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Research Communication

ENHANCEMENT OF SOLUBILITY OF EZETIMIBE BY LIQUISOLID TECHNIQUE

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Introduction

Bioavailability of a drug depends upon the drug solubility in an aqueous environment and drug permeability through lipophilic membranes. Usually only solubilised drug molecules can be absorbed by the cellular membranes to subsequently reach the site of drug action. The dissolution properties of a drug and its release from a dosage form have a basic impact on its bio-availability. The poor dissolution characteristics of water insoluble drugs are major challenge for pharmaceutical scientist.

Therapeutic effectiveness of a drug depends upon the bioavailability and ultimately upon the solubility of drug molecules. Solubility is one of the important parameter to achieve desired concentration of drug present in systemic circulation for pharmacological response. Different methods are employed to increase the dissolution characteristics of a poorly water soluble drugs are solid dispersion, inclusion complexation, precipitation technologies, lipid based drug delivery, size reduction techniques etc. Among them liquisolid compact is one of the most promising method to promote the dissolution. The liquisolid technique as described by Spireas is a novel concept, where a liquid may be transformed into a free flowing, readily compressible and apparently dry powder by simple physical blending with selected carrier and coating material. The liquid portion, which can be a liquid drug, a drug suspension or a drug solution in suitable non-volatile liquid vehicles, is included into the porous carrier material[8]. Inert, preferably water-miscible organic solvent systems with high boiling point such as liquid polyethylene glycols, propylene glycol, or glycerine are most excellent fitting as liquid vehicles. As the carrier is saturated with liquid, a liquid layer is formed on the particle surface which is instantly adsorbed by the fine coating particles. The liquisolid compacts are acceptably flowing and compressible powdered forms of liquid medications. In current generation inadequate solubility of drugs, which are demanding issue for industry throughout development of the ideal solid dosage unit. This technique is based upon the admixture of drug loaded solutions or liquid drug with appropriate carrier and coating materials. Addition of the additives improves the technique. The selection of non-toxic hydrophilic solvent, carrier, coating excipients and its ratios are independent of the individual chemical entities and it leads to enhance the solubility and bioavailability.

Determination of Standard Curve

Stock solution of 1000µg/ml of Ezetimibe was prepared by dissolving 10mg of drug in small quantity of methanol and diluted with methanol to 10ml. From this take 1ml and make up to 10ml using 0.05M acetate buffer pH4.5 to get a stock solution of 100µg/ml. From the above solution take 5ml and dilute to 50 ml using 0.05M acetate buffer pH 4.5 to get a stock solution of 10µg/ml. The stock solution was serially diluted to get solutions in the range of 2- 10µg/ml and λ_{max} of the solution was found out. The absorbance of the different diluted solutions was measured in a UV spectrophotometer at 232nm. A calibration curve was plotted by taking

concentration of the solution in µg/ml on X-axis and absorbance on Y-axis and correlation co-efficient "r" was calculated.

Determination of Solubility

The solubility of ezetimibe in water, acetate buffer pH 4.5 and three liquid vehicles, namely, polyethylene glycol 400, propylene glycol and tween 80 were studied by preparing saturated solutions of the drug in these solvents. Saturated solutions were prepared by adding excess amount of drug to the vehicle in a screw capped vials, were kept on an orbital shaker for 48 hours at 25°C. The screw capped vials were centrifuged at 500 rpm for further settling of undissolved crystalline material and thereby obtaining a clear supernatant. After centrifugation, accurately measured quantities of the filtered supernatant solutions were further diluted with methanol and analyzed spectrophotometrically at 232nm for their drug content.

Preparation of Liquisolid Tablets

10 mg of Ezetimibe drug was solubilised in three different non-volatile solvent systems (PG, PEG 400, Tween 80) with different drug: vehicle ratio (1:0.5, 1:1, 1:2, 1:3). Then required amount of carrier material (Avicel PH 102) was added to the above liquid by continuous mixing for a period of 10 to 20 minutes in a mortar. Then coating material (Aerosil 200) was added to the above mixture and mixed it thoroughly. Then to the above mixture 5% disintegrant (sodium starch glycolate) and glidant (talc) were added and mixed. The final mixture was compressed into tablet by direct compression.

Preparation of conventional tablet

Conventional tablet of Ezetimibe was prepared by mixing 10mg of drug with avicel, aerosil and sodium starch glycolate as disintegrant. Talc was added to the above mixture and then the powder was compressed into tablets.

Evaluation of Powder Blend

Preformulation study is the characterization of the physiochemical parameters of the drug substance by the application of biopharmaceutical principles with the goal of designing an optimum drug delivery system. The characterisation of drug and the drug–excipient compatibility information decides most of the subsequent events and approaches in development of the formulation. The prepared powder blend were subjected to evaluation as per the methods suggested in the Indian Pharmacopoeia like angle of repose, bulk density, tap density, compressibility index, hausner's ratio.

a. Angle of repose

The angle of repose is the maximum angle which is formed between the surface of a pile of powder and horizontal surface. It is determined by the funnel method. A funnel was kept vertically at a specified height and the funnel bottom was closed. 10 gm of sample was filled inside the funnel. Then funnel was opened to release the powder to form a smooth conical heap which just touches the tip of the funnel. From the powder cone, the radius of the heap (h) was measured. The angle of repose is represented as 'θ' and is calculated using the following equation:

$$\tan \theta = h/r \qquad \text{eq..... (3)}$$

Where,
$\theta = \tan^{-1} (h/r)$
h = height of the pile (cm),
r = radius of the pile (cm)

Table 1:
Low properties and corresponding angle of repose

FLOW PROPERTIES	ANGLE OF REPOSE (DEGREES)
Excellent	25-30
Good	31-35
Fair	36-40
Passable	41-45
Poor	46-55
Very poor	56-65
Very very poor	>66

b. Bulk density

The bulk densities of the samples were determined by transferring the accurately weighed sample of powder to the graduated 50 ml measuring cylinder. The initial volume (bulk volume) and weight was noted. The bulk density is calculated by the formula:

Bulk density = Weight of sample / Bulk volume eq..... (4)

c. Tapped density

An accurately weighed powder sample was transferred to the graduated 50 ml measuring cylinder and was placed on the tap density apparatus. The apparatus was operated for a fixed number of taps. The final volume (tap volume) of the tapped mass was noted. The tapped density was calculated by using the formula:

Tapped density = Weight of sample / Tapped volume eq..... (5)

Table 2:
Scale of flowability based on hausner's ratio

HAUSNER'S RATIO	FLOW CHARACTER
1-1.11	Excellent
1.12-1.18	Good
1.19-1.25	Fair
1.26-1.34	Passable
1.35-1.45	Poor
1.46-1.59	Very poor
>1.60	Very, very poor

d. Hausner's ratio

Hausner's ratio is the ratio of the initial volume of the powder mass to the final volume of the powder mass obtained after specified number of tapping.

e. Compressibility

The bulk density, cohesiveness of the material, surface area, size & shape and the moisture content influences the compressibility index. The compressibility index is determined from the bulk volume and tap volume. The basic method used for the determination of compressibility index is to measure the bulk volume and the final tapped volume after a fixed number of tapping until no change in volume occurs. It is represented in percentage.

% Compressibility = (Tapped density-Bulk density) / Tapped density X 100 eq.....(6)

Table 3:
Scale of flowability based on compressibility index

COMPRESSIBILITY INDEX	FLOW CHARACTER
≤10	Excellent
11-15	Good
16-20	Fair
21-25	Passable
26-31	Poor
32-37	Very poor
>38	Very, very poor

Compatibility Study FT-IR

IR spectra matching approach was used for detection of any possible chemical interaction between drug and excipients. A physical mixture (1:1) of drug and polymer was prepared and mixed with the suitable quantity of potassium bromide. About 100mg of mixture was compressed to form a transparent pellet using a hydraulic press at 6tons pressure. It was scanned from 4000 to 400 cm^{-1} in FT-IR spectrometer. The IR spectrum of the physical mixture was compared with those of pure drug and polymer and matching was done to detect any appearance or disappearance of peaks.

X-ray powder diffraction analysis

Crystallinity of the drug and the formulation was determined using the XRD-6000 diffractometer with copper target. The conditions were: 40 kV voltages; 30 mA current. The samples were loaded on to the diffractometer and scanned over a range of 20 values from 10° to 80° at a scan rate of 10.00 °/min.

Compression of Tablets

Weigh accurately about 250mg (according to table: 5) of the mixture blend and fed into the die of single punch tablet press and compressed at 1.5N compression force using 8mm concave punches.

Evaluation of Tablets

a. Weight variation test

20 tablets were selected at random and weighed individually. The average weight of each batch of tablet was calculated. Individual weights of the tablets were compared with the average weight. Since the tablet weighed around 250mg, IP specifies that the tablets pass the test if not more than two of the individual weights deviate from the average weight by more than 7.5%.

