American Journal of Advanced Drug Delivery

www.ajadd.co.uk

Original Article

Ezetimibe Solid Dispersions: Formulation, Development and *In vitro* Evaluation

Chaitanya P, Jyothi Penta*, Venkat Ratnam Devadasu, Raj Kumar Venisetty and Sateesh Kumar Vemula

Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India-506 001

Date of Receipt- 23/01/2014
Date of Revision- 26/01/2014
Date of Acceptance- 28/01/2014

Address for Correspondence
Department of Pharmaceutics, Chaitanya College of Pharmacy Education and Research, Kishanpura, Hanamkonda, Warangal, Andhra Pradesh, India-506 001
Tel. +91-8702559555.
E-mail: jyothispartan@gmail.com

ABSTRACT

Development of solid dispersions of poorly water soluble drugs is one of the most widely used approaches to enhance the solubility as well as dissolution rate. In the current investigation, ezetimibe is selected as model drug to improve the solubility and dissolution rate by solid dispersion method. Solid dispersions were prepared using solvent evaporation method by incorporating polyethylene glycol 4000, polyethylene glycol 6000 and gelucire 44/14 as carriers in different ratios and evaluated for solubility studies, drug-carrier compatibility studies and *in vitro* dissolution studies. Based on the solubility and drug release studies, formulations F4, F8 and F11 were selected to prepare in the form of tablets and compared with conventional tablets. From the *in vitro* dissolution study, tablets containing gelucire 44/14 showed almost complete drug release within the 15 min. The percent drug release in 15 min (Q_{15}) and initial dissolution rate for formulation F11 was 94.22±1.08%, 9.26%/min. These were very much higher compared to conventional tablets containing pure drug (23.87±1.13%, 2.38%/min). The relative dissolution rate was found to be 2.14 and dissolution efficiency was found to be 67.52 and it is increased by 4.0 fold with F11 formulation compared to conventional tablets. Thus, it is concluded that the formulation of gelucire 44/14 solid dispersions is a suitable approach to improve the solubility and dissolution rate of ezetimibe than pure form of drug.

Keywords: Conventional tablets, Dissolution efficiency, Initial dissolution rate, Relative dissolution rate, Solvent evaporation method, Solubility studies.

INTRODUCTION

The oral route of drug administration is the most common and preferred method of delivery due to convenience and ease of ingestion. But a drug with poor aqueous solubility will typically exhibit dissolution rate limited absorption, and a drug with poor membrane permeability will typically exhibit permeation rate limited absorption. Hence, two areas of pharmaceutical research that focus on improving the oral bioavailability of active agents include enhancing solubility and dissolution rate of poorly water-soluble drugs and enhancing permeability of poorly permeable drugs[1,2]. Enhancing the solubility and dissolution rate of drugs can be increased by a well-known process of fabricating solid dispersions[3]. This study focuses on the use of solid dispersion technologies to improve the dissolution of poorly water-soluble drugs and in turn their oral bioavailability. Solubility enhancement will increase the drug's acceptability and bioavailability by reducing the dose required and sometimes can result in faster onset of action[4,5]. Solid dispersions are molecular dispersions of drugs in a polymer in solid form. These can be prepared by various methods. Solvent evaporation method and fusion method are widely used depending upon the requirement[6].

Ezetimibe (EZB) is a poorly water soluble drug and act as a hypolipidemic agent[7]. In the present study our efforts are towards making a solid dispersion of EZB that can increase the solubility and dissolution rate. In the present study, solid dispersions of EZB were prepared using PEG 4000, PEG 6000 and gelucire 44/14 by solvent evaporation method. Some of the recent reported drugs as gelucire solid dispersions are glibenclamide[8], gliclazide[9], carvedilol[10], ritonavir[11] and lycopene[12]. These carriers act as continuous phase in the solid dispersion in which EZB is dispersed as internal phase.

MATERIALS AND METHODS

Materials

Ezetimibe was gift sample from MSN Laboratories, Hyderabad, India. Gelucire 44/14 was obtained as gift samples from Gattefosse. PEG 4000 and PEG 6000 were obtained from CDH, Delhi, India and all other reagents used were of analytical grade and obtained from S.D. Fine Chemicals, Mumbai, India.

Preparation of solid dispersions by solvent evaporation method

Solid dispersion of EZB with PEG 4000, PEG 6000 and gelucire 44/14 in different weight ratios were prepared by the solvent evaporation method (Table 1). Accurately weighed amount of drug and carriers in various ratios dissolved in ethanol in a round bottom flask and the solvent was evaporated at 45°C temperature. Solid dispersions (SD) were subsequently stored in a vacuum oven at room temperature for 48 h to remove the residual solvent. The dried solid dispersions were grinded in a mortar and pestle and passed through sieve # 60. and were stored in desiccators until use.

