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FORMULATION, CHARACTERIZATION AND *IN-VITRO* EVALUATION OF LIQUISOLID TABLETS OF EZETIMIBE

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ABSTRACT

Objective: To develop ezetimibe tablets using liquisolid technique to increase the solubility of ezetimibe tablets when compared to conventional tablets.

Methods: Ezetimibe liquisolid tablets were prepared by using liquisolid technique. The ezetimibe liquisolid formulations were characterized by pre- and post-compression parameters.

Results: Materials such as Aerosil, HPMC, grades of polyethylene glycol (PEG) showed an impact on parameters such as angle of repose, thickness, and hardness and drug release as shown in the graphs below.

Conclusion: In conclusion, the liquisolid technique was believed as a capable approach to enhance the ezetimibe solubility, Dissolution rate, Bio availability.

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

INTRODUCTION

Ezetimibe, an anti-lipidemic agent that, by inhibiting intestinal cholesterol absorption, decreases the level of blood cholesterol. Ezetimibe is a white-crystalline powder that is highly soluble in ethanol, methanol and acetone, but nearly insoluble in water. This medicine is chosen to boost the rate of dissolution as well as to improve bioavailability, by using liquisolid method **[1]**.

In this study ezetimibe tablets are prepared by using liquisolid technique in order to

improve the solubility. In the drug discovery, 40% of new drugs are suffering with low aqueous solubility that made to incomplete absorption and therapeutic activity **[2]**.

Some of the recently reported techniques to improve the dissolution rate of poorly soluble drugs are solid dispersions, crystal engineering, ball milling **[1]**, complexation **[2]**, self-emulsifying drug delivery systems and use of mesoporous silica carriers. Recently, liquisolid technique is considering as promising approach for the dissolution enhancement.

A liquisolid system refers to formulations formed by conversion of liquid drugs, drug suspensions or drug solution in non-volatile solvents, into dry, non-adherent, free flowing and compressible powder mixtures by blending the suspension or solution with selected carriers and coating materials **[3]**.

MATERIALS

Ezetimibe, Polyethylene glycol grades (PEG 200, 400, 600), HPMC (E15), Aerosil 200, Eudragit L100, PVP K30 **[4]**.

CALIBRATION

The stock solution of ezetimibe was prepared by dissolving 10 mg of pure drug in ethanol in a 10 ml volumetric flask. It was diluted as and when required. The absorbance of 10 ug/ml was measured against a solvent blank between 200- 300 nm, A calibration curve was obtained at 242 nm for a series of concentrations in the range of 5-20 ug/ml. it was found toobilinear hence, suitable for the Estimation of the drug the calibration graph is showed in **Figure 1**.

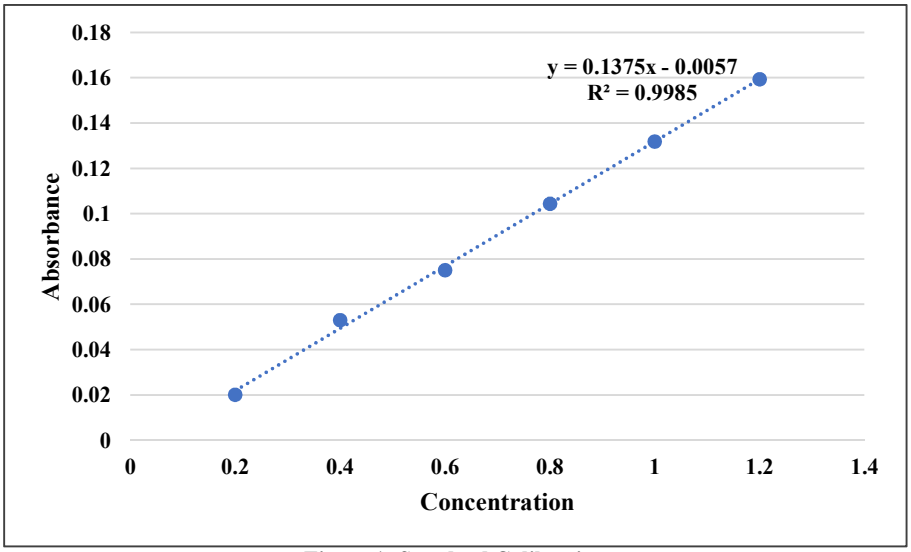

Figure 1: Standard Calibration

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 for 48 h at 25ºC±1ºC.then the solutions were filtered, diluted with distilled water and analysed by double beam UV-Visible spectrophotometer at a wavelength of 232 nm against blank (blank sample contained the same concentration of specific solvent used without drug **[1]**.