Table 4:
Weight variation limit as per IP

Percentage deviation allowed under weight variation test	
Average weight of tablet	**Percentage deviation**
≤ 80 mg	10 %
80 – 250 mg	7.5 %
≥ 250 mg	5 %

b. Hardness

Hardness of the tablet was measured by Pfizer tablet hardness tester. The tablets were held vertically in between the jaws which were pressed with hand until the tablet broken. The reading was noted from the needle of pressure dial which may be expressed in kilograms.

c. Friability

This was performed to evaluate the ability of tablet to withstand abrasions. Ten tablets were weighed and placed in the tumbling chamber of Roche friabilator which rotated for 100 revolutions at a speed of 25 rpm. The tablets were again weighed and the loss in weight indicated the friability. Friability value should not exceed 1% according to IP specification.

$$\% \text{ Friability} = \frac{A-B}{A} \qquad \text{eq.....(7)}$$

where, A = initial weight of tablets
B = weight of tablet after 100 revolution.

d. Assay of tablet

Ten tablets were randomly weighed and crushed. Calculated the average weight and taken the powder equivalent to 10 mg of Ezetimibe base in a 100 ml volumetric flask. Add few ml methanol and sonicated for 10 minute. Then volume made up to 100 ml with 0.05M acetate buffer pH 4.5. Then 1ml of resultant solution diluted to 100ml with 0.05M acetate buffer pH 4.5 and the absorbance was measured using UV spectrophotometer at 232nm.

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e. In-vitro Dissolution studies

The Ezetimibe release from different formulations was determined using a USP XXIII paddle apparatus 2 under sink condition. The dissolution medium was 500ml 0.05M acetate buffer pH 4.5 at 37 ± 0.5 °C; at 50 rpm, to simulate *in-vivo* conditions. The formulation prepared was subjected to dissolution tests for 45 minutes. Sample (10 ml) was withdrawn at predetermined time intervals, filtered through Whatmann filter paper and replaced by an equal volume of dissolution medium. Drug content in the dissolution sample was determined by UV spectrophotometer at 232nm.

Release Kinetics

The results of *in-vitro* release profile obtained for all the formulations were plotted in modes of data treatment as follows.

1. Cumulative percent drug release versus time (zero order kinetic model)
2. Log cumulative percent drug remaining versus time (first order kinetic model)
3. Cumulative percent drug release versus square root of time (Higuchi's model)
4. Log cumulative Percent Drug released versus log time (Korsmeyer model)

Drug release kinetics- model fitting of the dissolution data

Whenever a new solid dosage form is developed or produces, it is necessary to ensure that drug dissolution occurs in an appropriate manner. Drug dissolution from solid dosage forms has been described by kinetic models in which the dissolved amount of drug (Q) is a function of the test time, t or Q = f (t). Some analytical definitions of the Q (t) function are commonly used such as zero order, first order, higuchi, korsmeyer-peppas models. Other release parameters, such as dissolution time ($t_{x\%}$), dissolution efficacy (ED), difference factor *(f_1),* similarity factor *(f_2)* can be used to characterize drug dissolution / release profile.

1. Zero order kinetics

A zero-order release would be predicted by the following equation.

$$At = A_o - K_o t \qquad \text{eq.....(8)}$$

Where,

At = Drug release at time t
A_o = Initial drug concentration
K_o = Zero-order rate constant (hr)

When the data is plotted as cumulative percent drug release versus time if the plot is linear then the data obeys zero-order release kinetics, with a slope equal to k_o.

Use: This relation can be used to describe the drug dissolution of several types of modified release pharmaceutical dosage forms, as in case of some transdermal systems etc. the pharmaceutical dosage forms following this profile release the same amount of drug by unit of time and it is the ideal method of drug release in order to achieve a prolonged pharmacological action.

2. First order kinetics

A first order release would be predicted by the following equation.

$$\text{Log } C = \text{Log } Co - K_t / 2.303 \qquad \text{eq.....(9)}$$

Where

C = Amount of drug remained at time t
C_o = Initial amount of drug
K = First-order rate constant

When the data is plotted as log cumulative percent drug remaining versus time yields a straight line indicating the release follows first-order kinetics, the constant k can be obtained by multiplying 2.303 with slope values.

Use: The pharmaceutical dosage forms containing water-soluble drugs in porous matrices, follows this type of dissolution profile. The release of the drug is proportional to the amount of drug remaining in its interior so that the amount of drug release by unit of time diminishes.

3. Higuchi model

Drug release from the matrix devices by diffusion has been described by following higuchi's classical diffusion equation.

$$Q = [DE/ \tau(2A- ECs) C_{st}] \qquad \text{eq.....(10)}$$

Where,

Q = Amount of drug release at time t
D = Diffusion coefficient of the drug in the matrix
A = Total amount of drug in unit volume of matrix
C_s = The solubility of the drug in the matrix
E = Porosity of the matrix
T = Time in hrs at which q is the amount of drug is release

Equation-3 may be simplified if one assumes that D, Cs and A are constant. Then equation-3 becomes

$$Q = K_t \, ½ \qquad \text{eq.....(11)}$$

When the data is plotted according to equation-4 i.e. cumulative drug release versus Square root of time yields a straight line, indicating that the drug was released by diffusion mechanism. The slope is equal to k.

Use: The relation can be used to describe the drug dissolution from several types of modified release pharmaceutical dosage forms, as in case of some water soluble drugs.

4. Korsmeyer peppas model

In order to understand the mode of release of drug from swellable matrices, the data were fitted to the following equation:

$$M_t / M_\infty = Kt^n \qquad \text{eq.....(12)}$$

Where,
M_t / M_∞ = The fraction of drug released at time't'
K = Constant incorporating the structural and geometrical characteristics of the drug / polymer system.
n = Diffusion exponent related to the mechanism of release.

The above equation can be simplified by applying log on both sides we get

$$\text{Log } M_t / M_\infty = \text{Log } K + n \text{ Log } t \qquad \text{eq.....(13)}$$

When the data is plotted as a log of drug released versus log time, yields a straight line with a slope equal to n and the k can be obtained from y- intercept. The value of n for a cylinder is <0.45 for fickian release, >0.45 and < 0.89 for non-Fickian release, 0.89 for the case 2 release and > 0.89 for super case2 type release.

Stability Studies

The prepared formulations which showed best *in-vitro* results was selected and kept for stability testing for 3 days. The tablets were kept at 40± 2°C/ 75%±5%RH in a stability chamber and samples were withdrawn at initial, 1st , 2nd and 3rd month and evaluated for drug content, disintegration , dissolution study.

Results and Discussion

Calibration Curve of Ezetimibe

A calibration curve for Ezetimibe was constructed in 0.05M acetate buffer pH 4.5 by scanning the diluted drug solution at 232nm using UV spectrophotometer. The linearity of the calibration curve was found to be in the range of 2-10µg/ml. A regression coefficient value of0.998 was noticed for Ezetimibe.

Table 5:
Calibration curve of ezetimibe

CONCENTRATION (µg/ml)	ABSORBANCE at 232 nm
2	0.123
4	0.254
6	0.382
8	0.497
10	0.653

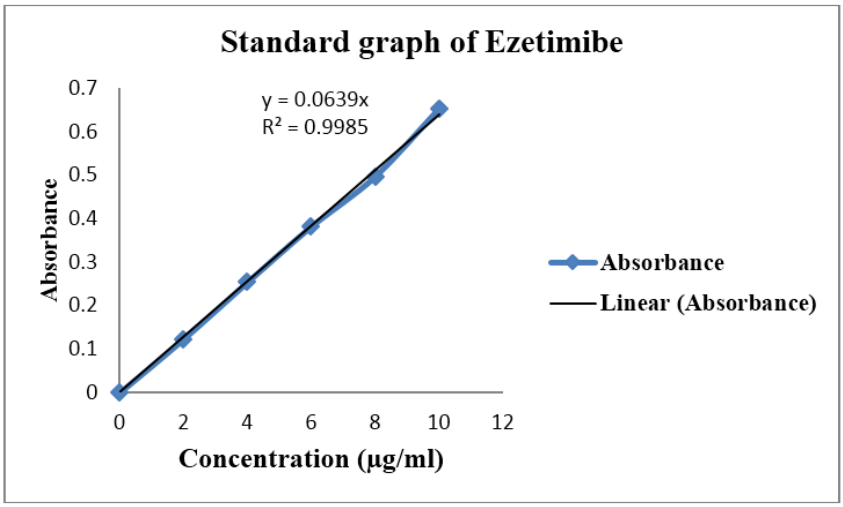

Figure No1: Standard graph of Ezetimibe

Solubility Studies

The solubility of Ezetimibe in different solvents was studied to select the suitable solvent to be used in the formulation. The results obtained were given in Table No: 6. Ezetimibe showed a maximum solubility of 0.950 mg/ml in tween 80 followed by 0.781mg/ml inpolyethylene glycol (PEG) and 0.672 mg/ml in propylene Glycol (PG). Maximum solubility of the drug is needed for preparing liquisolid compacts, as higher the solubility the more the drug will be dissolved in the vehicle prior to the adsorption on to the carrier particle. Tween 80 showed greater solubility of the drug than the other two solvents, it was selected as the suitable solvent for preparing Ezetimibe liquisolid compacts in this study.