Solubility studies

The solubility studies of different solid dispersion formulations were conducted in 0.1 N HCl, distilled water and 7.4 pH phosphate buffer. An excess amount of EZB solid dispersion was weighed and transferred into conical flasks which contain 10 ml of media. The content in conical flask were sonicated for 2 h at room temperature, there after the samples were placed on a shaker, agitated at room temperature for 48 h. Subsequently, the suspensions were filtered through a Whatman filter paper. The filtrate

was suitably diluted and analyzed spectro-photometrically at a wavelength of 232 nm using a double beam UV-Visible spectrophotometer.

Drug-carrier compatibility studies

The thermo grams were recorded for drug, carrier, and physical mixture using differential scanning calorimeter (Shimadzu, Japan). About 2–4 mg sample in an open aluminium standard pan was heated at a scanning rate of 5^0 C /min from a temperature 0 to 450 ^{0}C under a nitrogen gas flow[13]. FTIR spectra were recorded using an FTIR spectrophotometer (Shimadzu, Japan). The samples (drug, carrier, and physical mixture) were previously ground and mixed thoroughly with potassium bromide. The FTIR Spectra were recorded between 400 to 4000 cm^{-1}.

Dissolution studies of prepared solid dispersions

In vitro dissolution studies of prepared solid dispersions were carried out by using USP XXIV type II paddle method. Samples equivalent to 10 mg of ezetimibe was added to the 900 ml of 0.1N HCl at 37±0.5°C and stirred at 50 rpm. An aliquot of 5 ml was withdrawn at different time intervals with a syringe filter. The withdrawn volume was replaced immediately with same volume of dissolution medium in order to keep total volume constant. The filtered samples were assayed spectrophotometrically at 232 nm. The mean of at least three determinations were used to calculate the drug release.

Micromeritic properties of blend

The flow properties of powder are vital in the manufacture of tablets. The flow properties were studied through measuring the angle of repose, Carr's index and Hausner's ratio. 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:

$$\tan\theta = h/r \quad \ldots\ldots\ldots\ldots\ldots\ldots \quad (1)$$

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 (6.8 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. The bulk density of a 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. The apparatus was set for 500 tappings for 5 min at stroke height 20 mm, (100 strokes/min) 14. The Carr's Index is a measure of the propensity of a powder to be compressed and it is calculated using the following formula:

$$\text{Carr's Index} = [(\rho_{tap} - \rho_b)/\rho_{tap}]/\times 100 \ldots\ldots \quad (2)$$

In which, ρ_b is bulk density and ρ_{tap} is tapped density. Hausner's ratio is calculated from the ratio of bulk density and tapped density.

Preparation of fast dissolving tablets (FDTs)

From the results of dissolution and solubility studies, the fast dissolving tablets were prepared for selected solid dispersion preparations (Table 4). The FDTs were prepared by direct compression method. The solid dispersion powder equivalent to 10 mg of EZB, Crosspovidone and other tabletting

excipients were passed through a mesh no 60. The powdered solid dispersion was mixed with proper portion of Crosspovidone. Then excipients other than glidant and lubricant were added and mixed in a poly bag for 5-10 min. The obtained blend was lubricated with talc and magnesium stearate for another 5 min and the resultant mixture was directly compressed into tablets using rotary tabletting machine.

Evaluation of physical parameters

The designed formulations were studied for their physical properties like weight variation, hardness and friability. For estimating weight variation, 20 tablets of each formulation were weighed using an electronic weighing balance (AW 120, Shimadzu Corporation and Japan). The hardness of six tablets was measured using Monsanto tablet hardness tester. Friability was determined on ten tablets in a Roche friabilator (Electrolab, Mumbai, India).

Determination of drug content

For estimation of drug content, ten tablets were crushed, and 100 mg of the powder was accurately weighed and transferred to a 100 ml volumetric flask. Initially about 50 ml of 7.4 pH phosphate buffer was added to the volumetric flask and allowed to stand for 6-8 h with intermittent shaking to ensure complete solubility of the drug. Then the volume was made up to 100 ml with buffer, filtered and analyzed for EZB content at 232 nm.

In vitro disintegration time

In vitro disintegration time of FDT's was determined by following the procedure described by Gohel *et al*. Briefly, 10 ml of water at room temperature was taken in a petri dish of 10 cm in diameter. The tablet was then carefully placed in the centre of petri dish and the time required for the tablet to completely disintegrate into fine particles was noted. Measurements were carried out in triplicates.