PREPARATION OF LIQUISOLID TABLETS:

Using the technique mentioned in Spiraeas *et al* (liquisolid method). In the analysis **[5]**, the liquisolid tablets were prepared. To prepare the drug solution, ezetimibe was dissolved into non-volatile (PEG 4OO). Then the liquid drug was applied with a mixture of HPMC (carrier), Aerosil (coating material) and blended in a porcelain-mortar to prevent unnecessary crushing and reduction of particle size. The blending was conducted in three phases; In the first step, the drug was slowly mixed to allow for Uniform liquid drug delivery. In The mixture was dispersed as a mixture in the second step. Uniform coating on the mortar surface and the mortar surface stayed standing for a few minutes. A powder and thoroughly blended. The Ultimate Finale powder is compressed in an 8 mm die in rotary punch machine.

Table 1: Formulation table

Batches	Drug mg	PEG 400 mg	HPMC -E15	Aerosil Mg	Eudragit-L100	PVP-k30 Mg
F1	20	20.2	125	75	22.5	7.5
F2	20	20.2	112.5	87.5	22.5	7.5
F3	20	20.2	100	100	22.5	7.5
F4	20	20.2	150	50	22.5	7.5
F5	20	20.2	175	125	22.5	7.5
F6	20	20.2	137.5	62.5	22.5	7.5

PREFORMULATION STUDIES

FLOE PROPERTIES

Angle of repose

In a glass funnel of 25 ml capacity with a diameter of 0.5 cm, 5 g of precisely weighed blend samples were passed separately **[6]**. The funnel has been adjusted in such a way that 2.5 cm above the horizontal surface is the stem of the funnel. The sample was allowed to flow from the funnel, so the pile height h just reached the tip of the funnel by drawing a boundary, the diameter of the pile was determined along the circumference of the pile and taking the average of three

diameters. Angle of repose was calculated by formula:

$\theta = \tan -1 (h/r)$

Hauser's ratio: (HR) HR was obtained by using formula:

HR = Tapped density/Bulk density

Carr's index: (CI) **[23]** CI, which is calculated as follows

% CI = Tapped density Bulk density Tapped density ×100

FTIR SPECTRAL ANALYSIS

To check the compatibility between drugs and excipients, the FTIR study was conducted **[7]**. The FTIR Spectrophotometer (I. R Prestige-21 Shimadzu) was used to determine the infrared spectrum of ezetimibe, excipients, a drug with various excipients, physical mixture and the final liquisolid formulation using the KBR dispersion method **[8]**.

EVALUATION OF LIQUISOLID

Thickness:

The thickness was measured using Vernier calliper. Five tablets from each batch were used and average values were calculated **[9]**.

Hardness: The hardness of the tablets was determined using Monsanto hardness tester **[10]**. It is expressed in kg/cm^2. Six tablets from each formulation were tested for hardness.

Friability:

The test was performed using Roche friabilator (Electro lab).

Initial weight – final weight/final weight×100

Dissolution:

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 [(11)].5 ml of samples were withdrawn at 5,10,15,20,30,45,60 mins time intervals, then filtered using 0.45micron filter S (Millipore, +USA) and analysed using UV-Visible spectrophotometer at 232nm (n=3).

RESULTS

Solubility studies

The solubility of ezetimibe was comparatively more in poly ethylene glycol than propyllene glycol, tween-80 as shown in the following **Table 2**.

EVALUATION OF PRE COMPRESION-PARAMETERS (n=3)

They were evaluated for angle of repose, bulk density, tapped density, Carr's index before going to compression, to check the flow properties of the powder mixtures of different formulations **[6]**. **Table 3** shows all the findings and suggested the flow properties of powder mixtures. The resting angle is less than 40 and the compressibility index is less than 22, indicating the good flow required.