Table 6:
Solubility of Ezetimibe in different solvents

Solvents	Solubility (mg/ml)
Water	0.008
0.05M acetate buffer pH 4.5	0.041
Propylene Glycol	0.672
PEG 400	0.781
Tween 80	0.950

Application of New Mathematical Model for Design of Liquisolidsystem

The liquisolid technique as suggested by Spireas et al, states that the drug dissolved in a liquid vehicle is incorporated into carrier and coating materials having porous structure and closely matted fibres in its interior, is a phenomenon of both adsorption and absorption. Coating materials like Avicel PH 102 have high adsorptive capacity and greater surface area and thus gives the liquisolid systems the desirable flow and compaction properties.

The quantity of carrier material (Q) required, the quantity of coating material (q), liquid load factor (L_f) and excipients ratio (R) was calculated by using the following equations;

Amount of carrier material required (Q) = W/L_f eq..... (14)

Amount of coating material required (q) = Q/R eq.....(15)

Liquid load factor (L_f) = W/Q eq..... (16)
Excipient Ratio (R) = Q/q eq..... (17)

Where W is the weight of liquid medication, L_f is the Liquid load factor, R is the carrier and coating material ratio. The formulation table according to the above calculations is shown in the Table 7.

Table 7:
Formulation chart

Formulation code	Drug Concentration (% w/w)	R	L_f	Q (mg)	q (mg)	Fm
F1	66.66	20:1	0.0750	200	10	0.0142
F2	50	20:1	0.0703	284.6	14.32	0.0190
F3	33.33	20:1	0.0750	400	20	0.0285
F4	25	20:1	0.0680	588.0	29.40	0.0380
F5	66.66	20:1	0.0833	180	9	0.0101
F6	50	20:1	0.0823	243.1	12.1	0.0134
F7	33.33	20:1	0.0817	367	18.35	0.0201
F8	25	20:1	0.0820	488	24.42	0.0268
F9	66.66	20:1	0.0781	192	9.6	0.0117
F10	50	20:1	0.0797	251	12.6	0.0156
F11	33.33	20:1	0.0765	392.4	19.62	0.0234
F12	25	20:1	0.0784	510	25.5	0.0312

R -carrier: coating ratio, Q - weight of carrier, q - weight of coating material,
F_m - fraction of molecularly dispersed drug, L_f – liquid load factor

Evaluation of Flowability and Compressibility of Liquisolid Powders

Powder flow is a complicated matter and is influenced by so many interrelated factors, which includes physical, mechanical and environmental factors. Flow properties are crucial in handling and processing operations such as flow from hoppers, mixing and compression. These properties can be determined by evaluating parameters such as angle of repose, bulk density, tapped density, compressibility index and hausner's ratio. As the angle of repose 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. Table: 8 revealed that all the tested liquisolid systems had a satisfactory flow according to the obtained results of measuring the angle of repose for each liquisolid system. The range was from 27.58° to 33.76°. Powders with angle of repose greater than 50° have unsatisfactory flow properties; whereas minimum angles close to 20° correspond to very good flow properties.The prepared liquisolid systems can be arranged in ascending order, regarding the angle of repose measurements as follows: F10< F8< F4< F12< F2< F11< F7< F3< F6< F9< F5< F1. The bulk and tapped densities for Ezetimibe liquisolid powders were illustrated in Table :8, the mean densities of liquisolid powders were found to be from 0.3371 to 0.4027 g/cm^3 for bulk density and from 0.3938 to 0.4992 g/cm^3 for tapped density. Hausner's ratio was related to the inter particle friction, so that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow.The results revealed that F1,F2, F3, F5, F6, F7, F9, F10 had ratios of 1.12, 1.15, 1.23, 1.14, 1.19, 1.24, 1.19, 1.18 indicated good flowability. Compressibility is indirectly related to the relative flow rate, cohesiveness, and particle size of a powder. A compressible material will be less flowable, and powders with compressibility values greater than 20-21% have been found to

exhibit poor flow properties. From the results, F1,F2, F3, F5, F6, F7,F9, F10 had compressibility values less than 21 % showed good compaction properties.

Table 8:
Precompression studies

Formulation	Angle of repose (degree)	Tapped density (gm/cm³)	Bulk density (gm/cm³)	Hausner's ratio	Compressibiliy Index (%)
F1	27.58	0.4505	0.4022	1.12	10.72
F2	30.31	0.4541	0.3946	1.15	13.10
F3	29.56	0.4992	0.4027	1.23	19.33
F4	31.76	0.4923	0.3876	1.26	21.26
F5	28.45	0.3938	0.3371	1.14	14.39
F6	29.42	0.4380	0.3668	1.19	16.25
F7	29.64	0.4497	0.3625	1.24	19.39
F8	32.02	0.4419	0.3435	1.28	22.26
F9	28.66	0.4180	0.3506	1.19	16.12
F10	33.76	0.4254	0.3589	1.18	15.63
F11	29.64	0.4467	0.3495	1.27	21.75
F12	30.67	0.4431	0.3447	1.29	22.21
PCT	28.33	0.4432	0.3954	1.12	10.78

PCT = Prepared Conventional Tablet

Compatibility Studies

The spectrum obtained after the analysis is shown in figure no: 2 to 6. The spectrum of the standard and the samples were then superimposed to find out any possible interactions between the drug and the polymers. All the characteristic peaks of Ezetimibe mentioned in Table 9 were also found in the spectrum formulations. The results suggest that the drug is intact in the formulations and there is no interaction found between the drug and the excipient.

Table No 9:
Characteristics peaks of Ezetimibe

Serial number	Wavelength	Specification
1	$3260cm^{-1}$	O – H stretch
2	$1717cm^{-1}$	C = O stretch
3	$1443cm^{-1}$	C – N stetch
4	$1268cm^{-1}$	C –F stretch

