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Formulation and Evaluation of Ezetimibe Liquisolid Tablets: An Approach to Enhance the Dissolution Rate

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Authors' contributions

This work was carried out in collaboration between all authors. Author SKV designed and wrote the study protocol, and wrote the first draft of the manuscript. Author SA managed the literature searches, experimental process, analyses of the study performed the spectroscopy analysis and author VKB corrected the final manuscript and provided the required facilities. All authors read and approved the final manuscript.

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ABSTRACT

Background and the Purpose of the Study: Liquisolid compacts' using poorly water soluble drugs is considering as one of the novel pharmaceutical formulation technologies to improve the dissolution rate. This study was intended to improve the dissolution rate of ezetimibe by preparing liquisolid tablets.
Methods: In the preparation of liquisolid tablets, the following materials are used as carrier powder; polyethylene glycol (PEG) 400, tween 80 and propylene glycol as solvent, Avicel PH102 or starch or HPMC or PEG 4000 or PEG 6000 and Aerosil 200 are used as coating material. The interaction between drug and excipients was examined by differential scanning calorimetry (DSC)

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and Fourier transform infrared spectroscopy (FTIR). *In vitro* drug release studies of liquisolid and conventional tablets (control) were conducted and compared the both to study the improvement in dissolution rate. Then the best formulation was subjected to stability studies.

Results and Discussion: The results of DSC and FTIR studies revealed that there are no possible drug-excipient interactions. The percentage drug release of ezetimibe at 10 min (Q_{10}) and dissolution efficiency were increased from 23.86±1.08% and 11.61 for conventional tablet to 92.57±1.12% and 60.30 for the liquisolid formulation. From the stability studies, the similarity factor was found as above 50 that revealed the stability of the formulation.

Conclusion: In conclusion, the liquisolid technique was believed as a capable approach to enhance the ezetimibe dissolution rate.

Keywords: Carrier powder; coating material; dissolution efficiency; liquisolid compact; poorly soluble; similarity factor.

1. INTRODUCTION

Ezetimibe, hypolipidemic agent that reduceses blood cholesterol level by inhibiting intestinal absorption of cholesterol. Ezetimibe is available as white-crystalline powder, which has good solubility in ethanol, methanol and acetone but practically insoluble in water [1,2]. Hence this drug is selected to enhance the dissolution rate as well as to improve the bioavailability. Recent reported examples to enhance the drug release of ezetimibe using cyclodextrin complexes [3] and preparation of solid dispersions [4]. The present study was aspired to enhance the dissolution of ezetimibe using liquisolid compaction technique.

Nowadays, pharmaceutical industries facing several problems and challenges owing to global competition and increasing demand for better products. The oral route is the preferred route of drug administration, but the drug must be in solution form for the absorption to occur through gastro intestinal tract (GIT). The major rate limiting step in absorption is the dissolution rate for poorly soluble drugs [5]. Drugs, those showing less than 100 µg/ml aqueous solubility show the dissolution-limited and incomplete absorption [6]. In the drug discovery, 40% of new drugs are suffering with low aqueous solubility that made to incomplete absorption and therapeutic activity [7].

Some of the recently reported techniques to improve the dissolution rate of poorly soluble drugs are solid dispersions [8], crystal engineering [9], ball milling [10], complexation [11], self-emulsifying drug delivery systems [12] and use of mesoporous silica carriers [13]. Recently, liquisolid technique [14] is considering as promising approach for the dissolution enhancement. Liquisolid systems are described as dry, non-sticky powders with good compressibility as well as flowability obtained by alteration of liquid drugs, drug suspensions/ solutions in non-volatile solvents with chosen carriers and coating materials. In the preparation of liquisolid compacts, non-volatile solvents are incorporated to prepare drug solutions or suspensions, but the non-volatile solvents are not evaporated and drug is carried with in liquid system and is dispersed throughout the final product. “Spireas and Bolton [14]” were described the mathematical formulae to calculate the required quantities of carrier and coating material to convert liquid medication in to a free flowing solid. The liquisolid technique is considered as the successful approach to enhance the dissolution rate of carbamazepine [15], atorvastatin calcium [16], nimesulide [17] and fenofibrate [18].

