Research Article

Enhancement of Solubility and Dissolution Rate of Escitalopram Oxalate by Liquisolid Compact Technology

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ABSTRACT

The solubility and dissolution properties of any drug are vital determinants of its oral bioavailability. The dissolution rate of poorly soluble, highly permeable (BCS-II) drugs, such as Escitalopram oxalate, can be improved by application of the liquisolid (LS) technique. Liquisolid Compacts is defined as liquid medications such as solutions or suspensions of water insoluble drugs in appropriate nonvolatile liquid vehicles can be converted into suitably flowing and compressible powders by blending with particular powder excipients. Different liquisolid compacts of Escitalopram oxalate were prepared using a mathematical model for calculating required quantities of powder and liquid ingredients to produce an acceptably flowable and compressible admixture. Avicel PH 102, Aerosil 200 and sodium starch glycollate (SSG) were employed as carrier, coating material and disintegrant respectively. The prepared liquisolid systems were evaluated for their micromeritic properties, possible drug-excipients interactions by Infrared spectra (IR) analysis and for their tabletting properties. The release rates of liquisolid compacts were markedly higher compared with directly compressed tablets, due to increasing wetting properties and surface area of the drug. This study shows that the liquisolid technique is a promising alternative for improvement of the dissolution and oral bioavailability of water insoluble drugs.

Keywords: Escitalopram; Liquisolid compacts; Dissolution rate, BCS class II.

INTRODUCTION

The poor dissolution rate of water insoluble drugs is still a substantial problem confronting the pharmaceutical industry. A great number of newly developed, beneficial chemical entities do not reach the public merely because of their poor oral bioavailability due to inadequate dissolution. The BCS class II drugs for which the dissolution profile must be clearly defined and reproducible shows high absorption number (An) and low dissolution number (Dn). Drugs in this class are expected to have a variable dissolution profile due to the formulation and *in vivo* variables that, in turn, affect the absorption[1].Over the years, various solid dosage formulation techniques, to enhance the dissolution of poorly soluble substances, have been introduced with different degrees of success. The active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. The poor dissolution characteristics of water insoluble drugs are a major challenge for pharmaceutical formulation scientists. The use of water-soluble salts and polymorphic forms, reducing particle size to increase surface area, the formation of water soluble molecular complexes, solid dispersion, co-precipitation, lyophilization, microencapsulation, and the inclusion of drug solutions or liquid drugs into soft gelatin capsules are some of the major formulation tools which have been shown to enhance the dissolution characteristics of water-insoluble drugs[2].

The most common method is to increase surface area of the drug by micronization. But, in practice the effect of micronization is often disappointing, especially when the drugs are encapsulated or tableted.[3-5] Micronized drugs also have the tendency to agglomerate as a result of their hydrophobicity, thus reducing their available surface area. Different methods are employed to improve the dissolution characteristics of poorly water soluble drugs, like solubilization, pH adjustment, cosolvents, microemulsion, self emulsification, polymeric modification, drug complexation, particle, size reduction, use of a surfactant as a solubilizing agent, the pro-drug approach, and solid solutions.[6-7] Amongst these the most promising method for promoting dissolution is the use of

the liquisolid (LS) system.[8-10] Several researchers have shown that the liquisolid technique is the most promising method for promoting dissolution rate of poorly water-soluble drugs.[11-14] The technique of 'liquisolid compacts' is a new and promising addition towards such a novel aim for solubility and dissolution improvement. Liquisolid system refers to formulations formed by conversion of drug suspensions or solution in non-volatile solvents into dry, nonadharent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials. They are prepared by simple blending with selected powder excipients referred to as the carriers and the 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. The compression of these latter systems resulted in a significant 'Liquid Squeezing Out' phenomenon.[15-17]