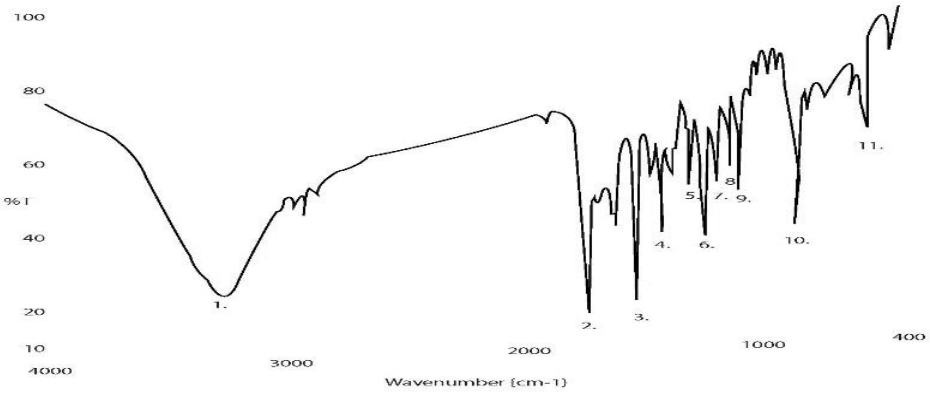

Figure No 2: IR Spectra of Ezetimibe

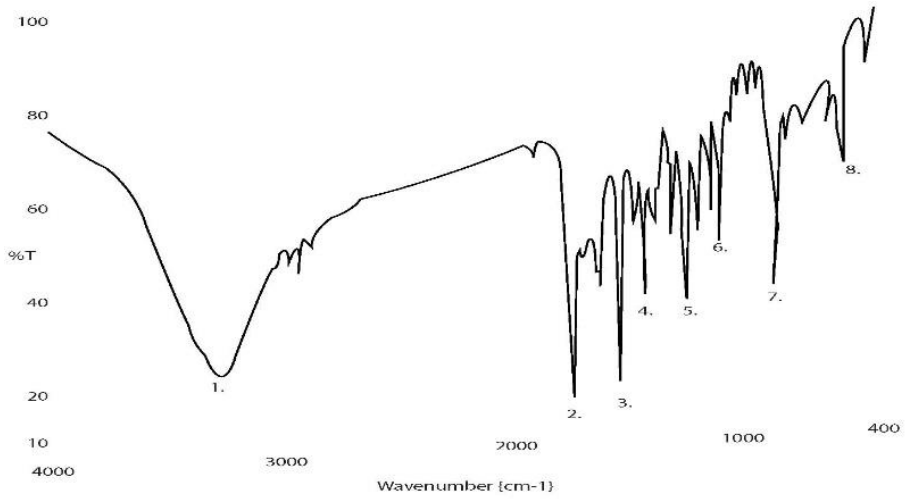

Figure No 3: IR spectra of Ezetimibe with SSG

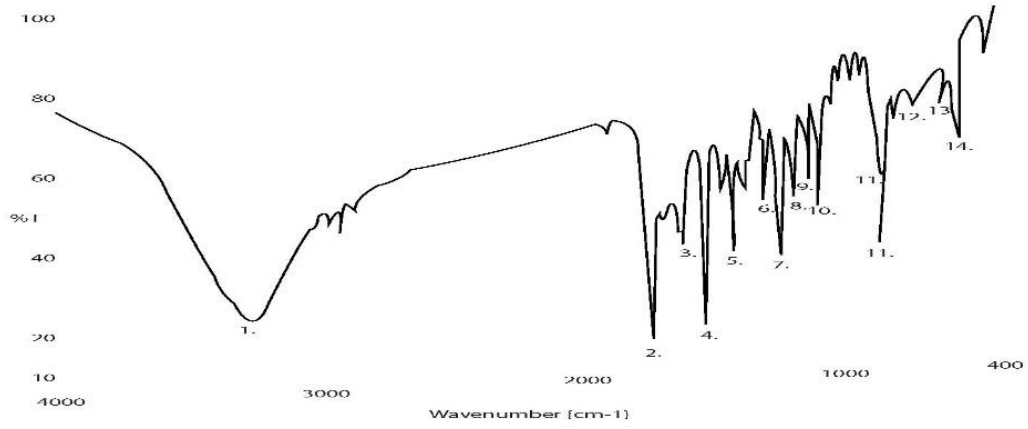

Figure No 4: IR spectra of Ezetimibe with MCC

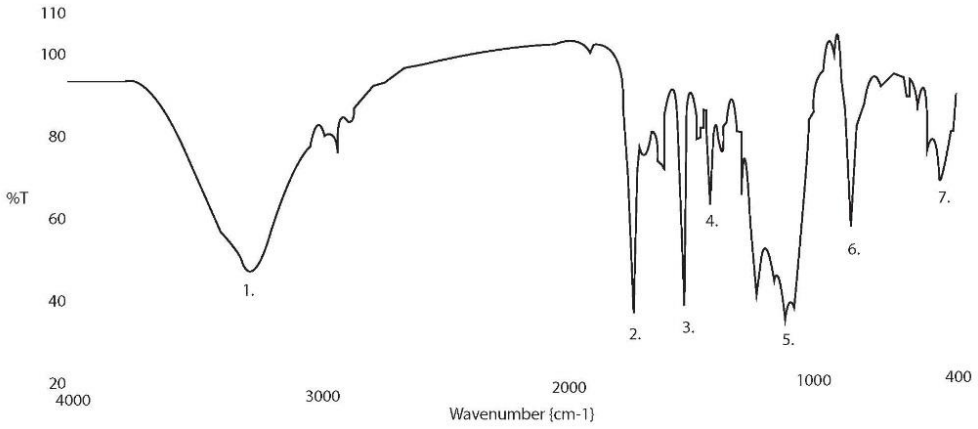

Figure No 5: IR spectra of Ezetimibe with Aerosil

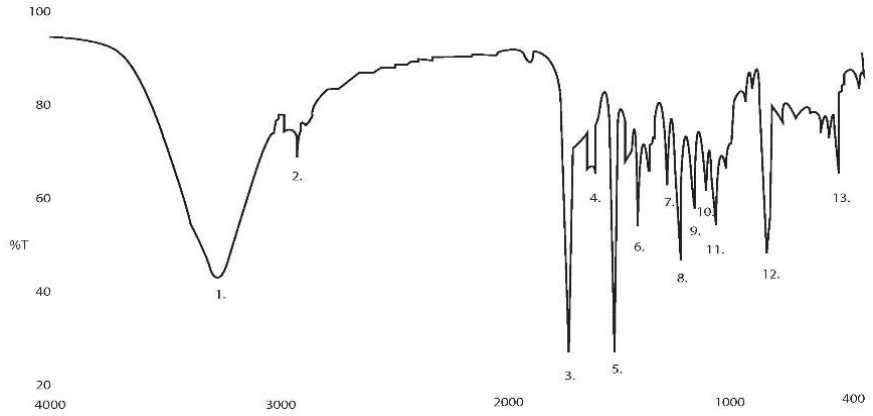

Figure No 6: IR spectra of LS formulation-F4

X-Ray Powder Diffraction (XRPD)

Figure No: 7 and 8shows the XRPD of pure drug and the liquisolid system, revealed that pure Ezetimibe was clearly in crystalline state as it showed sharp peaks at 2θ diffraction angles of 22.94°, 24.51° and 19.39°. The absence of characteristic peaks of Ezetimibe in the liquisolid system showed the conversion of drug to an amorphous or solubilized form. The absence of crystallinity in the liquisolid system is due to the solubilization of drug in the liquid vehicle. This amorphisation or solubilisation of Ezetimibe in the liquisolid system may contribute to the consequent improvement in the dissolution rate and therefore the bioavailability of Ezetimibe

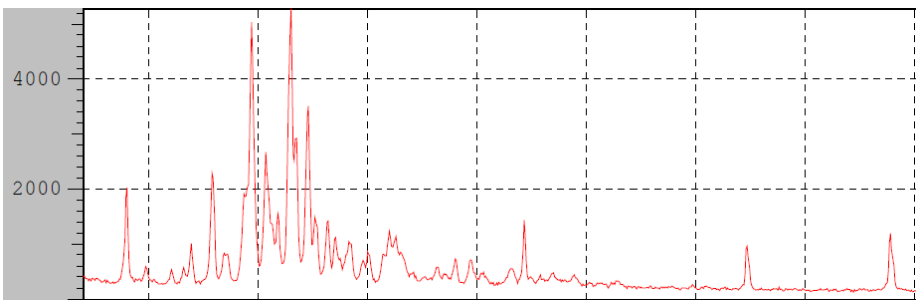

Figure No 7: X-ray diffraction of pure Ezetimibe

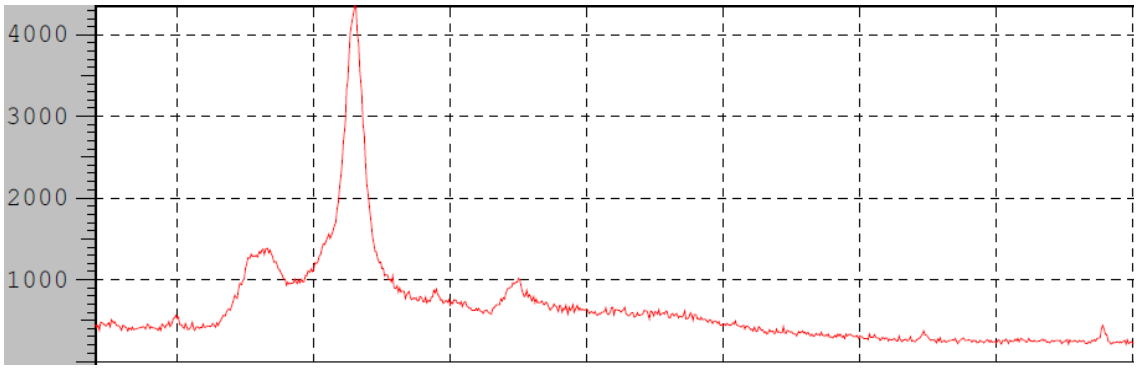

Figure No 8: X-ray diffraction of LS formulation-F4

Compression of Tablet

The liquisolid tablets were prepared by direct compression technique. The target weight of the prepared tablet was 250mg. The desired hardness is between 3-5kg/cm^2. All the tablets were found to be uniform in size and shape and no processing problems were encountered during compression process. Similarly conventional tablet of pure drug was also prepared by direct compression technique.

Evaluation of Post Compression Parameters

The mean hardness of each liquisolid formulation was determined and is listed in Table No: 10. Mean hardness of the prepared liquisolid tablets were in the range of 3.4 - 4.2 kg/cm^2, proved that the tablets had acceptable hardness. The percentage loss in weights were calculated and taken as a measure of friability was shown in the Table No: 10. All the Ezetimibe liquisolid tablets had acceptable friability as none of the tested formulation had percentage loss in tablet weights that exceed 1% and also no tablets were cracked or broken. Since all the prepared tablets met the standard friability criteria, they are expected to show acceptable durability and withstand abrasion in handling, packaging and transportation.

The release rate of a drug from a dosage form is dependent on its disintegration and the dissolution rate of the drug. Therefore, it is very important for liquisolid systems with enhanced drug release to ensure that disintegration is not the rate-limiting step and drug dissolution is not hindered by a slow disintegration of the dosage form. Disintegration time was found in the range of 57 – 123 sec (Table No: 10). F4 showed faster disintegration. This faster disintegration time indicate rapid release rates. From the weight variation test, the average percentage deviation of all tablet formulations was found to be within the IP limit and hence all the formulations passed the test. The results of all prepared tablets were summarized in Table No: 10. F7 showed maximum drug content and F2 & F11had minimum drug content. It was clear from Table No: 10 that all the investigated liquisolid tablets complied with the pharmacopoeial requirements with regard to their content uniformity, which was found to lie within the range of 97.3 to 99.2 %.