In vitro Dissolution Study

The release of EZB from FDTs was carried out using USP XXIV Type II dissolution apparatus (Electro lab, TDT-08L) at a rotation speed of 50 rpm, and a temperature of 37±0.5°C. The drug release studies were carried out in 7.4 pH phosphate buffer. An aliquot of 5 ml was collected at predetermined time intervals and replaced with fresh dissolution medium. The samples were filtered, by passing through 0.45 µm membrane filters (Millipore, USA) and analyzed spectrophotometrically at 232 nm.

Calculation of dissolution parameters

Cumulative percent drug release was plotted as a function of time and percent drug release in 15 min (Q15) was calculated. Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 15 min per 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. Relative dissolution rate (RDR) is the ratio between amount of drug dissolved from optimized formulation and that dissolved from the conventional formulation at 15 min[8].

Stability studies

The stability studies of prepared tablets were planned on the best formulation according to ICH guidelines. The packed samples (n=3) were stored in the stability chamber maintained at 40±2^{0}C and 75±5% RH for six months. After six months of storage, the samples were collected and analyzed for assay and *in vitro* dissolution rate. Then the data was analyzed using paired t-test to test the significant variation at 0.05 level of significance (LS). Then the similarity

index (F2) was calculated between dissolution rates of tablets before and after storage to prove the stability of tablets[14].

RESULTS

Solubility studies of EZB solid dispersions

The solubility studies were conducted in different media for all the prepared solid dispersions and compared with pure drug. The aqueous solubility of the solid dispersion formulations of different carriers was determined in different media i.e., 0.1 N HCl, distilled water and phosphate buffer pH 7.4. From the solubility studies, it was found that as the increase in pH of the media increased the solubility i.e. EZB showed greater solubility in 7.4 pH phosphate buffer when compared others. The solubility data of different formulations using different carriers showed in Table 2. From the results given in above tables, solid dispersions with Gelucire 44/14 showed grater solubility when compared to other carriers and as the carrier concentration increases, the solubility increased proportionally. From all the solid dispersions, formulation F11 showed highest solubility in 7.4 pH phosphate buffer i.e., 90.4 ± 0.88 mg/ml.

Drug-carrier compatibility studies

The thermograms of the EZB, gelucire 44/14, of EZB with gelucire 44/14 were shown in Figure 1. The DSC thermograms of EZB exhibited physical mixture a sharp endothermal peak around 163.87^{o}C corresponding to melting point. The DSC thermogram of gelucire 44/14 exhibited a broad endothermal peak around 49 ^{0}C corresponding to its melting point. The thermogram of physical mixture with gelucire 44/14 showed a short endothermal peak of drug at 164.62^{o}C indicating that there were no interactions between drug and carrier. The FTIR spectral analysis of pure EZB and physical mixture with gelucire 44/14 were showed the principal peaks at similar wave numbers (Figure 2). In FTIR studies the pure drug showed main peak at 3265.5cm^{-1}, and in physical mixture with gelucire 44/14 the peak obtained at 3265cm^{-1}. So there is no interaction between the drug and carrier.

Dissolution studies of prepared solid dispersions

Figure 3 demonstrated the EZB release patterns from the PEG 4000 solid dispersions. The cumulative mean percent of EZB released from above formulations varied from 35.16 ± 0.98% to 55.31 ± 2.98% in 15 min. In case of PEG 6000, Figure 4 demonstrated the EZB release. The cumulative mean percent of EZB released from above formulations varied from 61.85±1.56% to 63.08 ± 2.98% in 15 min. In case of Gelucire 44/14 Figure 5 demonstrated the EZB release patterns. The cumulative mean percent of EZB released from above formulations varied from 61.85 ± 1.56% to 94.22 ± 1.08% in 15 min. From all these formulations, tablets containing Gelucire 44/14 solid dispersions showed highest dissolution rate within 15 min i.e. 94.22±1.08% (F11).

Micromeritic properties of blend

The powder mixture for tablets were characterized with respect to angle of repose, bulk density, tapped density, Carr's index, and Hausner's ratio (Table 3). Angle of repose was less than 35° and Carr's index values were less than 21 for the powder mixture of all the batches indicating good to fair flowability. Hausner's ratio was less than 1.25 for all the batches indicating good flow properties.