In fundamental studies made by Spireas *et al*., flow and compression issues have been addressed with the use of the new formulation mathematical model of liquisolid systems, which is based on the flowable (Φ-value) and compressible (Ψ-number) liquid retention potentials of the constituent powders. The good flow and compression properties of the liquisolid system are encouraged by the large surface area and fine particle size. Hence, liquisolid compacts containing water-insoluble drugs are expected to display enhanced dissolution characteristics and, consequently, improved oral bioavailability.[18,19] It is claimed that if hydrophobic carriers such as Eudragit RL and RS are used instead of hydrophilic carries in liquisolid systems, sustained release systems can be obtained.[20-23] Therefore, it is suggested that the method have the potential to be optimized for the reduction of drug dissolution rate and thereby production of sustained release systems. In the liquisolid and powdered solution systems the drug might be in a solid dosage form, it is held within the powder substrate in solution, or in a solubilized, almost molecularly dispersed state. Therefore, due to their significantly increased wetting properties and surface of drug available for dissolution, liquisolid compacts of water-insoluble substances may be expected to display enhanced drug release properties, and consequently, improved bioavailability. According to literature survey the Piroxicam[11], Prednisolone[24], and Carbamazepine[24] Propranolol hydrochloride[25], Hydrochlorothiazide[26] liquisolid compacts were prepared for improving the physicochemical properties. Poorly water-soluble drugs (Escitalopram) involve many difficulties in the development of pharmaceutical dosage forms for oral delivery systems due to their low bioavailability. It has been established that the active ingredient in a solid dosage form must undergo dissolution before it is available for absorption from the gastrointestinal tract. i.e., the dissolution rate is often the rate-determining step in drug absorption. Therefore, the solubility and dissolution behavior of a drug are the key determinants of its oral bioavailability.

Escitalopram oxalate is a potent inhibitor of serotonin (5-HT) uptake that exhibit antidepressant activity. In spite of oxalate form it is sparingly soluble in water. This drug was selected due to their low solubility and high permeability (Class II, Biopharmaceutical Classification System, BCS), and thus the increase in solubility will improve their bioavailability.[27-29] In the present study, the effects of different excipients on the solubility and dissolution profile of Escitalopram oxalate using liquisolid compact technique were studied.

MATERIALS AND METHODS

1. Materials

The following gift samples were received: Escitalopram oxalate (Lupin Ltd. Jammu, India); Avicel PH 102 (Colorcon Ltd, Goa); Aerosil 200 (Colorcon Ltd, Goa). The following samples were purchased: propylene glycol (PG), polyethylene glycol 400 (PEG400), glycerin, methanol (Research lab), Nexito 10mg (Sun Pharma).All reagents used were of analytical grade.

2. Equipment

Electric balance (Contech), Ultraviolet spectrophotometer (Jasco 530V . UK), Single Punch tablet press (Lab press), Tablet Hardness tester (Dolphin), Friability tester (Electrolab), Disintegration tester (Electrolab), Dissolution apparatus, six spindle dissolution tester (Electrolab).

3. Experimental

3.1. Solubility studies

The solubility studies of Escitalopram oxalate were carried out as described by Spireas et al., (1998); Spireas and Sadu, (1998); Nokhodchi et al., (2005). In this study, the solubility of Escitalopram oxalate was determined in different solvents including: PEG 400, glycerin, propylene glycol and distilled water. Preparing saturated solutions of the drug in these solvents and analyzing its drug content spectrophotometrically performed

the test. The mixture was stirred using magnetic bead for 48 hours and then cooled to 25°C. The solutions were filtered and their concentration was determined by UV-spectrophotometer (Jasco V530, Japan) at 238 nm. The results were extrapolated to determine the percent w/w of Escitalopram in its saturated solution with the solvent under investigation.

3.2 Mathematical model- Determination of Liquid load factor (Lf)

The appropriate amounts of carrier and coating materials to produce acceptable flowing and compactable powders are calculated using Eqs. (1)– (3), based on the physical properties of powders termed ‘‘flowable liquid-retention potential” (F -value). The ratio (R) of the amount of carrier (Q) and coating (q) materials is closely related to the amount of liquid medication (W). The maximum amount of liquid loads on the carrier material, termed ‘‘load
factor” (Lf). The coating/carrier ratio (R) is important for determining the ‘‘optimum flowable load factor” (Lf) which gives acceptable flowing powders and is characterized by the ratio between (W) and (Q), as shown in Eqs. 1& 2.

$$Lf = FCA+FCO(1/R) \quad (1)$$

where F CA is the flowable liquid-retention potential of the carrier and F CO is the flowable liquid-retention potential of the coating material.

$$Lf = W/Q \quad (2)$$

From Eq. (2), the amount of Q can be determined and applied to the Eq. (3) to calculate the required amount of the coating (q) material. Then, the amounts of Q and q can be used to prepare liquisolid formulations. It had been proposed that R value of 20 (used with different carriers and coating materials) produces powder admixture with good flow and compactable properties [20, 22-29] Therefore, this ratio will be used in this research.[30]

$$R=Q/q \quad (3)$$

3.4 Compatibility Study

FTIR studies are performed to determine the chemical interaction and compatibility between the drug and excipients used in the formulation. The presence of drug peaks in the formulation and absence of extra peaks indicates there is no chemical interaction.