Table No: 10
Post compression studies

Formulation	Hardness(kg/cm²)	Friability (%)	Weight variation (mg)	Disintegration (sec)	Drug content (%)
F1	4.1	0.4	255± 5	78	98.2
F2	4.0	0.5	256 ±6	74	97.3
F3	3.8	0.4	253 ±3	63	98.4
F4	3.4	0.4	256± 4	57	98.6
F5	4.0	0.5	253± 4	101	97.6
F6	4.2	0.6	254± 3	104	98.4
F7	4.0	0.5	256 ±6	97	99.2
F8	4.1	0.6	256 ±5	83	98.5
F9	4.2	0.7	255 ±6	89	97.4
F10	3.9	0.6	253 ±4	86	98.1
F11	4.0	0.5	254 ±3	82	97.3
F12	3.6	0.4	256 ±2	60	98.7
PCT	3.9	0.5	253±3	123	97.3

PCT = Prepared Conventional Tablet

In-Vitro Dissolution Study

Figure No: 9 to 13 show the dissolution profile of 12 formulations, conventional tablet of pure drug and marketed tablet. Liquisolid compacts displayed more distinct *in-vitro* release characteristics than the conventional and marketed drug. Among all, F4 showed higher release rate (94.67%) at the end of the 45th min. Conventional tablet and marketed tablet showed only 48.67% and 61.33 % cumulative release. It was confirmed that at 10 min F4 had the highest drug release 53.65% compared with 15.42% for the conventional tablet. 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.

According to Noyes and Whitney, the drug dissolution rate (DR) is directly proportional not only to the concentration gradient (Cs-C) of the drug in the stagnant diffusion layer, but also to its surface area (S) available for dissolution. Moreover, since all dissolution tests for both Ezetimibe preparations were carried out at a constant rotational paddle speed (50 rpm/min) and identical dissolving media, it is assumed that the thickness (h) of the stagnant diffusion layer and the diffusion coefficient (D) of the drug molecules transported through it remain almost identical under each set of dissolution conditions. Therefore, the significantly increased surface area of the molecularly dispersed Ezetimibe in the liquisolid compacts may be principally responsible for their higher dissolution rates. The consistent and higher dissolution rate displayed by liquisolid compacts will improve the absorption of drug from the GI tract.

Table No 11:
Dissolution profile of prepared conventional formulation

Time (min)	% Cumulative drug release
5	12.25
10	15.42
20	22.81
30	35.36
45	48.67

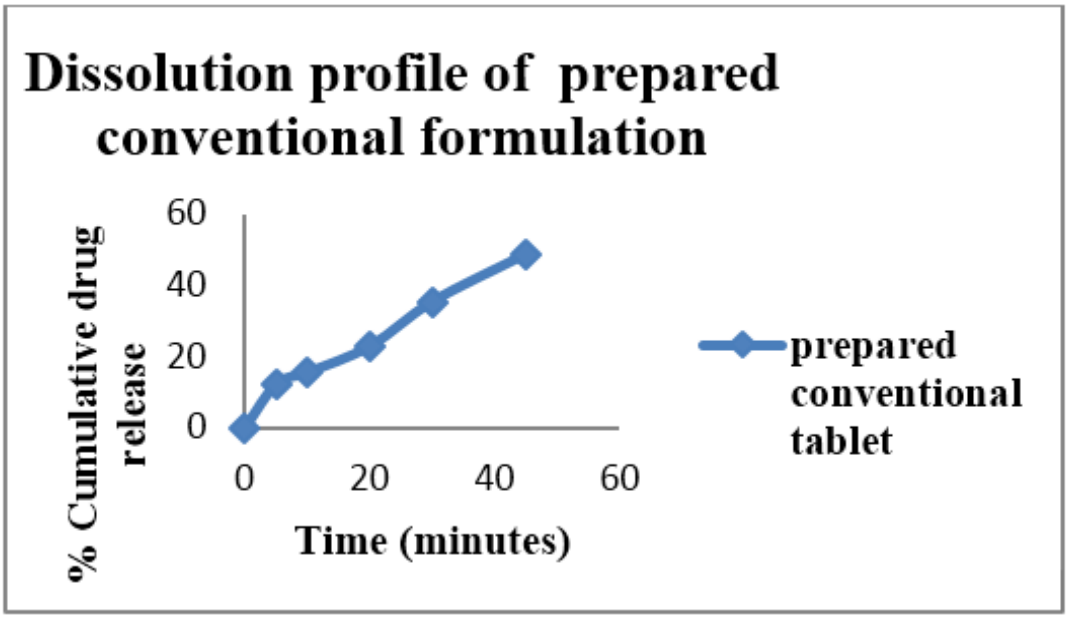

Figure No 9: Dissolution profile of prepared conventional formulation

Table No 12:
Dissolution profile of marketed formulation

Time (min)	% Cumulative drug release
5	19.10
10	25.49
20	38.19
30	52.23
45	61.33

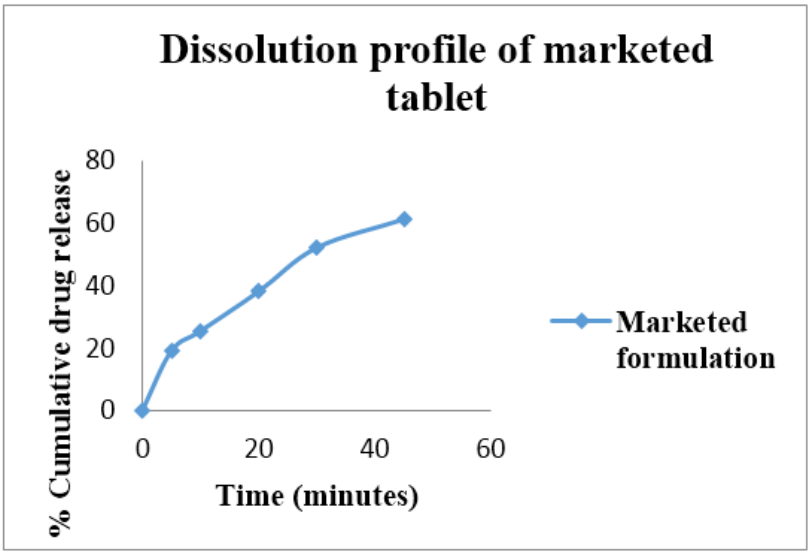

Figure No 10: Dissolution profile of marketed tablet

Table No 13:
Dissolution profile of liquisolid compacts with Tween 80

Time (min)	% Cumulative drug release of F1(1:0.5)	% Cumulative drug release of F2 (1:1)	% Cumulative drug release of F3 (1:2)	% Cumulative drug release of F4 (1:3)
5	34.39	32.51	36.91	44.92
10	48.45	49.38	50.49	53.65
20	62.96	65.73	71.10	72.52
30	77.56	78.35	82.75	89.44
45	85.29	87.95	90.63	94.67

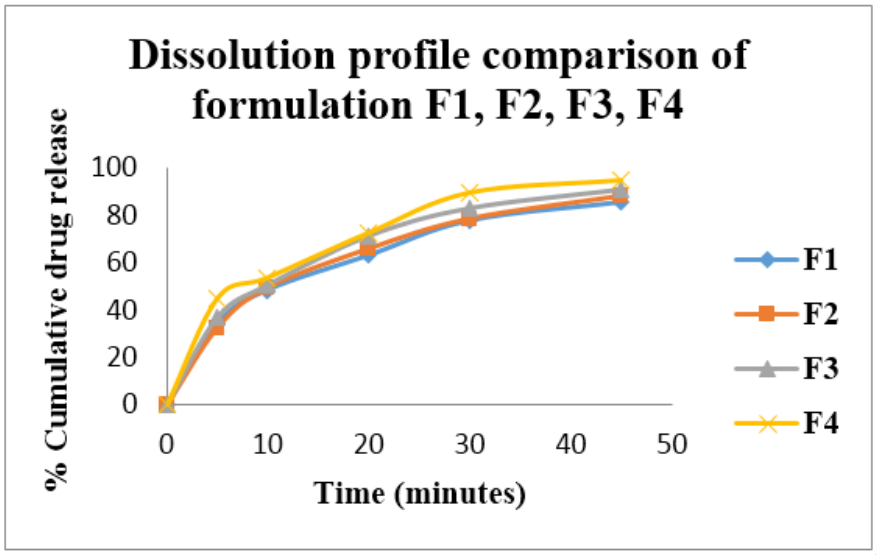

Figure No 11: Dissolution profile comparison of formulations F1, F2, F3& F4

Table No 14:
Dissolution profile of liquisolid compacts with PG

Time (min)	% Cumulative drug release of F5 (1:0.5)	% Cumulative drug release of F6 (1:1)	% Cumulative drug release of F7 (1:2)	% Cumulative drug release of F8 (1:3)
5	25	27.64	35.65	33.29
10	41.67	39.19	47.66	42.16
20	55.21	53.32	63.26	63.85
30	69.69	68.43	71.75	79.60
45	76.47	75.68	79.93	82.46