Evaluation of Fast Dissolving Tablets

Based on the solubility studies, the better solid dispersions were converted into tablets. Table 5 showed all the physical parameters determined for EZB tablets. In weight variation test, the pharmacopoeial

limits for the tablets of not more than 7.5% of the average weight and found to be 73±1.43-68±1.41 mg. The tablet hardness and friability were found to be 2.5-3.5 kg/cm^2 and 0.22-0.69%, demonstrating the integrity and strength of tablets. The tablets assay was found to contain 97.56±1.2%-103.08±1.2%. From the disintegration test, the prepared tablets were disintegrated rapidly and it was found in the range of 30±2.5-57±4.5 sec. The wetting time of the prepared tablets was found to be 22±2.4-42±4.0 sec.

Dissolution Studies of Fast Dissolving Tablets

From the *in vitro* dissolution studies, tablets made from Gelucire 44/14 solid dispersion (F11) showed fast dissolution (99.12 ± 1.78% in 20 min) than formulation F4 containing PEG 4000 (92.42 ± 0.78% in 60 min) and formulation F8 containing PEG 6000 93.98 ± 1.08% in 60 min)and improved significantly when compared to control tablet (58.62±0.99% in 60min). Figure 6 demonstrated the EZB release patterns by above formulations.

Calculation of dissolution parameters

The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for optimized formulation (F11) was 94.22±1.08%, 9.26%/min. These were very much higher compared to pure drug (23.87±1.13%, 2.38%/min). The improvement in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 2.14. The DE was found to be 67.52 and it is increased by 4.0 fold with optimized FDT formulation compared to conventional tablets (Table 6).

Stability studies

Manifest the prospective utility of the formulation, stability studies were carried out at 40±2°C and 75±5% RH for six months to measure the stability of drug. After storage of six months, the formulation was subjected to a drug assay and *In vitro* dissolution studies (Table 7) and from the statistical analysis there was no significant difference between before and after storage (P<0.05). The similarity index value between dissolution profiles of optimized formulation before and after storage was found to be 93.03.

DISCUSSION

The current investigation is aimed to develop the EZB solid dispersions to improve the solubility and dissolution rate. In this study, EZB solid dispersions were prepared by using solvent evaporation method by incorporating PEG 4000, PEG 6000 and Gelucire 44/14 as carriers. After preparation of solid dispersions, measurement of aqueous solubility is one of the key factors, which govern the dissolution rate and it is the rate limiting step in absorption of poorly soluble drugs. The solubility of EZB solid dispersion formulations of different carriers was determined in different media i.e., 0.1 N HCl, distilled water and phosphate buffer pH 7.4. From the solubility studies of different formulations, it was found that as the increase in pH of the media increased the solubility. All the formulations exhibited significant increase in solubility in phosphate buffer pH 7.4. Similar type of results observed in Patel *et al* study i.e., the solubility of flurbiprofen was measured in four different media and the results showed that the solubility of the flurbiprofen was highest at pH 7.2, and decreased as the pH decreases[15]. From the formulations with gelucire 44/14 as hydrophilic carrier, as increasing the drug to polymer from 1:1-1:3 ratio, the solubility of EZB was increased at a significant level, but after that, there was no proportional increase in solubility by increasing polymer ratio up to 1:4. From the solubility studies, all the formulations showed significant increase in solubility when compared to pure drug and

physical mixture of drug-carrier. The DSC and FTIR studies of pure drug, gelucire 44/14 and physical mixture of EZB-gelucire44/14 showed that there was no interaction between drug and carrier.

From the dissolution studies, in case of different formulations, formulations with gelucire 44/14 were showed increased dissolution rate when compared to PEGs. In the present study gelucire solid dispersions showed high solubility and faster dissolution of drug when compared to other polymers. In the reported study by Chauhan *et al* similar type of solubility enhancement was observed with gelucire solid dispersions[8]. This is due to the difference in the saturation solubility of physical mixtures and solid dispersions is also probably attributed to reduction of particle size during processing and the presence of amorphous form of drug in solid dispersions as compared with physical mixtures in which drug was present in crystalline form[8]. In this study, the formulation with 0.3% w/w gelucire 44/14 (F11) gave rapid dissolution rate when compared to other formulations. From the *in vitro* dissolution studies, EZB in the form of solid dispersion showed significant increase in dissolution rate when compared to tablets with pure EZB.

