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ENHANCEMENT OF SOLUBILITY AND DISSOLUTION RATE OF EZETIMIBE THROUGH LIQUISOLID TECHNIQUE

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ABSTRACT: The present study enlightens to enhance the dissolution profile, absorption efficiency and bioavailability of water insoluble drug like Ezetimibe. It is a poorly soluble, highly permeable drug and the rate of its oral absorption is often controlled by the dissolution rate in the gastrointestinal tract. There are several techniques to enhance the dissolution of poorly soluble drugs, in which the "liquisolid compacts" is a promising technique. Different formulations were prepared by using polyethylene glycol-400 as a non-volatile liquid vehicle, with drug and vehicle ratios of 1:5 and 1:7.5, microcrystalline cellulose (Avicel PH 102), starch were used as carrier materials and nm-sized silica gel (Aerosil-200) was used as coating materials. The empirical method introduced by Spireas and Bolton was applied to calculate the amounts of coating and carrier materials required to prepare Ezetimibe liquisolid tablets. Based upon this method, improved flow characteristics and hardness of the formulation has been achieved by changing the proportion of carrier and coating material ratio from 20:1 to 5:1. They were characterized for different physical parameters to comply with pharmacopoeial limits. In vitro dissolution profiles of the liquisolid formulations were studied and compared with conventional formulation in pH 4.5 acetate buffer. It was found that liquisolid tablets formulated with microcrystalline cellulose produced high dissolution profile and they showed significant higher drug release rates than conventional tablets due to increase in wetting properties and surface of drug available for dissolution. FTIR spectral studies showed that there is no interaction between the drug and excipients. Aging studies indicates that, there is no significant effect on dissolution rate and hardness of the formulation of fresh and stored at 40±2^{0}C/ 75±5% relative humidity for 45days. In conclusion, development of ezetimibe liquisolid tablets is a good approach to enhance the dissolution rate to improve bioavailability.

INTRODUCTION: Most of the new drug candidates entering drug development pipeline fail because of non-optimal biopharmaceutical properties i.e. rate and extent of absorption, rate of distribution, dose to achieve minimum effective concentration and to avoid side effects can exert a significant influence on the drug's absorption, distribution, metabolism, excretion, and toxicity.

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Over the years, tools of drug discovery have caused a perceptible shift in biopharmaceutical properties. So these properties have significant role in the bioavailability of the drugs [1].

Poorly water soluble drugs often require high doses in order to reach therapeutic plasma concentrations after oral administration. Improvement in the extent and rate of dissolution is highly desirable for such compounds, as this can lead to an increased oral bioavailability and subsequently to clinically relevant dose reduction [2].

The dissolution properties of a drug and its release from a dosage form have a basic impact on its bioavailability.

Solving solubility problems is a major challenge for the pharmaceutical industry with developments of new pharmaceutical products, since nearly half of the active substances being identified through the new paradigm in high throughput screening are either insoluble or poorly soluble in water. The dissolution rate of a drug is a function of its intrinsic solubility and its particle size [3].

A more recent technique, entitled "Liquisolid technology" or "powdered solution technology", has been applied to prepare water-insoluble drugs into rapid release solid dosage forms [4]. The concept of powdered solutions enables one to convert drug solutions or liquid drugs into acceptably flowing powders by a simple admixture with selected powder excipients (e.g., cellulose and silica). This method does not involve drying or evaporation [5]. It is well established that better bioavailability of a relatively water-insoluble drug is achieved when the drug is in solution form [6].

Liquid lipophilic drugs or solid drugs dissolved in nonvolatile, high-boiling point solvent systems (e.g., polyethylene & polypropylene glycols, glycerin, N,N-dimethylacetamide, various oils) have been formulated in powdered solutions by admixture with various carriers (e.g., cellulose) and coating materials (e.g., silica). This technique has been reported to produce improved dissolution profiles as compared to the commercially available products [7].

Ezetimibe, selected in the present work is chemically 1-(4-fluorophenyl)-3(R)-[3-(4-fluorophenyl)-3(S)-hydroxypropyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone belonging to the lipid lowering agents category. It inhibits the intestinal absorption of cholesterol [8]. Ezetimibe is a white crystalline powder having poor aqueous solubility characteristics [9] which leads to its limited dissolution resulting in poor bioavailability (35–65%). The dissolution is a rate limiting step for the absorption of poorly water-soluble drugs and hence drugs showing limited dissolution give poor therapeutic out come as a result of poor oral bioavailability [10].

The aim of the preset work is to increase the solubility and in-vitro dissolution of water insoluble drug Ezetimibe by formulating it into liquisolid tablets. The liquisolid tablets are prepared by using Avicel PH 102 and starch as carrier material, Aerosil 200 as coating material and PEG 400 as liquid vehicle. Different carrier, coating materials ratios are used to formulate the Ezetimibe liquisolid tablets.