4. Preparation of conventional tablet and liquisolid compacts.

A conventional formulation of Escitalopram oxalate was directly compressed into circular tablets, each containing 10 mg drug (denoted as DCT)). In addition, each DCT contained the following powder excipients: Avicel PH 102, Aerosil 200, Talc and Magnesium stearate. A 10 tablet batch was mixed in a mortar for 10 min. and the final admixture was compressed using a manual compression machine.

Calculated quantities of Escitalopram oxalate (10mg) and propylene glycol were accurately weighed in a 20-mL glass beaker and mixed well. Then it was incorporated into calculated quantities of carrier (Avicel PH 102) and coating materials (Aerosil-200). From the reported Φ-value the liquid load factor (*Lf*) was calculated.[31] Depending upon the type of vehicle in the formulation, different liquid load factors were employed in liquisolid preparations. Different concentrations of Avicel and silica were used to prepare different liquisolid formulations (LS1-12). The mixing process was carried out in three steps as described by Spireas *et al*.[19] In the first, the system was blended at an approximate mixing rate of one rotation per second for approximately one minute in order to evenly distribute liquid medication in the powder. In the second, the liquid/powder admixture was evenly spread as a uniform layer on the surface of a mortar and left standing for approximately 5 min to allow the drug solution to be absorbed inside powder particles. In the third, the powder was scraped off the mortar surface using an aluminum spatula. Then Sodium starch glycollate (5%) was added to this mixture and blended in a mortar. This provided the final formulation that was compressed into tablets using a single punch tablet compression machine. The important formulation characteristics of liquisolid compacts are shown in Table 1.

5. Precompression studies of the liquisolid system

Flow properties of the liquisolid system

The flow properties of the liquisolid systems 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 and freestanding cone method. The Bulk density and Tap densities were determined for the calculation of Hausner’s ratio and Carr’s Index.[32] Results are shown in Table 2.

Infra red spectra analysis

The infra red spectra of solid dispersions were recorded by the KBr method using a Fourier transform infrared spectrophotometer (FTIR-Shimadzu). A base-line correction was made using dried potassium bromide and then the spectrum of the pure drug, liquisolid system was obtained.

6. In vitro evaluation of liquisolid compacts

The hardness of liquisolid compacts was determined using a Pfizer hardness tester (Pfizer). The mean hardness of each formula was determined. The friability of prepared liquisolid compacts was determined using a digital tablet friability tester (Roche). The disintegration test was carried out using disintegration test apparatus as specified in the Indian Pharmacopoeia.[33] The weight variation test was performed as per USP [34] and results for all the batches of Escitalopram oxalate liquisolid compacts are shown in Table 3.

7. In vitro dissolution study of liquisolid compacts

The test was performed on the prepared Escitalopram oxalate liquisolid tablets and commercial product according to the USP dissolution procedures, apparatus USP Type II. Six individual tablets from each formula were tested. In all studies, the temperature of the dissolution medium was maintained at 37±0.5°C. The paddle rotated at 100 rpm. The dissolution medium was 900ml 0.1 N HCl pH 1.2 for 60 minutes. Samples of 5ml were withdrawn at regular time intervals 10, 20, 30, 40, 50 and 60 minutes, filtered, and analyzed spectrophotometrically at 238nm. Sink condition was maintain. The spectrophotometric readings were converted into cumulative percent of drug released using the standard calibration curve of Escitalopram oxalate previously constructed.

RESULTS AND DISCUSSION

Use of new mathematical model to design liquisolid systems

Escitalopram oxalate was selected as model drug for this study as a suitable candidate for immediate release. The liquisolid hypothesis of Spireas *et al* states that a drug candidate dissolved in a liquid nonvolatile vehicle and incorporated into a carrier material with a porous structure and closely matted fibers in its interior will exhibit both adsorption and absorption. A drug in the form of liquid medication will initially be absorbed in the interior of particles of the carrier and after saturation will be absorbed into internal and external surfaces of the carrier. Coating materials such as Aerosil 200 that have high adsorptivity and greater surface area allow liquisolid systems to provide desirable flow properties.[35] The mathematical model equation for Avicel PH 102 and Aerosil 200 in propylene glycol is given according to values of Phi (Φ) as cited by Spireas *et al*. (17,18).

$$Lf=0.16+3.31(1/R) \quad (4)$$

Based on this equation, Lf is calculated using different *R* values.