After the completion of solubility studies and dissolution studies, then the powder mixtures of solid dispersions were evaluated for physical parameters like angle of repose, tapped density, bulk density, hausner's ratio and Carr's index. The results of angle of repose (<40) and Carr's index (<22) indicates fair to passable flow properties of the powder mixture. Based on the above results, the prepared solid dispersions of F4, F8 and F11 formulations were converted into tablets and evaluated for physical parameters as well as *in vitro* dissolution rate. The prepared tablets were studied for their physical properties like weight variation, hardness, friability and drug content uniformity and they were complied with pharmacopoeial limits. The average percentage deviation of all tablet formulations was found to be within the mentioned limit. From the physical characterization, all tablet formulations were uniform in hardness, friability and drug content uniformity.

Then the tablets were subjected to *in vitro* drug release studies in 7.4 pH phosphate buffer. Among the F4, F8, F11 and conventional tablets, F11 formulation with gelucire 44/14 as hydrophilic carrier, the dissolution rate of EZB was increased at a significant level when compared other tablets. Many factors contributed to faster drug release rate such as decrease in particle size, decrease in agglomeration of particles, increase wettability and decrease in crystallinity of the drug and might be due to combined effect of improved wettability, emulsifying effect of carriers and reduction in particle size during the formation of solid dispersions[2,3].

Overall increase in the dissolution performance of the optimized formulation was described in terms of dissolution parameters (IDR, DE, RDR) and when compared with pure drug, all the above parameters were increased in case of F3 formulation. Similar type of improvement in IDR, DE, RDR was reported in the study of Vemula *et al*[16]. After storage of six months, the formulation was subjected to a drug assay and *in vitro* dissolution studies and the data showed that there was no significant change. The similarity index value was found as 93.03, which is more than 50 indicates similarity between the dissolution profile before and after storage[17]. Further the pharmacokinetic evaluation is needed to prove the capability of gelucire 44/14 solid dispersions to improve the bioavailability of EZB[18].

CONCLUSION

In the present study, ezetimibe solid dispersions were prepared using various weight ratios of carriers and evaluated for physiochemical properties. Dissolution rate of all formulations were shown greater than the conventional tablets due to intermolecular interactions between the polymer and drug. The percent drug release in 15 min (Q_{15}) and initial dissolution rate (IDR) for optimized formulation (F11) was 94.22±1.08%, 9.26%/min. These were very much higher compared to conventional tablets containing pure drug (23.87±1.13%, 2.38%/min). The improve-ment in the dissolution characteristics of a drug described in terms of dissolution efficiency (DE) and relative dissolution rate (RDR). The RDR was found to be 2.14. The DE was found to be 67.52 and it is increased by 4.0 fold with F11 FDT formulation compared to conventional tablets. In conclusion, development of the solid dispersions can be a promising alternative method to attain the fast dissolution rate and absorption for water-insoluble drugs like ezetimibe and it was achieved with gelucire 44/14 as carrier. Further the pharmacokinetic evaluation is needed to prove the capability of gelucire 44/14 solid dispersions to improve the bioavailability of ezetimibe.

ACKNOWLEDGEMENTS

The authors acknowledge MSN Laboratories, Hyderabad, India and Gattefosse for gift samples. The authors also thank to Management, Chaitanya College of Pharmacy Education and Research for providing facilities.

REFERENCES

1. Kaushik D, Dureja H, Saini TR. Mouth Dissolving Tablets: A Review. *Indian Drugs* 2004; 41: 187-193.
2. Dordunoo SK, Ford JL, Rubinstein MH. Preformulation studies on solid dispersions containing triamterene or temazepam in polyethylene glycols or Gelucire 44/14 for liquid filling of hard gelatin capsules. *Drug Dev Ind Pharm* 1991; 17: 1685–1713.
3. Patil MP, Gaikwad NJ. Preparation and characterization of gliclazide-polyethylene glycol 4000 solid dispersions. *Acta Pharm* 2009; 59: 57–65.
4. Chang R, Guo X, Burnside B, Couch R. A review of fast dissolving tablets, *Pharm Tech* 2000; 52-58.
5. Bhaskar C, Shyam S, Anant P. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur J Pharm Sci* 2005; 26: 219-230.
6. Vippagunta SR, Maul KA, Tallavajhala S, Grant DJW. 2002. Solid state characterization of nifedipine solid dispersions. *Int J Pharm* 2002; 236: 111–123.
7. Martindale. The complete Drug reference, 32nd ed., London: The Pharmaceutical press; 1999; 1473.
8. Chauhan B, Shimpi S, Paradkar A. Preparation and evaluation of glibenclamide-polyglycolized glycerides solid dispersions with silicon dioxide by spray drying technique. *Eur J Pharm Sci* 2005; 26: 219–230.
9. Devireddy SR, Veerareddy PR. Solubility and bioavailability improve-ment of glcclazide by solid dispersions using novel carriers. *Int J Drug Del* 2012; 4: 455-461.
10. Faisal W, O' Hora TR, O'Driscoll CMM, Griffin BT. A novel lipid-based solid dispersion for enhancing oral bioavailability of Lycopene- In vivo evaluation using a pig model. *Int J Pharm* 2013; 453 (2): 307-314.