MATERIALS AND METHODS:

Materials: Ezetimibe is a gift sample from Alpha Med Pvt. Ltd, Hyderabad, India. Avicel PH102 and Aerosil 200 are gift samples from Alpha Med Pvt. Ltd, Hyderabad, India. PEG 400 and Propylene glycol was purchased from SD fine chemicals, Mumbai, India. All other materials used were of Pharmaceutical grade.

Solubility studies: For the selection of best non-volatile solvents, solubility studies were performed. In this procedure, pure drug was dissolved in two different non-volatile solvents (propylene glycol and polyethylene glycol) and distilled water. Excess amount of pure drug was added to the above solvents. Obtained saturation solutions were shaken on the rotary shaker for 48 hours at 25 ^{0}C under constant vibration. After 48 hours period the saturated solution were centrifuged at 3000rpm for about 15 minutes and the supernatant was collected and analyzed by UV spectrophotometer. [11]

Calculation of loading factor (L_f) and "q" value: Loading factors were calculated for different carriers, using various solvents. By using $L_f = W/Q$ formula (W: Amount of liquid medication and Q: Amount of carrier material), the drug loading factors were obtained and used for calculating the amount of carrier and coating materials in each formulation. The results showed that if the viscosity of the solvent is higher, lower amounts of carrier and coating materials are needed to produce flowable powder[12].

Based on R value used, the corresponding q (amount of coating material) can be calculated for all formulations using the equation R =Q/q. **Table 1** represents the exact qualitative and quantitative composition for each formulation.

Precompression properties: All the liquisolid formulations were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio.

1. **Angle of Repose:** The angle of repose of physical mixtures of liquisolid compacts were determined by fixed funnel method. The accurately weighed physical mixtures of liquisolid compacts were taken in a funnel. The height of the funnel was adjusted to 2.5 cm. The powder was allowed to flow through the funnel freely into the surface until the apex of the heap of the powder just touching the funnel. The height and diameter of the powder cone was measured and angle of repose was calculated.

$$\text{Tan } \theta = h/r$$

Where, θ is the angle of repose, h is the height in cm, r is the radius in cm

2. **Bulk Density:** The loose bulk density and tapped density were determined by using bulk density apparatus. Apparent bulk density was determined by pouring the blend into a graduated cylinder. The bulk volume (V_b) and weight of the powder (M) was determined. The bulk density was calculated using the formula

$$\rho_b = M/V_b$$

Where, M is the mass of powder, V_b is bulk volume of powder

3. **Tapped Density:** The measuring cylinder containing a known mass of blend was tapped for a fixed time. The minimum volume (V_t) occupied in the cylinder and the weight (M) of the blend was measured. The tapped density was calculated using the formula

$$\rho_t = M/V_t$$

Where, M is the mass of powder, V_t is tapped volume of powder

4. **Carr's Index (%):** The compressibility index has been proposed as an indirect measure of bulk density, size and shape, surface area, moisture content and cohesiveness of material because all of these can influence the observed compressibility index. The simplest way for measurement of free flow of powder is Carr's Index, a indication of the ease with which a material can be induced to flow is given by Carr's index (CI) which is calculated as follows:

$$\text{CI (\%)} = \frac{\text{Tapped density} - \text{Bulk density}}{\text{Tapped density}} \times 100$$

5. **Hausner's Ratio:** Hausner's ratio is an indirect index of ease of powder flow. It is calculated by the following formula. [12]

Hausner's Ratio=

$$\text{Tapped density } (\rho_t) \,/\, \text{Bulk density } (\rho_b)$$

Where ρ_t tapped density and ρ_b is bulk density.

Preparation of Liquisolid Tablets:

Preparation of Drug Solution: For the preparation of liquisolid compacts of Ezetimibe, a non-volatile solvent is chosen for dissolving the drug. From the results of solubility studies and evaluation of flow properties, liquisolid powders containing PEG 400 as the liquid medicament, MCC (avicel PH 102) as carrier and colloidal silica (aerosil 200) as the coating material is selected for the preparation of liquisolid compacts.

Various ratios of carrier to coating materials were selected and different ratios of drug: solvents were selected. According to desired quantities drug and PEG 400 were accurately weighed in a beaker and then stirred constantly, until a homogenous drug solution was obtained. Selected amounts (W) of the resultant liquid medication were incorporated into calculated quantities of carrier contained in a mortar.

Mixing: The mixing procedure was conducted in three stages. During the first stage, the system was blended with carrier at an approximate mixing rate of one rotation/sec for approximately one minute for even distribution of the liquid medication into the powder. In the second mixing stage, calculated quantities of coating material was added to the system and blended for 2 min.