Solubility studies

Escitalopram oxalate was selected as the model drug for these studies since it is a very poorly water soluble drug and a suitable candidate for testing the potential of rapid release liquisolid compacts. All the standard curves of Escitalopram oxalate solutions obeyed Beer's law which was linear over the concentration range tested from 5–100 µg/ml. The solubility in distilled water, propylene glycol, polyethylene glycol and glycerin was found to be 5.42 mg/ml, 21.92 mg/ml, 14.33 mg/ml, and 10.65 mg/ml respectively.

Precompression study of liquisolid system

Flow properties of the liquisolid system

The flow properties of the liquisolid powder system are influenced by physical, mechanical as well as environmental factors. Therefore, different flow parameters were employed. As the angle of repose (θ) is a characteristic of the internal friction or cohesion of the particles, the value of the angle of repose will be high if the powder is cohesive and low if the powder is non-cohesive. LS-7 shows good flow properties with a θ value of 30.09 and is considered as a liquisolid system with acceptable flowability. Carr's index up to 16 was considered acceptable as a flow property. Hausner's ratio was related to the inter particle friction; powders with a low inter particle friction had a ratio of approximately 1.25 indicating a good flow. The LS- system with a Carr's index of 17.44 and a Hausner' s ratio of 1.21 was considered for further study and results for all the batches of liquisolid compacts are shown in *table 2.*

IR spectra analysis

The IR spectrum showing percentage transmission (T%) versus wave number of Escitalopram oxalate is shown in *Fig. 1* with characteristic peaks of C-N bending and C-O at 1222.87 and 1103.28 cm^{-1} , respectively. Also cyno (CN) group at 2250 cm^{-1}. From the figure it is evident that Escitalopram oxalate in

liquisolid compact undergoes no chemical reaction with any of the excipients used in the preparation of liquisolid compacts.

In vitro evaluation of liquisolid compacts
Content uniformity
A fundamental quality for all pharmaceutical formulations is a precise dose of drug from one tablet to another.

Hardness
Hardness was found to be in the range of 1.5 ± 0.5 kg/cm^2 to 5.16 ± 0.76 kg/cm^2. It is seen that as the amount of Avicel goes on increasing, hardness also increases. With decrease in R values, hardness was decreased. This low hardness could be attributed to the less amount of added Avicel and poor compressibility of Aerosil. Tablets with low hardness were not considered because they were not able to withstand abrasion in handling.

Weight variation
Weight variation test revealed that the tablets were within the range of Pharmacopoeial specifications. All the formulations passes weight variation test.

Disintegration time
The disintegration time test revealed that the liquisolid tablet formulae disintegrated within 15 min which is as per specifications given for the uncoated tablets in the IP. Microcrystalline cellulose has disintegration property, which could facilitate disintegration of tablets and dissolution of drug. Because of the presence of a nonvolatile solvent acting as a binding agent in the liquisolid formulation, delayed disintegration time is expected. However, in the liquisolid tablets containing microcrystalline cellulose, a fast disintegration of tablet occurred which can be explained by the disintegrating property of microcrystalline cellulose. In addition use of SSG accerlated the disintegration of tablets by virtue of its ability to absorb a large amount of water when exposed to an aqueous environment.

In vitro dissolution studies
The results of in vitro percentage amount of drug released at different time intervals plotted against time to obtain the release profiles. All the liquisolid compacts showed higher drug release than the pure drug. The enhanced dissolution rates of liquisolid compacts compared to pure drug may be attributed to the fact that, the drug is already in solution in PG, while at the same time, it is carried by the powder particles (microcrystalline cellulose and silica).Thus, its release is accerlated due to its markedly increased wettability and surface availability to the dissolution medium. The wettability of the compacts by the dissolution media is one of the proposed mechanisms for explaining the enhanced dissolution rate from the liquisolid compacts. PG facilitates wetting of drug particles by decreasing interfacial tension between dissolution medium and tablet surface.
Fig.2 shows the dissolution profile of LS-7, DCT and marketed tablet of Escitalopram oxalate. Liquisolid compacts displayed more distinct *in-vitro* release characteristics than their directly compressed counterparts. The percentage drug release at the end of the 60th min was 95.40% for LS-7 and 64.21% for DCT.
Since the liquisolid compacts contain a solution of the drug in non volatile vehicle used for preparation of the liquisolid compacts, the drug surface available for dissolution is tremendously increased. In essence, after disintegration, the liquisolid primary particles suspended in the dissolving medium contain the drug in a molecularly dispersed state, whereas the directly compressed compacts are merely exposed micronized drug particles. Therefore, in the case of liquisolid compacts, the surface area of drug available for dissolution is much greater than that of the directly compressed compacts