2. MATERIALS AND METHODS

2.1 Materials

Ezetimibe was a gift sample from MSN laboratories, Hyderabad, India, Aerosil 200, Avicel pH102, Crosspovidone, and HPMC-E15 were gift samples from Aurabindo Pharmaceuticals Hyderabad, India. All other chemicals used were of analytical grade.

2.2 Solubility Studies

Solubility studies of the ezetimibe were carried out in PEG 400, tween-80, and propylene glycol to select the best non-volatile solvent for dissolving ezetimibe. Saturated solutions were prepared by adding excess drug to the vehicles and shaking on the incubator shaker (Jeiotech, Korea) for 48 h at 25ºC±1ºC. After this period the solutions were filtered through a 0.45 µm Millipore filter, diluted with distilled water and

analyzed by double beam UV-Visible spectrophotometer (Systronics, Hyderabad) at a wavelength of 232 nm against blank (blank sample contained the same concentration of specific solvent used without drug).

2.3 Binding Capacity of Adsorbents for the Solvents

The capacity of carrier material to hold liquid and behave like dry powder is called as binding capacity and it was determined by following procedure. The constant weights of (5 g) of the different powder excipients were taken and non-volatile solvent was added (1:1 drug to solvent ratio) in an increment of 0.01ml. The mixture was triturated after each addition to help distribution of the liquid throughout the powder particles. The addition of vehicle and the trituration was continued until mortar contents start to look like dry powder [19].

2.4 Calculation of Load Factor

In liquisolid system, the carrier and coating materials can retain only certain amounts of liquid while maintaining acceptable flow and compression properties depending on the excipients ratio used. The excipients ratio R (R = Q/q) of powder is defined as the ratio between the weights of carrier (Q) and coating (q) materials present in the formulation [20]. Preparation of a liquisolid system with an acceptable flowability and compressibility is possible if a maximum liquid on the carrier material is not exceeded. This characteristic amount of liquid is termed the liquid load factor (Lf). The Lf is defined as the weight ratio of the liquid medication (w) and carrier powder (Q) in the system (i.e., Lf = W/Q) [21]. To calculate the loading factor, non-volatile solvent (liquid medication without drug) was added to 10 g of carrier material and blended for 1min. To this coating material was added and triturated.

2.5 Determination of Flow Properties of Liquisolid Powders

Liquisolid powder mixtures of different formulations were evaluated for angle of repose, bulk density, tapped density and compressibility index. The fixed funnel method was employed to measure the angle of repose (θ) and it was calculated using the following formula:

$$\tan \theta = h/r$$

in which, θ is the angle of repose, h is the height of the cone and r is radius of the cone base. To measure the angle of repose, a funnel was fixed to a stand so that the lower tip of funnel was 2.5 cm above the surface. A graph paper was placed on a flat surface. The powder blend was allowed to fall freely on the graph paper through the funnel (6.9 cm diameter), till the tip (8 mm diameter) of heap formed just touches the funnel. The radius of heap was noted and from this angle of repose was determined. Angle of repose less than 30° suggests free flowing properties of the material [22].

The bulk density of a liquisolid powder is determined by measuring the volume of a known mass of powder sample that may have been passed through a screen, into a 50 ml graduated cylinder. Tapped densities of powder samples were determined by a tap density apparatus (Intelli, Kshitij Innovations, India). The apparatus was set for 500 tappings for 5 min at stroke height 20 mm, (100 strokes/min). The compressibility index (Carr's Index) is a measure of the propensity of a powder to be compressed. It is determined from the bulk and tapped densities and is calculated using the following formula:

$$\text{Carr's Index} = [(\rho_{tap} - \rho_b) / \rho_{tap}] / \times 100$$

in which, ρ_b is bulk density and ρ_{tap} is tapped density [22].

2.6 Preparation of Liquisolid Tablets

Using the method described by "Spireas et al. [20]", the liquisolid compacts were prepared in this study. Ezetimibe was dissolved in non-volatile solvent (PEG-400 or propylene glycol or tween-80) to prepare the drug solution. The mixture of carrier-coating materials (Avicel PH102 or starch or HPMC or PEG 4000 or PEG 6000 as the carrier powder and Aerosil 200 as the coating material) was added to the liquid medication and blended in a porcelain mortar avoiding excessive trituration and particle size reduction. The mixing was done in three stages; in the first stage, drug was mixed slowly to allow uniform distribution of liquid medication. In second stage the mixture was spread as a uniform layer on the surface of the mortar and left standing for few minutes. In the final stage 5% of disintegrant (Crosspovidone) was added to the powder and mixed thoroughly. The final mixture was compressed into tablets with 12 mm round flat punches using 16 station rotary

tabletting machine (Cadmach, Ahmedabad, India).