The liquid/powder admixture was evenly spread as a uniform layer on the surfaces of the mortar and left standing for approximately 5min to allow the drug solution to be absorbed in interior of the powder particles. In the third stage, the powder was scraped off from the mortar surfaces by means of aluminium spatula, then producing the final liquisolid formulation to be compressed. Similar formulations were prepared by using starch as carrier materials [13].

Preparation of Conventional Tablets of Ezetimibe: Tablet containing Ezetimibe was prepared by mixing 10 mg of drug with microcrystalline cellulose (Avicel PH102) sodium starch glycolate 10% (w/w) as a disintegrant and mixed for 10 min. Glidant and lubricant are added and then directly compressed by tablet punching machine.

TABLE 1: COMPOSITION OF EZETIMIBE LIQUISOLID FORMULATIONS

Formulation	Drug: PEG400	R	Lf	Avicel PH 102 (mg)	Starch (mg)	Aerosil 200 (mg)	Total tablet weight (mg)
F1	1:5	5	0.30	200	-	40.0	310.0
F2	1:5	10	0.30	200	-	20.0	290.0
F3	1:5	15	0.30	200	-	13.3	283.3
F4	1:5	20	0.30	200	-	10.0	280.0
F5	1: 7.5	5	0.425	200	-	40.0	335.0
F6	1: 7.5	10	0.425	200	-	20.0	315.0
F7	1: 7.5	15	0.425	200	-	13.3	308.3
F8	1: 7.5	20	0.425	200	-	10	305.0
F9	1:5	5	0.30	-	200	40.0	310.0
F10	1:5	10	0.30	-	200	20.0	290.0
F11	1:5	15	0.30	-	200	13.3	283.3
F12	1:5	20	0.30	-	200	10.0	280.0
F13	1: 7.5	5	0.425	-	200	40.0	335.0
F14	1: 7.5	10	0.425	-	200	20.0	315.0
F15	1: 7.5	15	0.425	-	200	13.3	308.3
F16	1: 7.5	20	0.425	-	200	10.0	305.0

R- Ratio of carrier and coating material, $\mathbf{L_f}$ **–** liquid load factor. All formulations contain 10 mg of sodium starch glycolate

Evaluation of Liquisolid Tablets:

1. **Weight Variation:** Twenty tablets were randomly selected from each formulation and individually weighed. The average weight and weight variation were calculated as described in I.P.

% Weight variation =

$$\frac{\text{Individual weight} - \text{Average Weight}}{\text{Average Weight}} \times 100$$

2. **Thickness:** The thickness of liquisolid tablets was determined by using Screw gauge. Thicknesses of ten individual tablets from each batch were measured and averages of the results were calculated.

3. **Hardness:** The hardness of the tablets was determined by using Monsanto hardness tester. Five individual tablets from each batch were selected and hardness was determined.

4. **Friability:** The friability values of the tablets were determined using a Roche-type friabilator, and it was determined as per I.P Percentage friability was calculated using the following equation;

$$\text{Friability} = ([W_O - W] / W_O) \times 100$$

Where, W_O = weight of the tablet at time zero before revolution, W = weight of the tablet after 100 revolutions.

5. **Disintegration Test:** Disintegration test was performed as per I.P

6. **Drug Content:** Twenty tablets from each formulation were randomly selected and powdered in a mortar and weight equivalent to10 mg of the drug was taken in the 100 ml of volumetric flask and methanol was added and made up to the mark and kept on rotary shaker for about 30 mins & then the solution was filtered and the absorbance was measured at 232 nm after appropriate dilution. The analysis was carried out in triplicate and the average drug content was calculated. [14]

7. **Dissolution test of Ezetimibe Liquisolid Tablets (USFDA Dissolution method):** Drug release from Ezetimibe liquisolid tablets was determined by using dissolution test United States Pharmacopoeia (USP) 24 type II (paddle).

Dissolution medium**:** 0.45% SLS in 4.5 pH Acetate buffer

Volume	:	500 ml
Temperature	:	at 37°C± 0.5°C
Speed	:	50 rpm.

5ml aliquots of dissolution media were withdrawn each time at suitable time intervals (5, 10, 20, 30, 45 and 60 minutes.) and replaced with fresh medium. After withdrawing, samples were filtered and analyzed after appropriate dilution by UV-spectrophotometer. The concentration was calculated using standard calibration curve.

Calculation of Dissolution Parameter: Cumulative percent drug release was plotted as a function of time and percent drug release in 10 minutes (Q_{10}) was calculated.

- **Initial Dissolution Rate (IDR)** was calculated as percentage dissolved of drug over the first 10 minutes per minute. (%/min)
- **Dissolution Efficiency (DE)** was calculated from the area under the dissolution curve at time t (measured using the trapezoidal rule) and expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time [15].

$$DE = \frac{\int_0^t Y \times dt}{Y_{100} \times t} \times 100\%$$

- **Relative Dissolution Rate (RDR)** is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 10 minutes.
- **Dissolution Rate (D_R)** was calculated in the form of amount of drug (in µg) dissolved per min, presented by each table formulation during the first 10 min of the dissolution process, were calculated as follows [16].