CONCLUSION
Escitalopram oxalate exhibits high permeability through biological membranes, but its absorption after oral administration is limited by its low dissolution rate due to its very low aqueous solubility. Hence, the use of the liquisolid technique was chosen to enhance the dissolution properties of Escitalopram oxalate. The liquisolid compacts were prepared using Avicel PH 102 and Aerosil 200 as the carrier and coating material, respectively. The powder excipients ratio was directly proportional to the in vitro release of Escitalopram oxalate from their formulations. Finally, Liquisolid technique can be used to improve the solubility, and the in-vitro release of Escitalopram oxalate as a model for a BCS class II drug.

ACKNOWLEDGEMENT
The authors are thankful to Lupin Ltd, Jammu, India for providing Escitalopram oxalate as gift sample for this research work. The authors are thankful to the principal of the STES's Smt. Kashibai Navale College of Pharmacy, Pune Dr. S. D. Sawant for the providing necessary facilities for the experimental work.

Table 1: Formulation table of Escitalopram oxalate liquisolid compacts

Formulation batch code	Drug concentration in Propylene glycol (%, w/w)	R	Lf (mg)	Avicel PH 102 (mg) (Q = W/Lf)	Aerosil 200 (mg) (*q* = Q/*R*)	SSG %
LS-1		5	0.226	133.81	26.0	5
LS-2	10	10	0.822	72.99	14.59	5
LS-3		20	0.491	52.31	10.46	5
LS-4		50	0.325	224.03	22.40	5
LS-5		5	0.226	122.19	12.21	5
LS-6	20	10	0.822	87.57	8.75	5
LS-7		20	0.491	337.94	16.89	5
LS-8		50	0.325	184.33	9.21	5
LS-9		5	0.226	131.1	6.60	5
LS-10	30	10	0.822	486.72	9.70	5
LS-11		20	0.491	265.25	5.30	5
LS-12		50	0.325	190.09	3.80	5

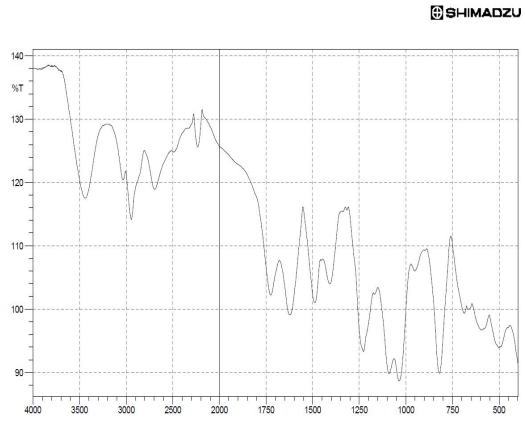
Table 2: Flow properties of Escitalopram oxalate liquisolid compacts (mean ± SD, *n* = 3)

Liquisolid (LS) system	Angle of repose (θ)	Carr's compressibility index*	Hausner's ratio
LS-1	36.28 ± 1.04	14.30 ± 1.98	1.30 ± 0.030
LS-2	35.22 ± 0.95	17.25 ± 1.40	1.31 ± 0.032
LS-3	34.24 ± 0.60	17.47 ± 1.11	1.31 ± 0.010
LS-4	34.02 ± 0.35	16.66 ± 1.21	1.30 ± 0.012
LS-5	33.89 ± 0.55	19.49 ± 1.44	1.24 ± 0.030
LS-6	32.24 ± 1.01	18.65 ± 1.47	1.19 ± 0.010
LS-7	31.94 ± 0.98	17.44 ± 1.33	1.21 ± 0.030
LS-8	31.80 ± 0.80	16.12 ± 1.20	1.24 ± 0.005
LS-9	30.89 ± 1.31	19.46 ± 1.32	1.23 ± 0.015
LS-10	30.09 ± 1.31	17.33 ± 1.33	1.24 ± 0.030
LS-11	29.58 ± 0.82	19.68 ± 1.06	1.25 ± 0.031
LS-12	29.03 ± 1.25	18.58 ± 1.61	1.26 ± 0.012

.