11. Sinha S, Ali M, Baboota S, Ahuja A, Kumar A, Ali J. Solid dispersion as an approach for bioavailability enhancement of poorly water-soluble drug ritonavir. *AAPS Pharmscitech* 2010; 11(2): 518-527.
12. Potluri RHK, Bandari S, Jukanti R, Veerareddy PR. Solubility enhancement and physicochemical characterization of carvedilol solid dispersion with gelucire 50/13. *Arch Pharm Res* 2011; 34(1): 51-57.
13. Mettu SR, Veerareddy PR. Formulation, evaluation and pharmacokinetics of flurbiprofen fast dissolving tablets. *Brit J Pharm Res* 2013: 3(4): 617-631.
14. Vemula SK, Veerareddy PR. Formulation, evaluation and pharma-cokinetics of ketorolac tromethamine time-dependent colon targeted drug delivery system. *Exp Opin Drug Del* 2013; 10(1): 33-45.
15. Patel JH, Tiwari P, Patel JS. Solid dispersion based tablets of poorly soluble drug ezetimibe. Am J Pharmtech Res 2011; 1(1): 18-24.
16. Vemula SK, Veerareddy PR. Fast disintegrating tablets of flurbiprofen: Formulation and characterization. *Lat Am J Pharm* 2011; 30(6): 1135-1141.
17. Vemula SK, Bontha VK. Colon targeted gaur gm compression coated tablets of flrbiprofen: Formlation, development and pharmacokinetics. *Bio Med Res Int* 2013; Article ID 287919.
18. Bandarkar SF, Ibrahim SK. Lyophilized Gliclazide poloxamer, solid dispersions for enhancement of *in vitro* dissolution and in vivo bioavailability. *Int J Pharm Pharmaceut Sci* 2011; 3(2): 122–127.

Table 1. Formulation of Ezetimibe Solid Dispersion

Formulation Code	Ingredients in (mg)			
	Ezetimibe	PEG 4000	PEG 6000	Gelucire 44/14
F1	10	10	-	-
F2	10	20	-	-
F3	10	30	-	-
F4	10	40	-	-
F5	10	-	10	-
F6	10	-	20	-
F7	10	-	30	-
F8	10	-	40	-
F9	10	-	-	10
F10	10	-	-	20
F11	10	-	-	30
F12	10	-	-	40

Table 2. Solubility of studies of EZB Solid Dispersions in Various Solvents (mg/ml)

S. No	0.1 N HCl	Distilled Water	7.4 pH Buffer
F1	7.3 ± 0.87	33.5+1.56	38.59±0.56
F2	9.32 ± 1.4	40.59+0.77	46.50±0.28
F3	5.12±0.19	30.23±0.09	42.43± 0.32
F4	5.52±1.09	36.62±0.19	60.03± 0.09
F5	8.28±1.79	38.12+0.19	41.28±1.02
F6	4.56±1.79	29.95±1.79	38.43±0.16
F7	14.9 ± 0.11	37.2 ± 0.99	45.3± 0.14
F8	18.4 ± 0.16	53.3 ± 0.65	61.95± 1.57
F9	16.9 ± 0.16	44.0 ± 0.14	48.3 ± 1.18
F10	26.3 ± 0.26	60.25 ± 1.46	71.8 ± 0.64
F11	35.1 ± 0.81	82.1 ± 0.17	90.4 ± 0.88
F12	28.9 ± 1.24	79.1 ± 0.11	81.13± 2.12

Table 3. Evaluation of pre-compression parameters (Mean ± SD, n=3)

Formulation	Angle of Repose (^{0})	Bulk Density (gm/cc^3)	Tapped Density (gm/cc^3)	Carr's Index (%)	Hausner's Ratio
F4	23.31±1.6	0.32	0.354	18.2	1.15±0.01
F8	31.32±1.6	0.307	0.382	20	1.21±0.02
F11	33.22±1.1	0.304	0.387	21	1.23±0.01

Table 4. Composition of Ezetimibe Tablets using Optimized Solid Dispersions

Formulation Code	Ingredients in mg		
	F4	F8	F11
EZB Solid dispersion equivalent to 10 mg EZB	50	50	40
Crosspovidone	6	6	6
Avicel pH 102	41	41	51
Magnesium stearate	1	1	1
Talc	2	2	2
Total Tablet weight	100	100	100