D_R = 5 X (% drug dissolved in first 10 min)

8. **Fourier Transform Infrared (FTIR) Spectroscopy:** The FTIR samples (Ezetimibe pure drug and optimized liquisolid formulation) were recorded, using FT-IR system in the frequency range of 4000–400 cm^{-1} at 4 cm^{-1} resolution. This technique uses very small amount of each sample which is directly loaded into the system and samples were prepared in KBr disc (2 mg sample in 200 mg KBr).
9. **Stability Studies:** Stability studies were carried out for 45 days for the optimized formulation of Liquisolid tablets at a temperature 40±2°C/ RH 75±5%. The tablets were observed visually for color change and estimation of content at regular intervals of 15 days.

RESULTS AND DISCUSSION:

Solubility Studies: The solubility of Ezetimibe in Propylene glycol, PEG-400 and distilled water, was given in **table 1**. The solubility studies show that the Ezetimibe has higher solubility in polyethylene glycol (PEG 400) when compared with other solvents.

TABLE 2: SOLUBILITY STUDIES OF EZETIMIBE IN VARIOUS SOLVENTS

SOLVENT	SOLUBILITY(mg/ml)
Poly ethylene glycol- 400	15.24
Propylene glycol	9.62
Distilled water	0.0101

Spectral Analysis: Analysis by FTIR spectroscopy was carried out to assess any possible interaction between drug and hydrophilic carriers. **Figure 1 and 2** depicts the FTIR spectra of drug and optimized liquisolid formulation respectively. The spectra showed no substantial shifting of the position of the functional groups. The peaks are only broadened, indicating no major interaction between EZE and hydrophilic carriers. Although hydrogen bonding could be expected between the hydrogen atom of the OH– group of EZE and the lone electron pairs of the carrier oxygen atoms, this could not be demonstrated. The stretches found in spectra were shown in **table 2**.