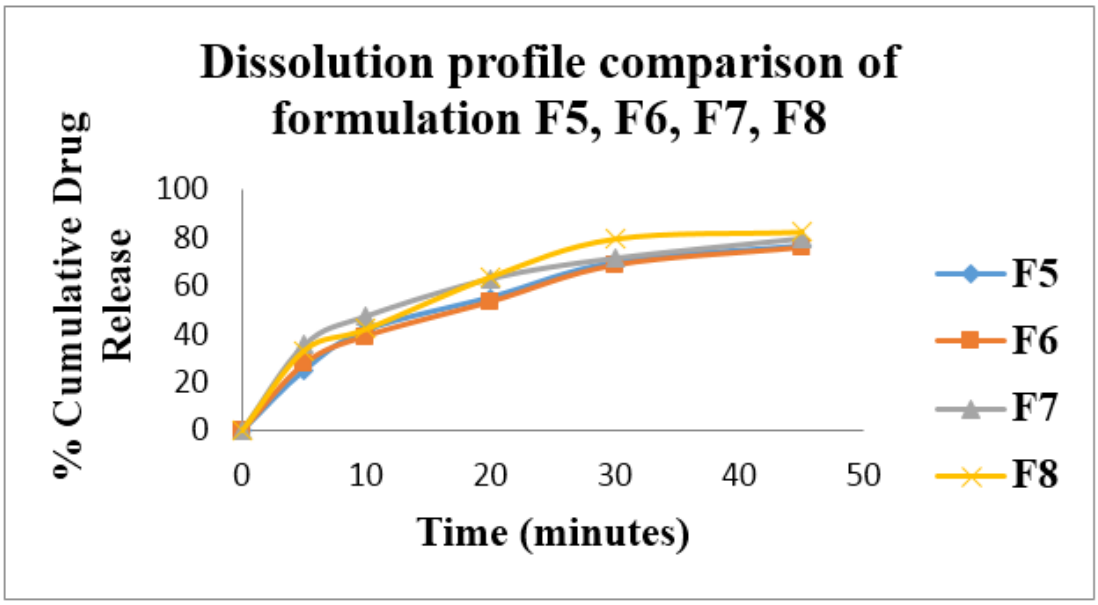

Figure No 12: Dissolution profile comparison of formulations F5, F6, F7& F8

Table No 15:
Dissolution profile of liquisolid compacts with PEG 400

Time (min)	% Cumulative drug release of F9 (1:0.5)	% Cumulative drug release of F10 (1:1)	% Cumulative drug release of F11 (1:2)	% Cumulative drug release of F12 (1:3)
5	35.49	37.85	29.22	42.45
10	44.36	48.92	43.09	51.60
20	65.94	66.85	68.88	72.98
30	72.54	73.79	76.47	79.93
45	80.25	81.50	83.55	91.57

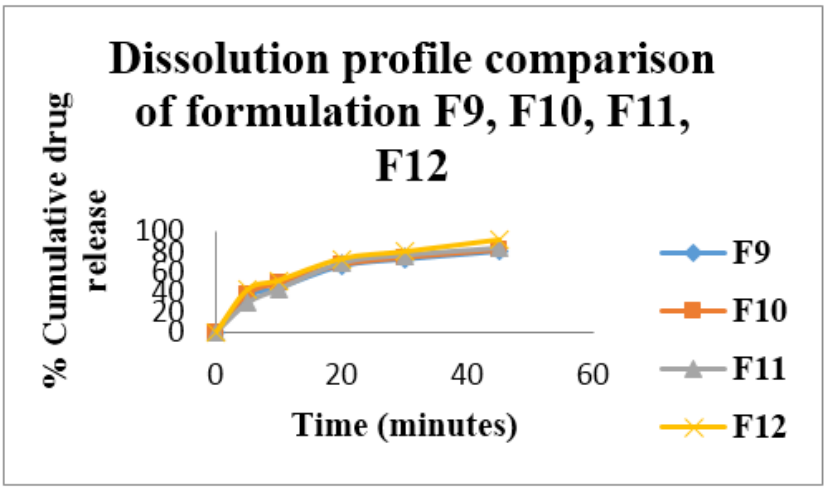

Figure No 13: Dissolution profile comparison of formulations F9, F10, F11& F12

Table No 16:
Dissolution profile of optimised formulation and prepared conventional formulation

Time (min)	% Cumulative drug release of optimised formulation (F4)	% Cumulative drug release of prepared conventional formulation
5	44.92	12.25
10	53.65	15.42
20	72.52	22.81
30	89.44	35.36
45	94.67	48.67

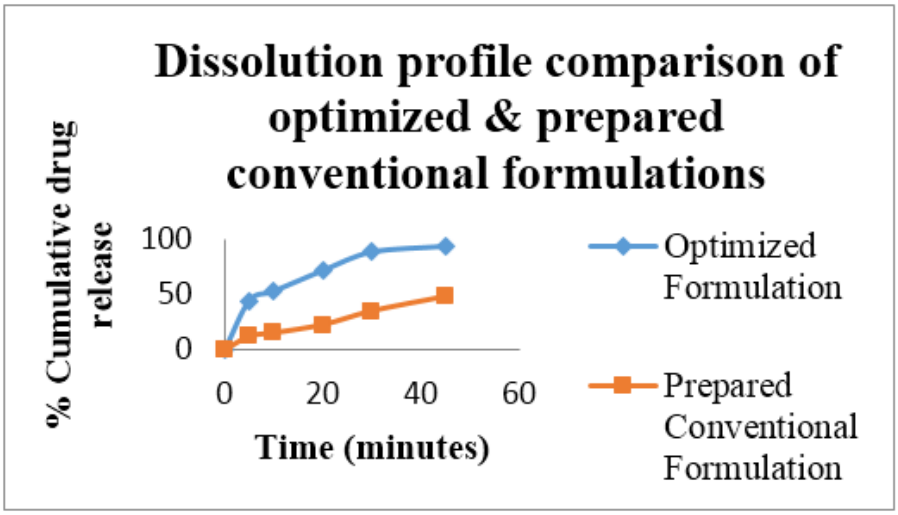

Figure No: 15 Dissolution profile comparison of optimised & prepared conventional

Table No 17:
Dissolution profile of optimised
and marketed formulation

Time (min)	% Cumulative drug release of optimised formulation (F4)	% Cumulative drug release of marketed formulation
5	44.92	19.10
10	53.65	25.49
20	72.52	38.19
30	89.44	52.23
45	94.67	61.33

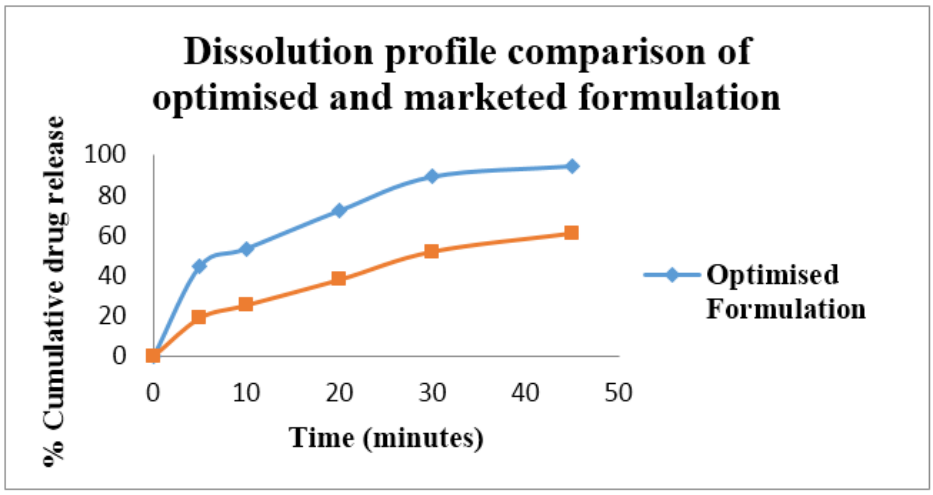

Figure No 16: Dissolution profile comparison of optimised & marketed formulation

Table No 18:
Dissolution profile of optimised, marketed
and conventional formulation

Time (min)	% Cumulative drug release of optimised formulation (F4)	% Cumulative drug release of marketed formulation	% Cumulative drug release of prepared conventional formulation
5	44.92	19.10	12.25
10	53.65	25.49	15.42
20	72.52	38.19	22.81
30	89.44	52.23	35.36
45	94.67	61.33	48.67

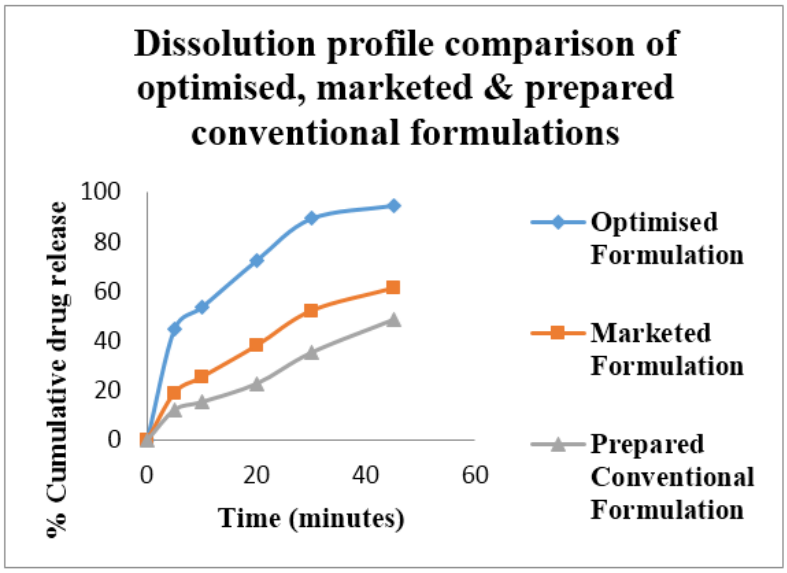

Figure No 17: Dissolution profile comparison of optimised, marketed &prepared conventional formulation.