FTIR SPECTRAL ANALYSIS

Spectra exhibited peaks, indicating the presence of =C-H, -C-F and C=O, stretching and bending functional groups. Thus, the FTIR Spectral analysis indicated that there were no drug interactions. The detailed spectra elucidations were shown in **Figure 2.0, 2.1, 2.2** are indicated in **Table 4**.

The FTIR spectral analysis of the drug is shown in **Figure 2.0**.

EVALUATION OF POST COMPRESSION PARAMETERS

In **Table 5**, the physical properties of ezetimibe tablets were given. All the formulations were found to be within the pharmacopeia limit, i.e., not more than 5% of the average weight, in order to verify the tablet weight variance. The hardness and friability of the tablets, i.e., 3.0±0.25 to 3.8±0.62 kg/cm^2 and less than 1% respectively, were found to be uniform. Material uniformity of the tablets has been found in the range of 95.2±0.28%-99.8±1.74%.

DISSOLUTION

It was found that the cumulative mean percentage of ezetimibe released from liquisolid compacts containing various amounts of carrier materials (from F1 to F6) ranged from 15.6±0.081% to 96.67±0.680% in the first 10 minutes **[4]**. This means that the drug's rapid release from the above formulations is observed. The optimized F5 formulations from the dissolution study showed that 79.1 percent of drug release in the first 10 minutes **(Figure 3, 4)**.

Table 2: Solubility

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

Table 3: Pre formulation parameters

Formulation	Angle of repose	Bulk density (gm/cc3)	Tapped density (gm/cc3)	Carrs index (%)
F1	32.3±0.42	0.324	0.345	8.6
0F2	24.3± 0.89	0.341	0.371	8.08
F3	14.3± 0.23	0.331	0.4330	23.5
F4	14.5 ± 0.49	0.359	0.362	0.82
F5	24.1± 4.2	0.302	0.341	11.4
F6	15.3± 1.02	0.320	0.462	30.73

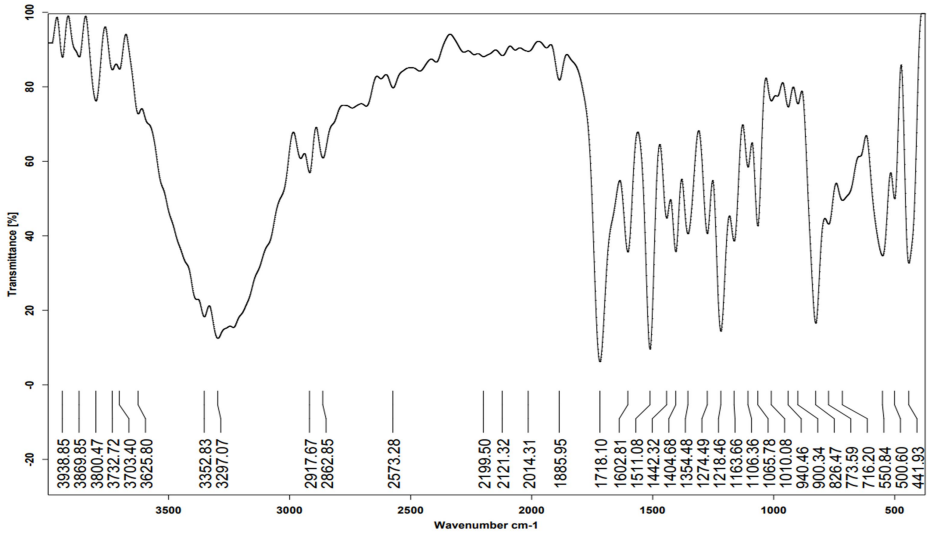

Figure 2.0: Drug (Ezetimibe)