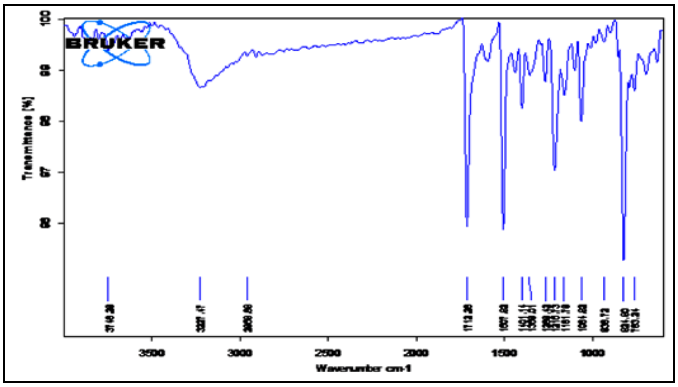

FIGURE 1: FTIR OF EZETIMIBE

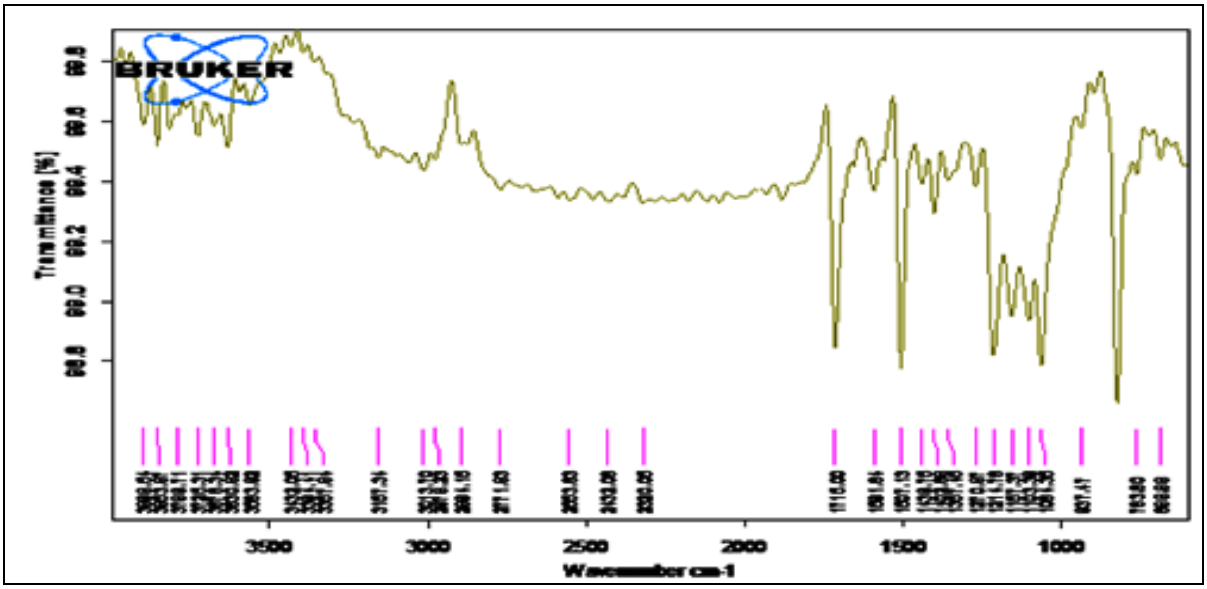

FIGURE 2: FTIR OF OPTIMIZED FORMULATION F8

TABLE 2: FTIR SPECTRA OF PURE DRUG AND OPTIMIZED FORMULATION

PEAK	IN PURE DRUG	IN OPTIMIZED (F8)
O-H stretch (Alcohol)	3746.29 cm-1	3725.31 cm-1
O-H stretch (Phenol)	3227.47 cm-1	3357.84 cm-1
C-H stretch (Methylene)	2958.68 cm-1	2978.23 cm-1
C-F stretch	1359.01 cm-1	1357.45 cm-1
C-H stretch	1269.42 cm-1	1270.87 cm-1

Pre Compression Evaluation Studies: All the liquisolid formulations were evaluated for angle of repose, bulk density, tapped density, Carr's index and Hausner's ratio. Their values were listed in **table 3**.

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 and when decrease in the coating material weight there is increase in the angle of repose value which leads to good to fair flow of powder mixtures. In addition to Carr's index, Hausner's ratio was related to the inter particle friction. Hausner's ratio showed that powders with low inter particle friction, had ratios of approximately 1.25 indicating good flow.

TABLE 3: EVALUATION OF PRE COMPRESSION PARAMETERS OF FORMULATIONS F1-F16

Formulation	Angle of repose* (θ)	Bulk density (gm/cc)	Tapped density (gm/cc)	Carr's index (%)	Hausner's ratio
F1	18.12±1.6	0.292	0.357	18.2	1.14
F2	22.31±1.2	0.291	0.354	17.7	1.151
F3	26.11±1.1	0.323	0.398	18	1.22
F4	28.73±1.0	0.315	0.402	21	1.21
F5	30.21±1.9	0.302	0.378	20.1	1.14
F6	32.54±1.3	0.323	0.403	19	1.15
F7	33.22±1.1	0.302	0.375	20.2	1.2
F8	34.34±1.2	0.315	0.402	21	1.21
F9	20.34±1.2	0.316	0.402	21	1.13
F10	24.87±1.6	0.325	0.405	19.7	1.15
F11	26.37±1.0	0.323	0.398	18	1.11
F12	29.54±1.8	0.298	0.351	17.6	1.28
F13	28.54±1.8	0.289	0.351	17.6	1.28
F14	30.12±1.1	0.302	0.378	20	1.23
F15	32.22±1.5	0.320	0.412	22	1.20
F16	36.25±1.2	0.320	0.412	22	1.45

Post Compression Evaluation Studies for Ezetimibe Liquisolid Compacts: All the prepared liquisolid tablets were evaluated for weight variation, thickness, hardness, disintegration time, drug content and drug release. The results were listed in **table 4**. All the liquisolid tablets were evaluated for their post compression parameters. In weight variation test, all the liquisolid compact formulae comply with Pharmacopoeial limits i.e., not more than 5% of the average weight as per I.P 2007. The mean hardness of each liquisolid formula was determined and proving that all the liquisolid tablet formulae had acceptable hardness. The hydrogen bonds between hydrogen groups on adjacent cellulose molecules in microcrystalline cellulose may account almost exclusively for the strength and cohesiveness of compacts [16]. All the formulations showed uniform thickness. All the Ezetimibe liquisolid tablets had acceptable friability as none of the tested formulae had percentage loss in tablets weights that exceed 1% and no tablet was cracked, split or broken in either formula. The disintegration time for all the liquisolid tablets prepared were found to be within the Pharmacopoeial limits. The disintegration test revealed that all the liquisolid tablets prepared were disintegrated in less than 5mins. The drug content uniformity for all the liquisolid formulations was found to be in the limits of 96.8±1.76 to 103.3±0.61.