Effect of drug concentration on release rates

Figure No: 18 shows that formulation with smaller drug concentration (25 %w/w) have a higher dissolution rate than a higher drug concentration (66.66% w/w).

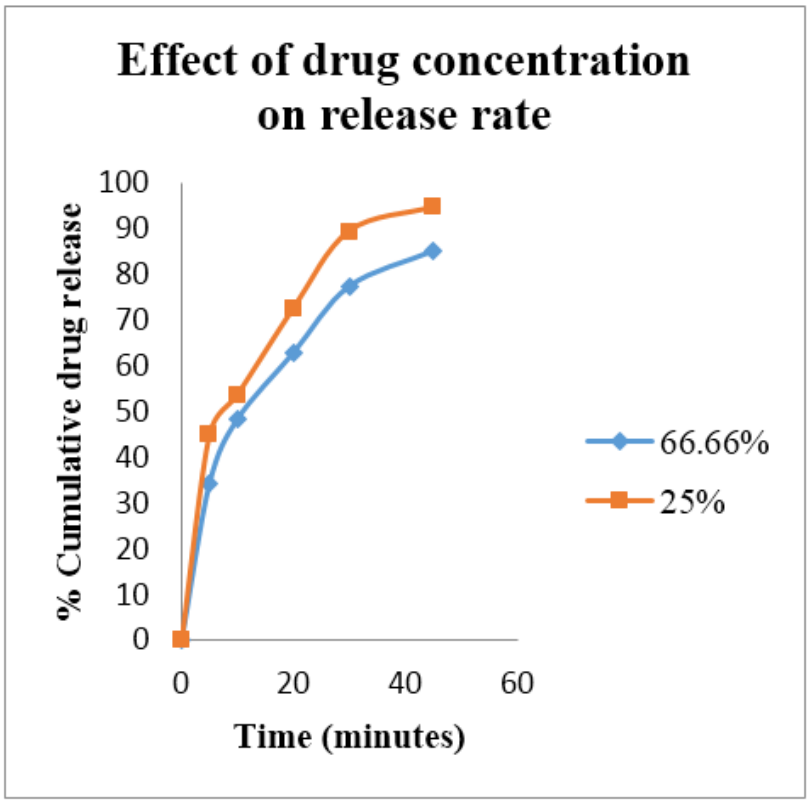

Figure No 18: Effect of drug concentration on release rate

Drug within the liquisolid is completely dissolved in the liquid vehicle it is located in the powder substrate still in a solubilised, molecularly dispersed state. The effect of drug concentration on release can be explained by the dissolved drug in the liquid medication as follows :

$$FM = C_L / C_D \qquad \text{eq.....(18)}$$

Where FM is the fraction of molecularly dispersed or dissolved drug in liquisolid medication of the prepared liquisolid formulation, C_L is the saturation solubility of Ezetimibe in the liquid vehicle and C_D is the drug concentration in the liquid medication.

$$FM = 1 \text{ if } C_L \geq C_D$$

The saturation solubility of Ezetimibe in tween 80 is 0.950 mg/ml, by applying eq(18), it can be calculated that 3.800% of the drug was solubilised in F4, 2.850% of drug was solubilised in F3, 1.900% of drug in F2 and 1.425 % in F1. Higher the drug concentration in the liquisolid formulation, higher the fraction of undissolved drug in the liquid vehicle, decreases the release rate of drug. F4 has 3.800 % of drug available in solubilised form promote higher dissolution rate than F1, F2 and F3. It was proven that FM is directly proportional to the drug dissolution rate. Another explanation for this phenomenon is that high concentration of the drug could precipitate within the silica (Aerosil) pores; thus, drug dissolution rate would be reduced. The potential of Ezetimibe to precipitate within the silica pores is depending on the solubility of the drug in the solvent, the degree of saturation of the drug solution or the interactions between drug and excipients.

Release Kinetics

In-vitro release data obtained for the formulation F4 (Table No: 19) was subjected to kinetic analysis. The cumulative percentage drug release data obtained were fitted to Zero order, first order, Higuchi's square root of time and Korsmeyer-Peppas equation to understand the mechanism of drug release from the Ezetimibe compacts (Figure No: 19 to 22). Higuchi model explains the diffusion controlled release mechanism. The slopes and the regression coefficient of determinations (R^2) were listed in Table No: 24. The coefficient of determination indicated that the release data was best fitted with first order kinetics. The slope value (n) obtained from peppas plot was 0.364, which indicates that the formulation followed fickian mechanism of drug release.

Table No 19:
Release kinetics of liquisolid compacts

Release kinetics	R^2	Intercept	Slope
Zero order	0.800	25.39	1.843
First order	0.982	1.908	-0.026
Higuchi	0.971	6.625	14.30
Korsmeyer-Peppas	0.981	1.386	0.364