Table 5. Physical Properties of EZB Tablets

Formulation	Weight variation* (mg)	Hardness† (Kg/cm^2)	Friability (%)	Disintegration time‡ (sec)	Drug content‡ (%)
F4	101.4±1.28	3.1±0.45	0.38	123±5	99.83±1.15
F8	100.20±3.82	3.4±0.29	0.33	135±5	98.33±1.82
F11	101.05±4.12	3.2±0.10	0.45	112±4	99.93±1.50

* All values represent mean ± standard deviation, n=20; † n=6; ‡ n=3

Table 6. Dissolution Parameters of EZB conventional and (F11) tablets (Mean ± SD n=3)

Formulation	(Q_{15})*	IDR (%/min)	DE	RDR
Optimized (F11)	94.22±1.08	9.26	67.52	2.14
Conventional tablet	39.62±1.29	2.38	15.27	

Table 7. Stability Studies of EZB F11 tablets (n=3)

Time (min)	Before storage	After 6 months Storage	*T-test* at 0.05 LS	Similarity Factor (F2)
0	0.00±0.00	0.00±0.00	Not Significant	93.03
5	61.82±1.12	60.85±1.42		
10	81.28±1.98	80.92±0.58		
15	94.22±1.08	93.96±0.82		
20	99.67±1.79	98.12±0.93		
% Assay	99.93±1.50	98.78±1.15	Not Significant	--