TABLE 4: EVALUATION OF POST COMPRESSION PARAMETERS OF FORMULATIONS F1- F16

Formulation	Weight variation (mg) (n=20)	Thickness (mm) (n=6)	Hardness (kg/cm^2) (n=6)	Friability (%) (n=10)	Disintegration time (sec) (n=6)	Drug Content (%)
F1	310.0± 0.15	4.6±0.02	4.0±0.25	0.15	190	97.7±1.74
F2	290.0± 1.05	4.5±0.02	3.8±0.06	0.22	220	99.06±0.28
F3	283.3 ± 1.28	4.5±0.02	3.3±0.24	0.13	160	97.7±0.70
F4	280.0 ± 0.12	4.4±0.01	3.1±0.42	0.22	170	98.6±0.28
F5	335.0 ± 1.4	3.2±0.35	4.4±0.01	0.24	115	103.3±0.61
F6	315.0± 1.8	3.5±0.61	4.5±0.02	0.33	100	96.8±1.76
F7	308.3± 1.4	3.2±0.35	4.6±0.02	0.24	90	97.8±0.61
F8	305.0±2.3	3.5±0.45	4.5±0.03	0.46	83	98.9±0.97
F9	310.0± 1.15	4.4±0.02	4.4±0.25	0.45	195	97.9±1.74
F10	290.0± 0.75	4.1±0.02	4.3±0.06	0.52	220	98.3±0.28
F11	283.3 ± 1.92	3.8±0.02	4.6±0.24	0.13	160	97.8±0.70
F12	280.0 ± 0.12	4.4±0.01	4.1±0.42	0.42	170	98.03±0.28
F13	310.0± 2.15	4.9±0.02	3.4±0.25	0.65	195	101.9±0.13
F14	290.0± 1.75	4.6±0.01	3.6±0.06	0.72	202	97.1±0.32
F15	283.3 ± 1.92	4.8±0.02	3.8±0.64	0.33	169	100.5±0.57
F16	280.0 ± 0.57	4.9±0.01	3.5±0.42	0.32	163	101.6±0.34

***In vitro* Release Studies:** The percent of Ezetimibe released from liquisolid compacts containing varying amounts of carrier and coating materials (from F-1 to F-16) was found to vary from 21.58±1.17 to 87.99±1.95% in first 10min (**Figure 3, 4, 5 and 6**). This indicates the fast release of drug is observed from above formulations. The formulation F-8 showed the highest drug release 97.24±2.11% when compared to all other formulations. The %drug release of all the formulations were showed in **table 5, 6, 7 and 8**.

From the obtained results, it was displayed that there is a relationship between the powder excipient ratio and the *in vitro* release of Ezetimibe from liquisolid tablets. An increase in the R-value results in an enhanced release rate if microcrystalline cellulose and colloidal silica are used as carrier and coating materials, respectively.

Liquisolid compacts with high R-values contain high amounts of microcrystalline cellulose, low quantities of colloidal silica, and low liquid/powder ratios. This is associated with enhanced wicking, disintegration and thus, enhanced drug release.

In contrast, if high amounts of colloidal silica are used, which means that the R-value is low, the liquisolid compact is overloaded with liquid formulation due to a high liquid load factor. In such cases, even though drug diffusion out of the primary particles may be rapid, oversaturation might occur resulting in local precipitation/ recrystallization of the drug and thus decreased release rates [15, 5].

Moreover, as colloidal silica is a hydrophobic material high amounts of it can cause retardation of drug release.

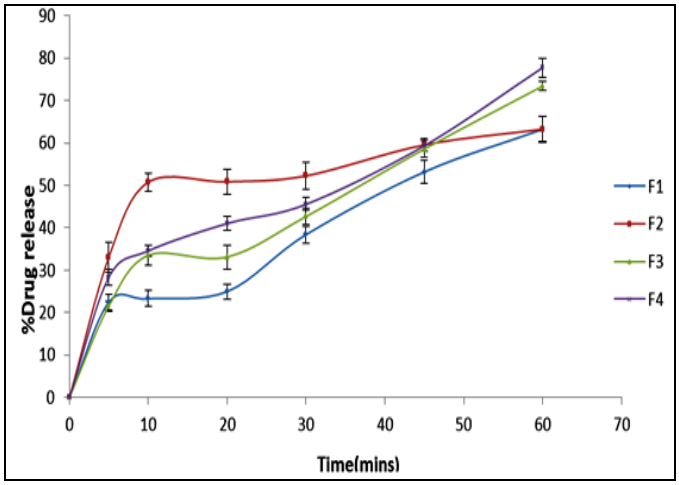

FIGURE 3: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1:5 EZETIMIBE DRUG SOLUTION BY USING AVICEL PH 102 AS CARRIER