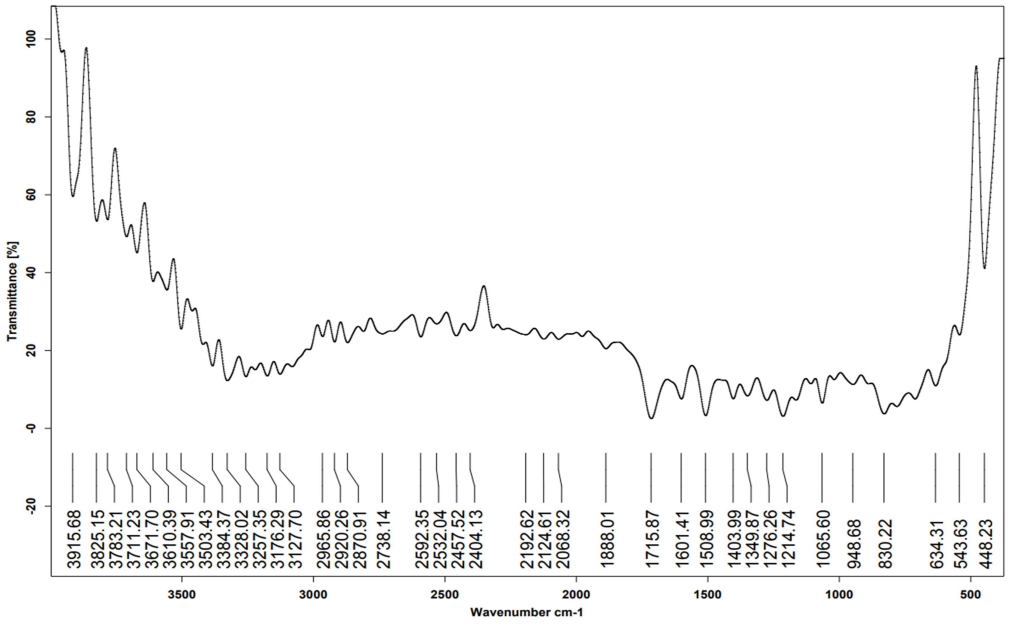

Figure 2.1: (HPMC -E15)

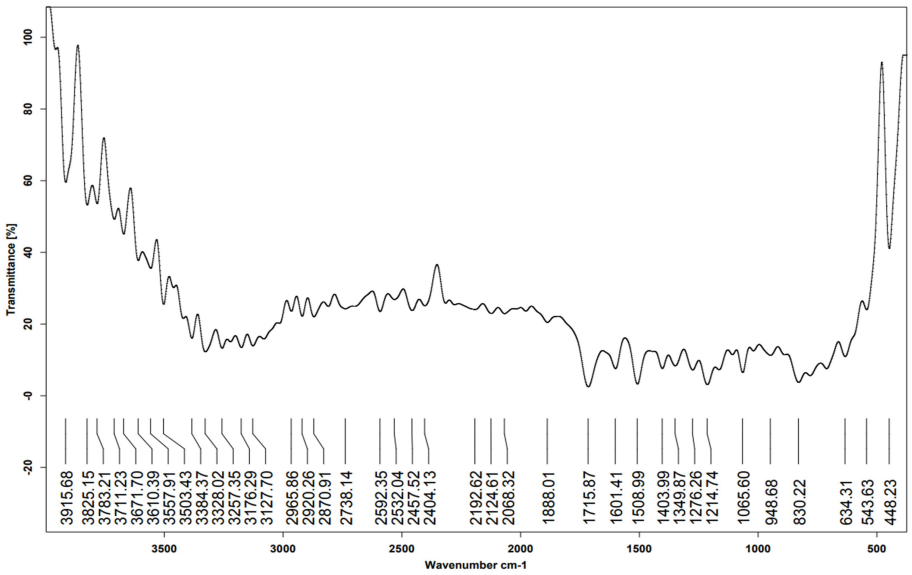

Figure 2.2: (Aerosil)

Table 4: Interpretations data for pure drug

Functional Group	Wave number	Soluplus	EDS	EPS
C-H stretching	3133.85	3101.99	3111.62	3125.21
C=O stretching	1718.01	1638.19	1618.06	1638.19
C-H Bending	1510.01	1411.36	1407.84	1406.3
C-F Stretching aromatic	851.77	---	819.51	866.67