2.7 Evaluation of Liquisolid Tablets

After the compression of liquisolid tablets, they were evaluated for weight variation, hardness, friability and drug content uniformity. To check the weight variation, randomly picked 20 tablets were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation, Japan). Tablet hardness was measured using Monsanto tablet hardness tester (n=6) and the friability of six tablets was measured using Roche friabilator (Electrolab, Mumbai, India). *In vitro* disintegration time (n=3) was measured using Electrolab disintegration apparatus. Then to check the uniformity of drug content, randomly selected ten tablets were powdered and 100 mg of above powder was accurately weighed and transferred to a 100 ml volumetric flask, prepared the solution and estimated the drug content spectrophotometrically at 232 nm (Indian Pharmacopoeia, 1996).

2.8 *In vitro* Dissolution Studies

To check the improvement in dissolution rate, *in vitro* drug release studies were conducted using USP paddle method for both liquisolid and conventional tablets. The dissolution was carried out using 900 ml of dissolution medium i.e., 0.1N HCl (pH 1.2) at 37±0.5ºC temperature and 50 rpm rotation speed. 5 ml of samples were withdrawn at pre=planned time intervals, then filtered using 0.45 micron filter (Millipore, USA) and analyzed using UV-Visible spectro-photometer at 232nm (n=6) [23].

2.9 Determination of Dissolution Para-meters

From the results of *in vitro* dissolution studies, a graph was plotted between the cumulative percent drug release and time. From the above graph, the percent drug release in 10 min (Q_{10}) was determined. Then calculated the initial dissolution rate (IDR) in first 10 min using Q_{10} value. Dissolution efficiency (DE) was computed using the trapezoidal rule from area under the dissolution curve at time t. Relative dissolution rate (RDR) is calculated as the ratio between amount of drug dissolved from best liquisolid and conventional tablets in 10 min [24,25].

2.10 Drug-Excipient Interaction Studies

Differential scanning calorimetry (DSC) study was carried out on pure drug and the best formulation using DSC (Perkin-Elmer, Shelton, U.S) under nitrogen (nitrogen flow rate 50 ml/min) and at a standard heating rate of 15ºC/minute over a temperature range of 50ºC-350ºC. The Fourier transform infrared spectra (FTIR) of pure drug and the best formulation were recorded between 400 to 4000 cm^{-1} with the help of KBr disk method using an FTIR spectrometer (Perkin Elmer FTIR, Perkin Elmer Inst. USA). From the both studies, resultant peaks were compared to check the drug-excipient interactions.

2.11 Stability Studies

Stability studies were planned with the help of ICH guidelines for the best formulation (F5). The tablets (n=3) were sealed in aluminum packaging coated inside with polyethylene and stored in the humidity chamber at 40±2ºC and 75±5% RH for six months [26]. Then the collected samples after six months were analyzed for assay and *in vitro* dissolution rate. The results were subjected to statistical analysis using paired *t*-test at 0.05 level of significance. Finally, similarity factor was calculated between dissolution rates of F5 tablets before and after storage to check the similarity in results [27,28].

3. RESULTS

3.1 Solubility Studies

The solubility of ezetimibe in PEG-400, Propylene glycol, Tween-80 is given in Table 2. The table shows that the ezetimibe has highest solubility in PEG-400.

3.2 Flow Properties of Liquisolid Powders

Before going to compression, to check the flow properties of the powder mixtures of different formulations, they were evaluated for angle of repose, bulk density, tapped density, Carr's index. All the results were shown in Table 3 and they indicated the flow properties of powder mixtures. The angle of repose is less than 40 and compressibility index is less than 22 indicate the required good flow of powders for tablet compression.