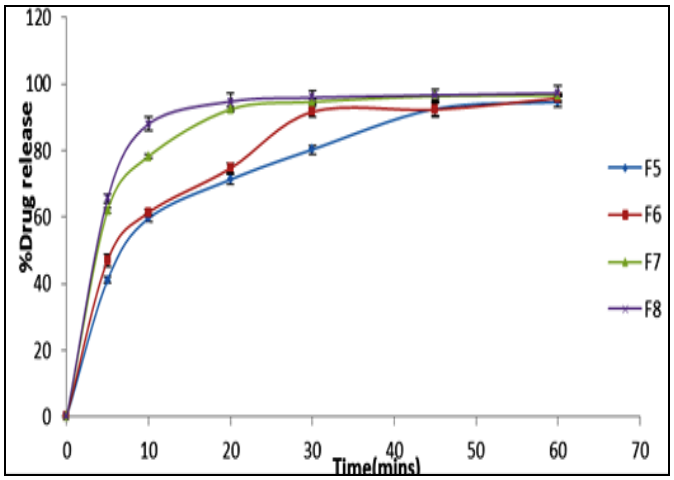

FIGURE 4: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1: 7.5 DRUG: SOLVENT BY USING AVICEL PH 102 AS CARRIER

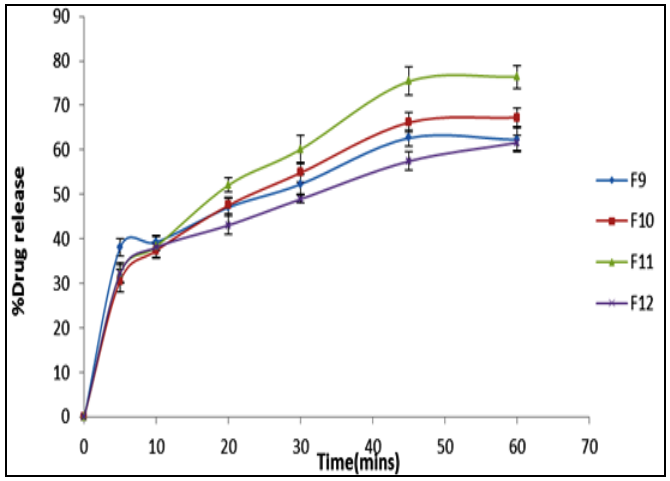

FIGURE 5: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1:5 EZETIMIBE DRUG: SOLVENT BY USING STARCH AS CARRIER

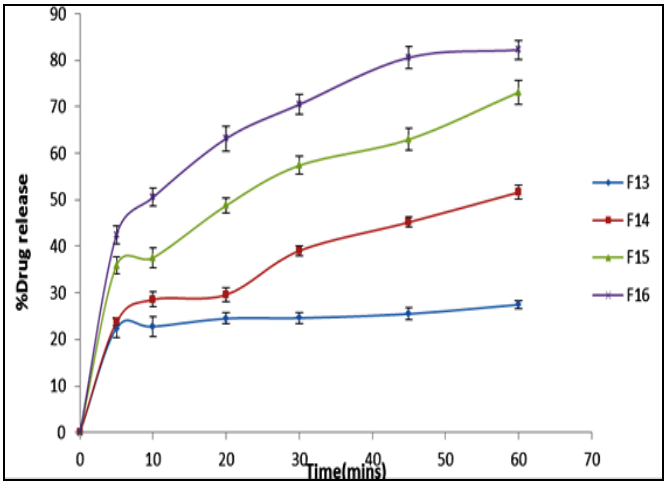

FIGURE 6: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1: 7.5 DRUG: SOLVENT BY USING STARCH AS CARRIER

Therefore, Spireas *et al*, recommend a minimum R-value of 20. When starch in used as carrier material there was not much enhanced drug release observed than the Avicel PH 102.

Dissolution profiles of directly compressed tablets, marketed formulation (Ezentia) and optimized F8 formulation was plotted in **figure 7**. The graph depicts that the F8 formulation has the better release than that of the marketed formulation and directly compressed tablet.

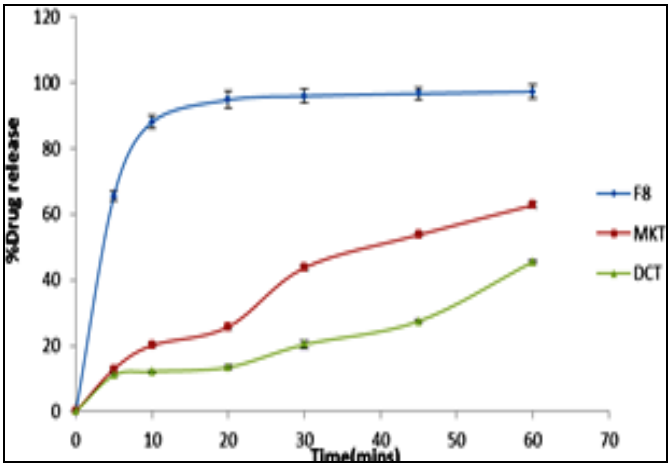

FIGURE 7: DISSOLUTION PROFILES OF OPTIMIZED FORMULATION (F8), MARKETED FORMULATION AND DIRECTLY COMPRESSED TABLET

Overall increase in the dissolution performance of the optimized formulation described in terms of dissolution parameters (IDR, Q_{10}, D_R, DE) compared to marketed tablets (showed in **table 9**) could be due to the lesser disintegration time and increased wetting properties and surface area available for drug dissolution.