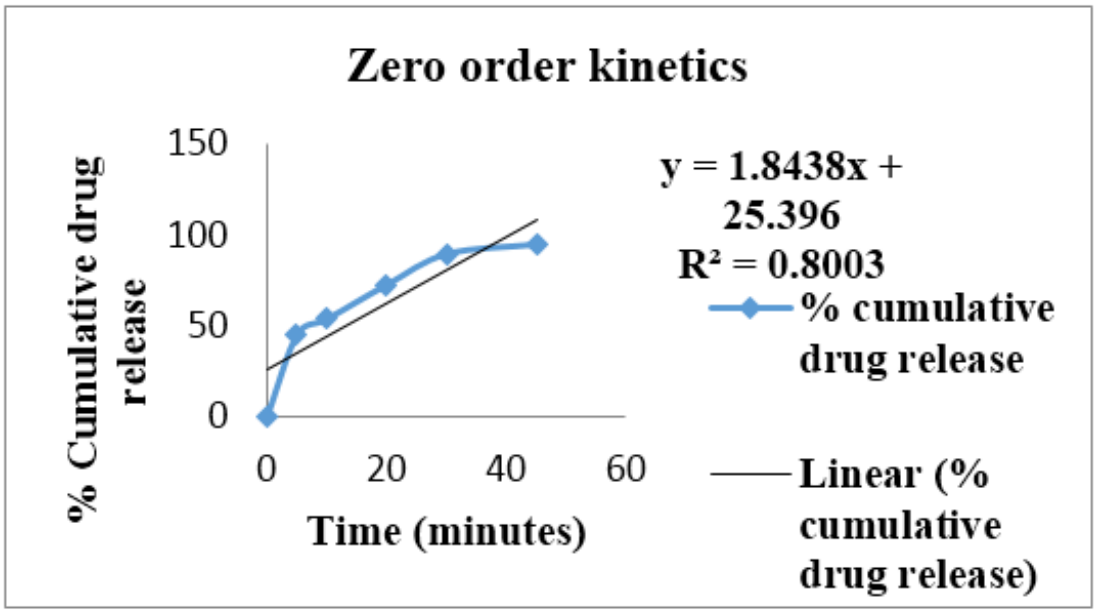

Figure No 19: Release profile of LS formulation-F4 according to zero order

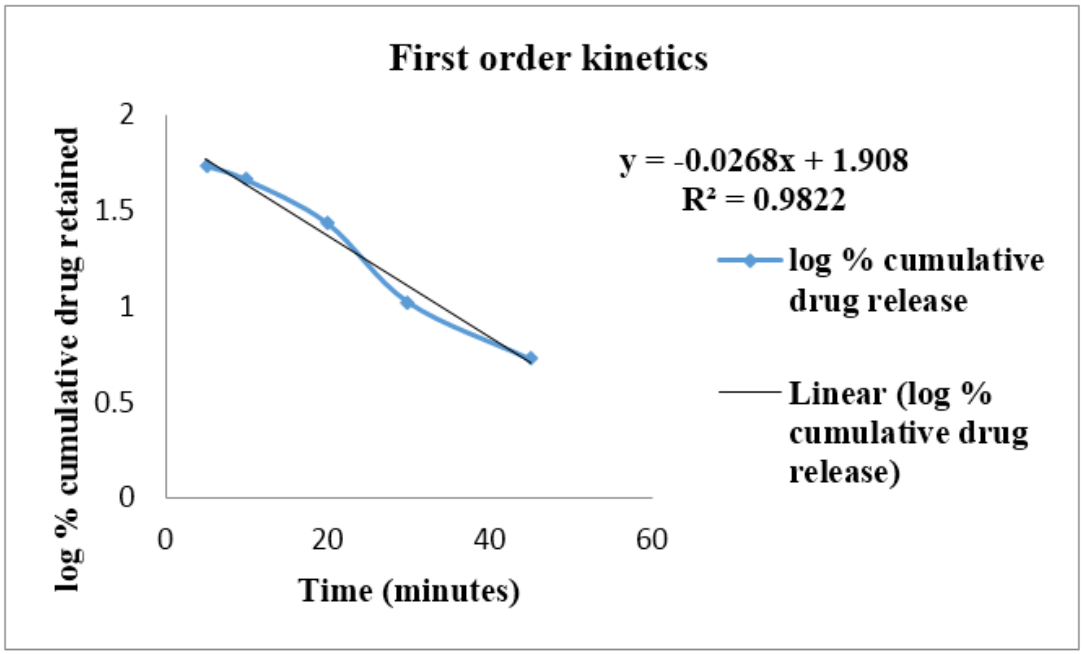

Figure No 20: Release profile of LS formulation-F4 according to first order

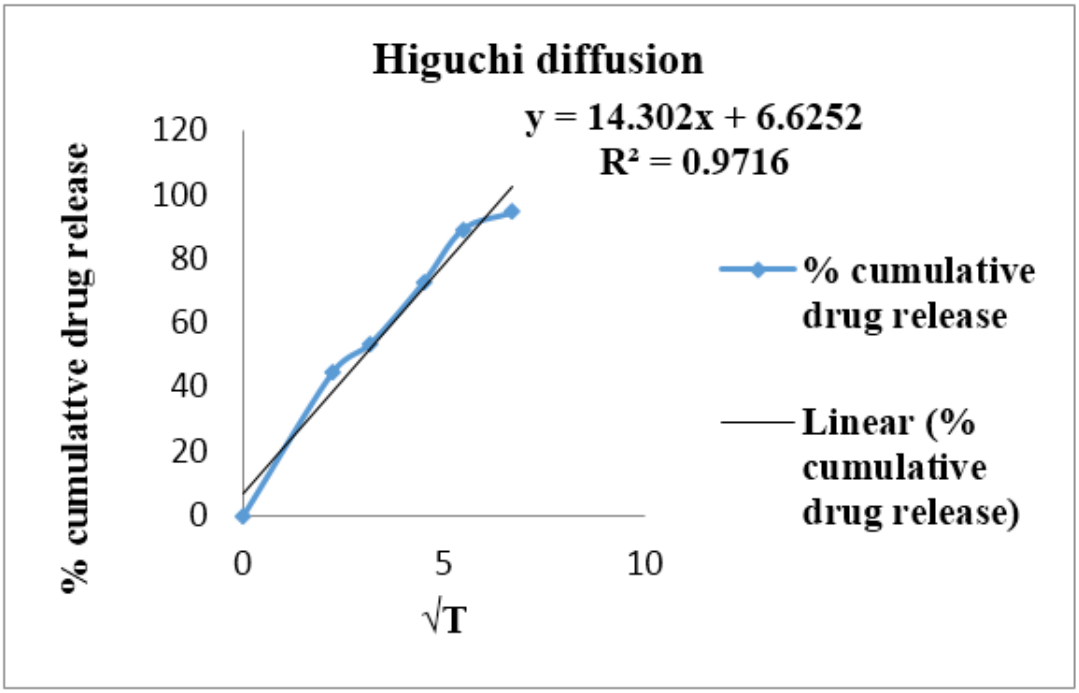

Figure No 21: Release profile of LS formulation-F4 according to higuchi diffusion

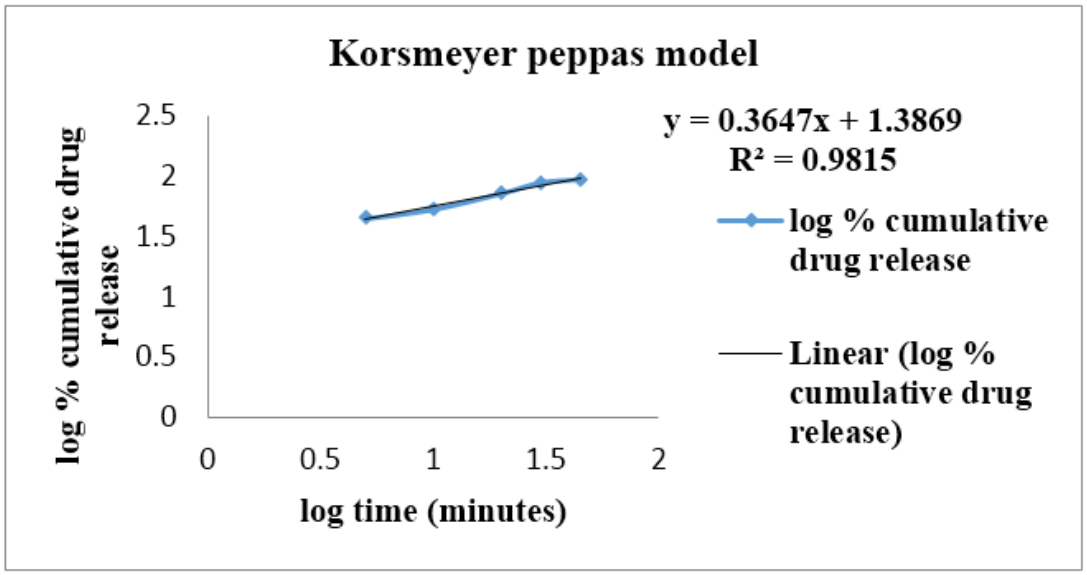

Figure No 22: Release profile of LS formulation-F4 according to korsmeyer peppas model

Stability Studies

The purpose of stability testing is to provide evidence on how the quality of a drug substance or drug product varies with time under the influence of a variety of environmental factors such as temperature, humidity, and light, and to establish a re-test period for the drug substance or a shelf life for the drug product and recommended storage conditions. Here the tablets were loaded at accelerated condition at $40^0C \pm 2^0C/75\%$ RH±5%RH in a stability chamber.

Samples were withdrawn at initial, 1st, 2nd and 3rdmonths and evaluated for drug content, disintegration time and dissolution. The results showed that the drug content, disintegration and dissolution rate of liquisolid tablets was not significantly affected by storing the tablets at 40°C / 75% RH for a period of 3months. This indicates that the technology is a promising technique to enhance the release rate without having any physical stability issues.

Table No 20:
Results of stability studies for F4

40°C ± 2°C / 75 % RH ± 5%					
S.no	**Parameter**	**F4**			
		Initial	**1st month**	**2nd month**	**3rd month**
1.	Drug content (%)	98.6	98.2	97.7	97.4
2.	Disintegration time (sec)	57	57	58	59
3.	Dissolution (%CR)	94.67	94.51	93.78	93.35

Conclusion

Solubility is one of the important parameter to achieve desired concentration of drug in systemic circulation. The drugs which are poorly water soluble will be inherently released at a slow rate owing to their limited solubility. The dissolution rate is often the rate determining step in the drug absorption. The challenge for these drugs is to enhance the rate of dissolution or solubility. There are different techniques available for the improvement of solubility, among them liquisolid technique is the most promising technique which promotes the solubility and dissolution of water insoluble drugs. In this study Ezetimibe liquisolid compacts were prepared by using tween 80, PEG 400 and PG as non-volatile solvents. Avicel PH 102 and Aerosil 200 were used as the carrier and coating material, respectively. The flow properties of Ezetimibe liquisolid powder blend showed an acceptable flowability and good compaction properties. FTIR spectra revealed that there was no interaction between the drug and the excipient. XRPD studies showed complete inhibition of crystallinity in the Ezetimibe liquisolid compacts suggesting that the drug has been transformed into amorphous form having more solubility than the pure drug. The hardness, friability, weight variation, disintegration and drug content were within the acceptable limits of IP standards. *In-vitro* drug release were performed for all formulations and showed maximum release rate for F4 (tween 80, 1:3) formulation. The lower the drug concentration in a liquisolid formulation, more will be the amount of drug solubilised in the liquid vehicle. F4 showed enhanced release rate than conventional and marketed tablet. Based on mathematical data revealed from models, it was concluded that the release data was best fitted with first order kinetics. Stability studies showed that there were no significant changes in physical and chemical properties of liquisolid tablet of formulation F4 after 3 months.

This research work has produced encouraging results in terms of increasing the *in-vitro* dissolution of poorly soluble drugs such as Ezetimibe using liquisolid technology and we expect a good correlation between the *in-vitro* and *in-vivo* performance of the formulations. The technique being simple and effective can also be extended to other poorly soluble drugs. The *in-vivo* performance of the liquisolid compacts need to be studied using animal models to claim a complete success in the development of these formulations.

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