Table 1. Formulation of ezetimibe liquisolid systems

Liquisolid system*	Ezetimibe (mg)	Liquid vehicle	Carrier	Coating material	Loading factor	Final weight (mg)
F1	10	PEG 400	Avicel	Aerosil	0.23	600
F2	10	PEG 400	Starch	Aerosil	0.06	600
F3	10	PEG 400	HPMC	Aerosil	0.04	600
F4	10	PEG 400	PEG 4000	Aerosil	0.05	600
F5	10	PEG 400	PEG 6000	Aerosil	0.11	600
F6	10	PG	Avicel	Aerosil	0.23	600
F7	10	PG	Starch	Aerosil	0.13	600
F8	10	PG	HPMC	Aerosil	0.063	600
F9	10	PG	PEG 4000	Aerosil	0.063	600
F10	10	PG	PEG 6000	Aerosil	0.06	600
F11	10	Tween-80	Avicel	Aerosil	0.18	600
F12	10	Tween-80	Starch	Aerosil	0.08	600
F13	10	Tween-80	HPMC	Aerosil	0.07	600
F14	10	Tween-80	PEG 4000	Aerosil	0.11	600
F15	10	Tween-80	PEG 6000	Aerosil	0.08	600

**Each formulation contains ezetimibe to liquid vehicle is in 1:1 ratio, carrier to coating material in 20:1 ratio. To make the tablet, each formulation contains 10% crospovidone, 2% talc, 1% magnesium stearate and lactose to make up the tablet weight to 600 mg; *In each formula R=Q/q; 480/24=20*

3.3 Evaluation of Liquisolid Tablets

The physical properties of ezetimibe tablets were given in Table 4. To check the tablet weight variation, all the formulations were found to be within the pharmacopoeial limits i.e., not more than 5% of the average weight. The hardness and friability of the tablets was found to be uniform i.e., 3.0±0.25 to 3.8±0.62 kg/cm^2 and less than 1% respectively. The tablets uniformity of content was found to be uniform and in the range of 95.2±0.28%-99.8±1.74%.

Table 2. Solubility studies of ezetimibe in non volatile solvents

S. no	Solvent	Solubility (mg/ml)
1	PEG 400	81.2
2	Propylene glycol	41.5
3	Tween-80	22.6

Table 3. Evaluation of pre compression parameters of ezetimibe tablets (n=3)

Formulation	Angle of repose	Bulk density (gm/cc^3)	Tapped density (gm/cc^3)	Carr's index (%)
F1	23.31±1.6	0.321	0.354	18.2
F2	39.56±1.6	0.352	0.402	20
F3	39.56±1.6	0.351	0.402	20
F4	25.11±1.4	0.343	0.398	18
F5	20.13±1.5	0.306	0.357	17.7
F6	33.44±1.5	0.326	0.405	18
F7	35.87±1.6	0.325	0.408	19.5
F8	36.34±1.6	0.307	0.382	20
F9	33.22±1.1	0.304	0.387	21
F10	35.21±1.8	0.303	0.387	22
F11	30.64±1.3	0.321	0.345	21
F12	36.35±1.5	0.325	0.408	20
F13	33.52±1.9	0.309	0.402	21.5
F14	31.13±1.5	0.320	0.398	22
F15	25.73±1.1	0.334	0.387	19

Table 4. Evaluation of post compression parameters ezetimibe drug solution (n=3)

Formulation	Weight variation (mg)	Hardness (kg/cm^2)	Friability (%)	Disintegration time (sec)	Content of uniformity (%)
F1	598±0.12	3.6±0.06	0.12	120±5	95.2±0.28
F2	582±1.05	3.6±0.62	0.16	124±5	97.0±0.76
F3	585±0.12	3.3±0.42	0.25	220±4	96.6±0.28
F4	580±0.83	3.4±0.42	0.15	125±5	96.2±0.70
F5	602±0.83	3.0±0.25	0.12	115±4	99.8±1.74
F6	590±1.5	3.5±0.35	0.13	119±5	96.9±0.61
F7	583±1.7	3.4±0.61	0.24	117±4	97.2±1.67
F8	596±1.33	3.3±0.35	0.25	119±5	97.9±0.16
F9	592±1.11	3.8±0.42	0.14	118±2	96.6±0.82
F10	586 ±0.14	3.0±0.25	0.33	118±4	95.8±1.47
F11	582±1.22	3.3±0.86	0.25	120±4	97.2±0.28
F12	579±1.78	3.5±0.28	0.13	120±5	98.6±0.70
F13	580±0.45	3.8±0.62	0.14	150±5	97.2±0.8
F14	576±0.47	3.7±0.52	0.15	123±5	96.8±0.26
F15	597±0.34	3.2±0.64	0.26	115±5	96.8±0.9

