nonvolatile solvents is an simple and cost effective tool for enhancing solubility and dissolution of hydrophobic drugs. If solvents used are modified surfactants more advantages in terms of solubility as well as dissolution can be availed.

V.ACKNOWLEDGEMENTS

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