TABLE 5: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1:5 EZETIMIBE DRUG SOLUTION BY USING AVICEL PH 102 AS CARRIER. DATA REPRESENTS MEAN ± S.D (n=3)

Time (mins)	F1	F2	F3	F4
5	22.47±1.94	33.09±3.57	21.58±1.17	28.33±1.92
10	23.22±1.88	50.75±2.15	33.52±2.26	34.57±1.38
20	24.96±1.81	50.84±3.0	33.3±2.83	41.02±1.71
30	38.37±2.01	52.25±3.20	42.65±1.91	45.5±1.52
45	53.17±2.72	59.54±1.64	58.57±1.91	59.33±1.37
60	63.21±2.94	63.24±3.10	73.40±1.13	77.7±2.22

TABLE 6: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1: 7.5 DRUG: SOLVENT BY USING AVICEL PH 102 AS CARRIER. DATA REPRESENTS MEAN ± S.D (n=3)

Time (mins)	F5	F6	F7	F8
5	41.19±0.90	47.12±1.84	61.98±0.86	65.58±1.40
10	59.67±1.13	61.39±1.11	78.25±0.65	87.99±1.95
20	71.30±1.56	74.69±1.45	92.39±0.79	94.75±2.62
30	80.32±1.28	91.62±1.40	94.64±0.55	95.92±2.0
45	92.54±2.11	92.29±2.06	96.31±0.61	96.65±1.78
60	94.59±1.43	95.72±1.61	96.55±0.23	97.24±2.11

TABLE 7: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1:5 EZETIMIBE DRUG: SOLVENT BY USING STARCH AS CARRIER. DATA REPRESENTS MEAN ± S.D (n=3)

Time (mins)	F9	F10	F11	F12
5	38.11±1.96	30.62±2.49	32.32±2.26	32.27±1.95
10	39.25±1.40	37.4±1.83	38.29±2.38	38.09±0.73
20	47.08±2.0	47.52±1.73	52.08±1.54	43.08±1.99
30	52.29±2.21	54.86±2.04	60.13±3.05	48.93±0.81
45	62.66±1.85	66.14±2.15	75.39±3.16	57.46±2.11
60	62.28±2.58	67.29±2.05	76.44±2.57	61.63±1.72

TABLE 8: DISSOLUTION PROFILES OF FORMULATIONS CONTAINING 1: 7.5 DRUG: SOLVENT BY USING STARCH AS CARRIER. DATA REPRESENTS MEAN ± S.D (n=3)

Time (mins)	F13	F14	F15	F16
5	22.42±1.99	23.73±0.85	35.89±1.76	42.48±1.90
10	22.75±2.22	28.56±1.62	37.55±2.08	50.32±1.91
20	24.47±1.16	29.60±1.58	48.77±1.50	63.18±2.71
30	24.59±1.17	39.04±1.16	57.36±1.95	70.5±2.16
45	25.49±1.25	45.18±1.06	62.98±2.42	80.6±2.29
60	27.47±0.94	51.62±1.50	73.13±2.59	82.21±2.0

TABLE 9: DISSOLUTION PARAMETERS OF OPTIMIZED FORMULATION (F8), MARKETED FORMULATION AND DIRECTLY COMPRESSED TABLET

Formulation	Q_{10}	D_R (µg/min)	Initial Dissolution Rate (%/min)	D.E	R.D.R.
Optimized (F8)	87.99±1.95	439.95	8.79	91.0742	4.37±0.02
Marketed tablet (Ezentia)	20.10±0.59	100.5	2.01	60.97413	
DCT	12.16±0.34	60.8	1.21	47.17221	

Stability Studies: Stability studies for the optimized tablets were carried out at a temperature of 40±2°C/ RH 75±5% for a period of 45 days. Tablets were evaluated for physical appearance and assay. Tablets have not shown any significant change in physical appearance and drug content during stability studies. Hence, it was concluded that the optimized tablets have good stability during their shelf life.

CONCLUSION: Ezetimibe has solubility and dissolution limited bioavailability. Hence Liquisolid technique was chosen to develop the liquisolid compacts of Ezetimibe, to achieve fast dissolving effect and to enhance the bioavailability. The Ezetimibe liquisolid tablets were prepared by using Avicel PH 102 and starch as carrier materials, Aerosil 200 as a coating material and PEG-400 as a non-volatile solvent with different ratios of R values and drug: solvent ratios. The dissolution efficiency (DE) of optimized formulation (F-8) was increased by 1.5 times when compared to marketed formulation and 2 times when compared to directly compressed tablet. It is concluded that Ezetimibe liquisolid compacts showed significant increase in dissolution as compared to direct compressed tablets and marketed tablets.

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