3.4 *In vitro* Dissolution Study

The cumulative mean percent of ezetimibe released from liquisolid compacts containing different quantities of carrier materials (from F1 to F15) was found to vary from 13.56±0.98% to 92.57±1.12% in first 10 min. This indicates the fast release of drug is observed from above formulations. From the dissolution study, the optimized formulations F5 showed that 92.57% drug release in the first 10 min where as the control conventional tablets showed 23.86% in 10 min. Fig. 1 was shown the dissolution curves of F1-F15 formulations. It also explains the comparison between F5 liquisolid and control conventional tablets.

For the F5 tablets, the calculated Q_{10} and IDR were found to be 92.57±1.12% and 9.26 %/min respectively and improved significantly when compared to conventional tablets (23.86±1.08% and 2.39 %/min). The RDR was found to be 3.87. Finally, the DE was found to be 60.30 for F5 and it is increased much, when compared with the control conventional tablet (Table 5).

3.5 Drug- Polymer Interaction Studies

DSC curves obtained for pure ezetimibe and optimized formulation (F5) were showed in Fig. 2. The endothermic peak of ezetimibe was found 163.87ºC and for optimized formulation (F5) was observed 162.87ºC. In FTIR studies (Fig. 3) the pure drug peaks were observed at 3265.5 cm^{-1}, PEG6000 at 3415 cm^{-1}, 28045 cm^{-1} and in case of optimized formulation the peaks were obtained at 3416.5 cm^{-1}, 2352 cm^{-1}, 3265 cm^{-1}.

3.6 Stability Studies

The results of stability studies of F5 tablets were shown in Table 6. The statistical analysis results revealed that there was no significant difference in the drug release and assay between before and after storage (P<0.05). Similarity factor was calculated using dissolution results of F5 liquisolid tablets and it was found to be 83.82 that is greater than 50, shown the similarity between the dissolution rates of before and after storage [27,28].

Table 5. Dissolution parameters of ezetimibe optimized formulation (F5) and conventional tablet (n=3)

Formulation	(Q_{10})*	IDR (%/min)	DE	RDR
Optimized formulation (F5)	92.57±1.12	9.26	60.30	3.87
Conventional tablet	23.86±1.08	2.39	11.61	

Table 6. Stability studies of ezetimibe optimized formulation F5 (n=3)

Time (min)	Before storage	After 6 months	*t*-test at 0.05 LS	Similarity factor (f_2)
0	0.00±0.00	0.00±0.00	Not significant	83.82
5	74.32±0.96	72.64±0.85		
10	92.57±1.12	90.12±1.54		
15	99.78±1.38	97.56±1.16		
% Assay	99.8±1.74	98.2±1.28	Not significant	-

4. DISCUSSION

Ezetimibe, hypolipidemic agent, has a poor water solubility that limits the oral absorption and bioavailability. Hence the current study was intended to enhance the dissolution rate which in turn would increase the absorption. In the present study ezetimibe liquisolid tablets were prepared by using polyethylene glycol 400 (PEG 400) as a non-volatile liquid vehicle Avicel PH102 or starch or HPMC or PEG 4000 or PEG 6000 as the carrier powder and Aerosil 200 as the coating material in different ratios and they were characterized for different physical parameters and drug release studies to find the optimized formulation that shows fast dissolution rate.

Drug solubility in non-volatile vehicle is most important aspect in formulation of liquisolid systems. The dissolution rate will improve if the drug forms the molecular dispersion in non-volatile solvent; hence drug needs the good soluble non-volatile solvent. From the results of solubility studies (Table 2), PEG 400 was found to be suitable solvent for ezetimibe. The optimum amount of PEG 400 incorporated in to the formulation depends upon the acceptable flow and compressibility of the powder material.