Table 5: Evaluation parameters

Formulation	weight variation(mg)	Hardness Kg/cm2	Friability (%)	Disintegration Time(sec)	Content uniformity (%)
F1	511.3± 1.6	4.13± 0.09	0.12	120.6± 2.4	93.2± 1.0
F2	539.3± 14.0	4.0± 0.08	0.22	119.3± 1.24	95±0.7
F3	549.6± 12.2	4.16 ±0.2	0.14	122.0± 0.81	91±0.95
F4	534.6 ±10.7	3.23± 0.20	0.23	116.6 ± 1.6	96±0.7
F5	590.3± 9.8	3.76± 0.18	0.18	118.6 ±1.24	99.7±0.2
F6	540.3 ±17.3	5.23± 0.20	0.23	118.0± 4.3	98±1.04

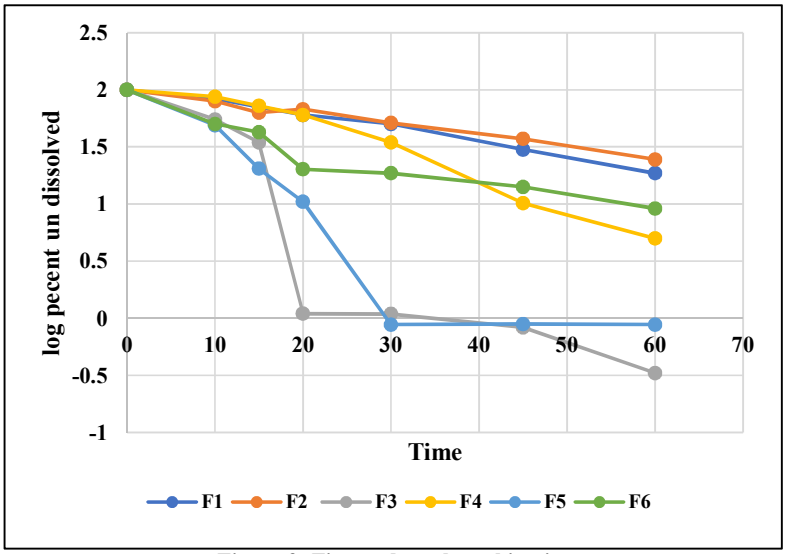

Figure 3: First order release kinetics

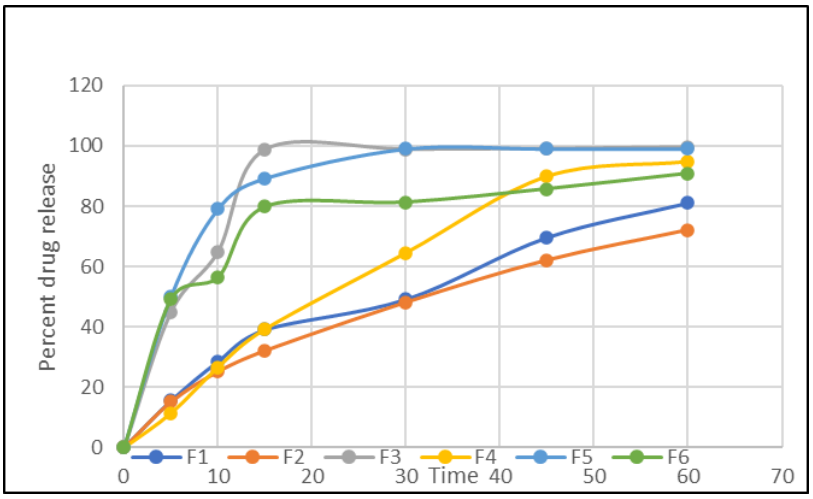

Figure 4: In-vitro dissolution graph

CONCLUSION

In order to increase the dissolution rate of poorly soluble ezetimibe, the liquisolid technique was considered one of the important techniques available from the above findings. In liquisolid formulation, the dissolution of ezetimibe has been significantly improved compared to conventional tablets, so the liquisolid process can be a promising path to improving the rate of dissolution of poorly soluble drugs.

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