Table 3: Results of invitro liquisolid compact evaluation (mean ± SD, *n* = 3)

Liquisolid (LS) system	Friability (%)	Hardness (kg/cm2)	Weight variation (mg)	Disintegration time (sec)	Content Uniformity	% Drug release
LS-1	0.96	1.66 ± 0.28	282.50 ± 0.112	118.00 ± 12.4	95.42 ± 3.27	85.72
LS-2	0.81	2.33 ± 0.57	154.95 ± 0.094	105.00 ± 7.55	97.64 ± 2.43	91.09
LS-3	0.74	3.83 ± 0.28	128.90 ± 0.162	109.69 ± 13.2	98.53 ± 1.92	91.88
LS-4	0.43	4.50 ± 0.50	374.50 ± 0.416	84.67 ± 11.0	96.75 ± 3.19	94.79
LS-5	0.26	4.83 ± 0.57	204.70 ± 0.169	86.00 ± 9.16	98.95±3.22	86.03
LS-6	0.30	5.83 ± 0.76	146.28 ± 0.136	62.33 ± 14.3	96.84 ± 2.05	90.70
LS-7	0.33	5.16 ± 0.76	488.15 ± 0.071	86.00 ± 8.07	101.24 ±2.8	95.40
LS-8	0.84	1.50 ± 0.76	265.65 ± 0.22	123.33 ± 11.0	96.48 ± 2.18	87.99
LS-9	0.51	3.00 ± 0.86	189.73 ± 0.147	119.00 ± 7.00	95.83 ± 2.21	72.44
LS-10	0.50	4.16 ± 0.57	636.74 ± 0.103	105.00 ± 6.55	97.87 ± 2.74	88.55
LS-11	0.47	4.83 ± 0.76	347.07 ± 0.87	100.00 ± 16.3	100.95 ± 3.30	84.59
LS-12	0.24	4.66 ± 0.28	248.64 ± 0.141	98.00 ± 4.00	101.66 ± 1.98	83.08
DCT	0.52	4.16 ± 0.57	450.09 ± 0.138	147.25 ± 5.00	101.22 ± 1.67	64.21



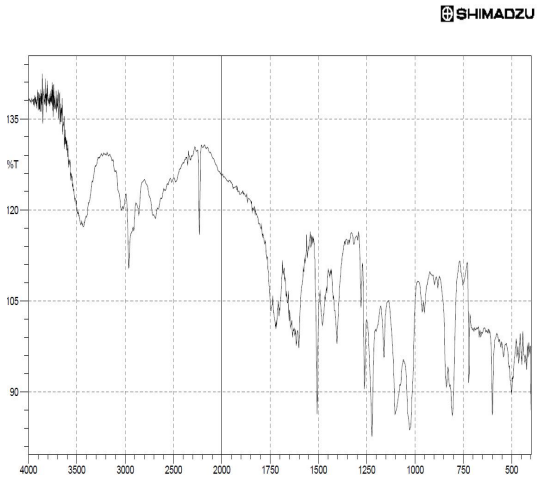


Fig. 1: IR spectra of Escitalopram oxalate plain drug and liquisolid compact

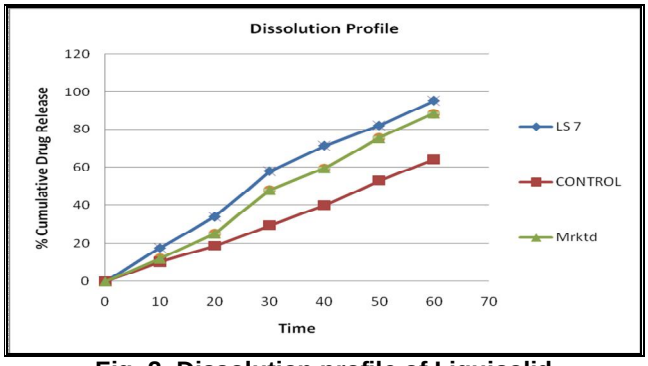


Fig. 2: Dissolution profile of Liquisolid compact DCT and marketed tablet

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