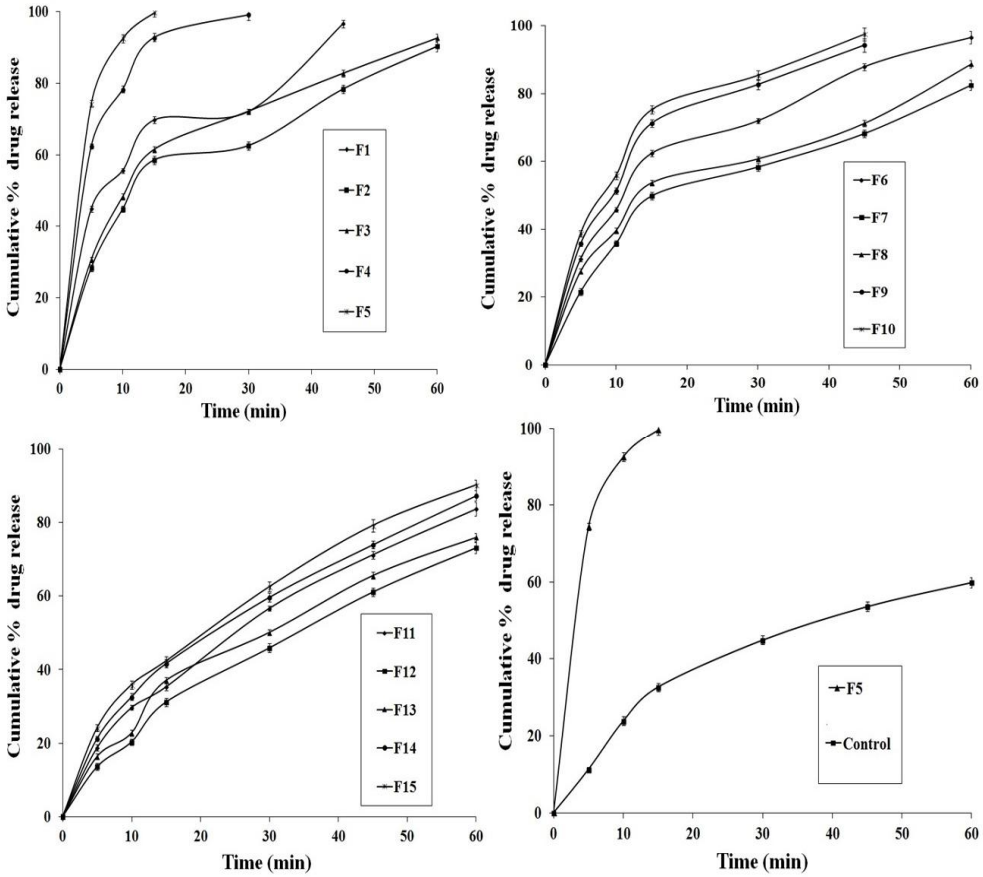

Fig. 1. Dissolution profile of ezetimibe liquisolid and conventional tablets

The angle of repose is less than 40 and compressibility index is less than 22 indicate the required good flow of powders for tablet compression. Formulations with PEG 400 showed better results (angle of repose and Carr's index) when compared to formulations containing PG and tween 80.

The liquisolid tablets were evaluated for tablet physical properties like weight variation, hardness, friability and drug content uniformity they were complied with pharmacopoeial limits. The tablets should contain adequate hardness to oppose the breakage during handling and at the same time it should disintegrate after swallowing. The weight variation test revealed that all the formulations were found to be within the pharmacopoeial limits i.e., not more than 5% of the average weight (Indian Pharmacopoeia, 1996). These results showed that all the tablet formulations were found uniform in hardness, friability and drug content uniformity.

From the *in vitro* drug release studies, a formulation F5 was considered as the best formulation to produce fast release of the ezetimibe when compared to other formulations. The enhancement in dissolution rate of the liquisolid tablets is probably due to the drug presenting in a solublized state, which contributes to increased wetting properties, thereby improving the dissolution rate [7]. From the calculations of DE and RDR, F5 formulation showed better improvement in dissolution and it is considered as optimized formulation. Overall increase in the dissolution performance of the optimized formulation was described in terms of dissolution parameters (IDR, DE, RDR) and compared with conventional tablet. DE of ezetimibe was increased by 4.5 times when compared with conventional tablet.

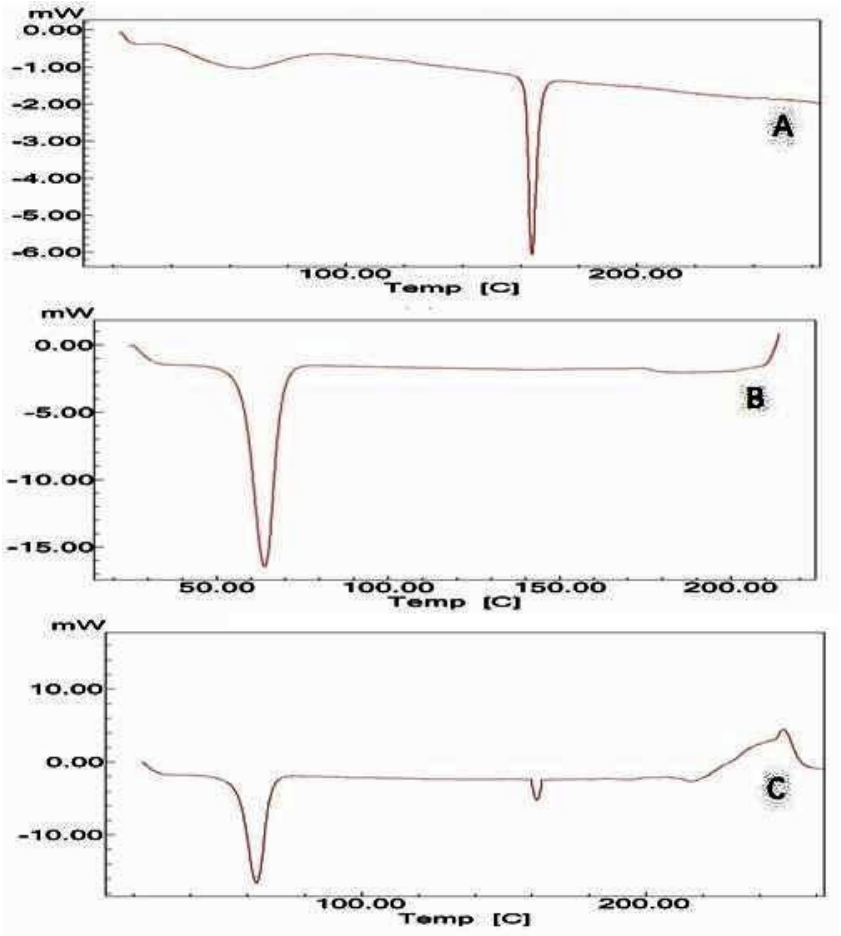

Fig. 2. DSC thermograms of A) Ezetimibe B) PEG 6000 C) Optimized formulation

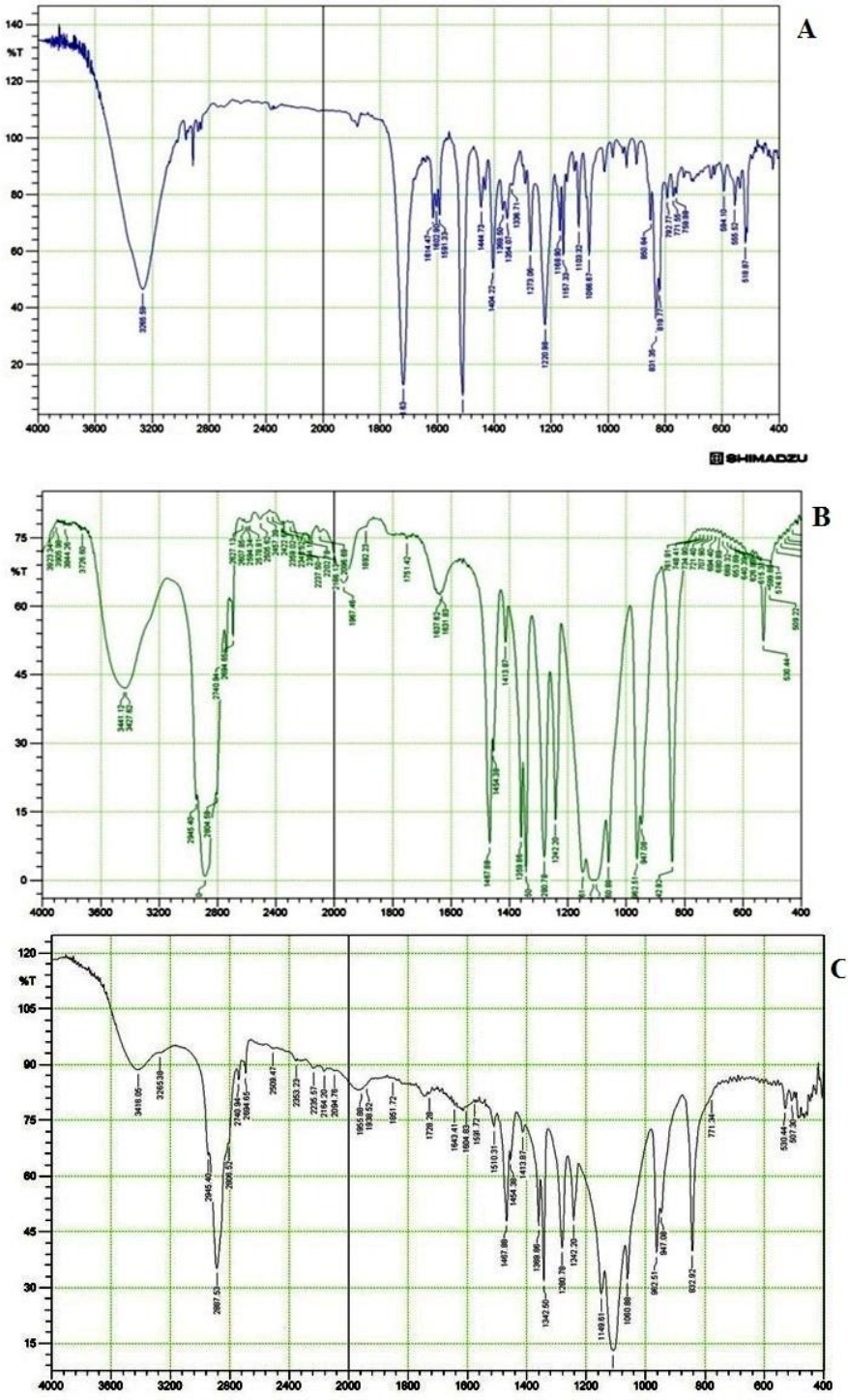

Fig. 3. FTIR Spectral studies of A) Ezetimibe B) PEG 6000 C) Optimized formulation

DSC and FTIR studies showed that the absence of drug-excipient interactions. This is proved by the careful comparison of pure drug and best formulation peaks from the both DSC and FTIR studies. From the stability studies, calculated similarity factor was found to be 83.82 that is

greater than 50 indicates the stability of formulation.

From the above results, PEG 400 is considered as the best solvent when compared to PG and tween 80 in terms of solubility and flow properties. In comparison of different carrier materials, PEG 6000 is the best carrier due to its hydrophilic nature and acceptable physical properties of tablets. The increased dissolution from liquisolid formulation could be due to, presence of drug in solubilised state in the formulation, which contributes to the increased wetting properties, thereby improved the *in vitro* dissolution rate. Correspondingly, as the tablet formulation disintegrates in dissolution media, the drug will be presented in a state of molecular dispersion, which leads to enhance the effective surface area of the particles available for dissolution. In conclusion, development of the liquisolid compacts can be a promising alternative technique for water-insoluble drugs to achieve the fast dissolution rate.

5. CONCLUSION

From the above results, to enhance the dissolution rate of poorly soluble ezetimibe, liquisolid technique was considered as one of the significant techniques available. The dissolution of ezetimibe was significantly increased in liquisolid formulation compared to conventional tablets. The DE of ezetimibe was increased by 4.5 times in optimized liquisolid formulation F5 when compared with conventional tablet. DSC and FTIR spectra indicate there were no drug-excipient interactions. Significant improvement in the both wetting property and effective surface area of the particles is considered as the major reason to enhance the dissolution rate from the liquisolid tablets. Thus the liquisolid technique can be a promising approach to enhance the dissolution rate of poorly soluble drugs.

CONSENT

It is not applicable.

ETHICAL APPROVAL

It is not applicable.

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COMPETING INTERESTS

Authors have declared that no competing interests exist.

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