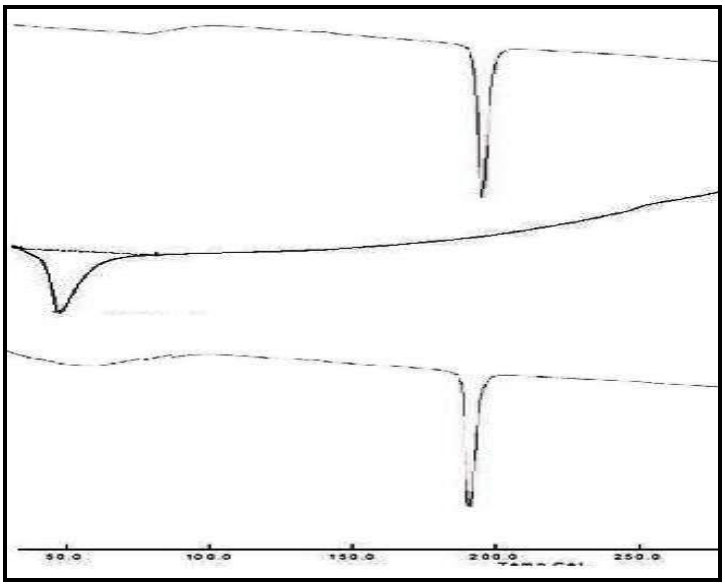

Figure 1. DSC thermograms of A) EZB B) Gelucire 44/14 C) F11 physical mixture

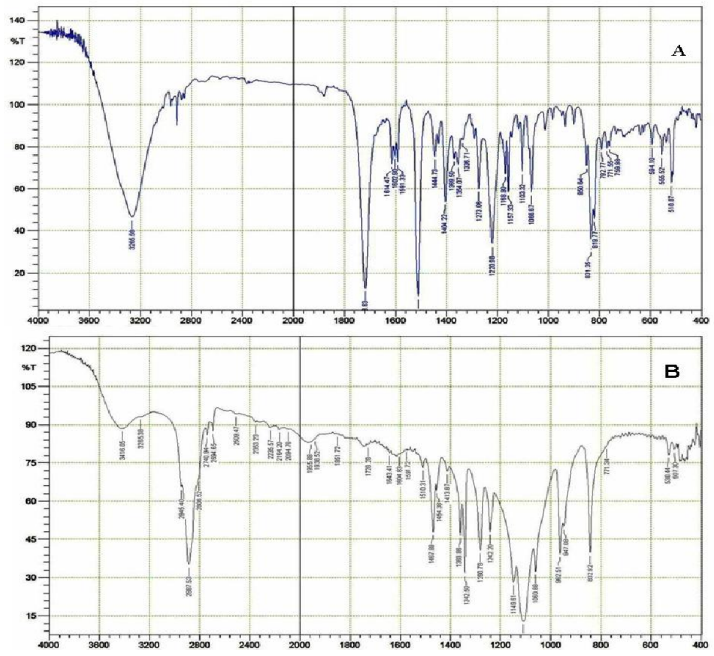

Figure 2. FTIR spectra of A) EZB B) F11 physical mixture

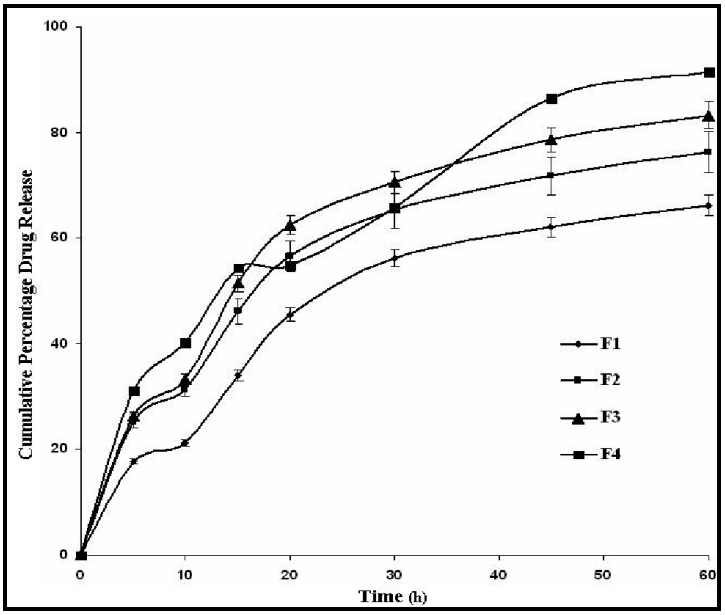

Figure 3. Dissolution studies of EZB Solid Dispersions using PEG 4000

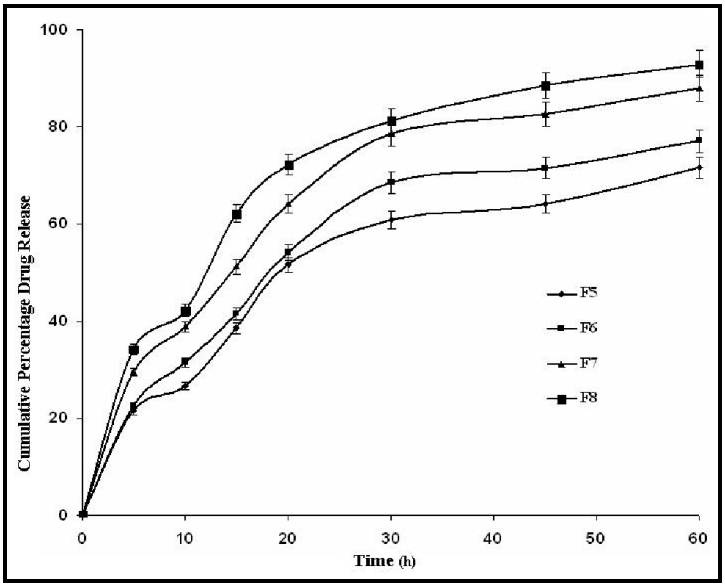

Figure 4. Dissolution studies of EZB Solid Dispersions using PEG 6000

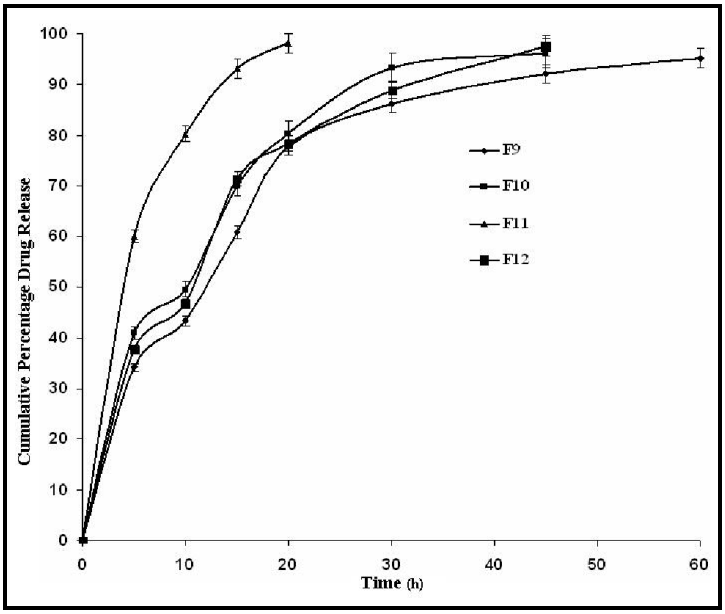

Figure 5. Dissolution studies of EZB Solid Dispersions Gelucire 44/14

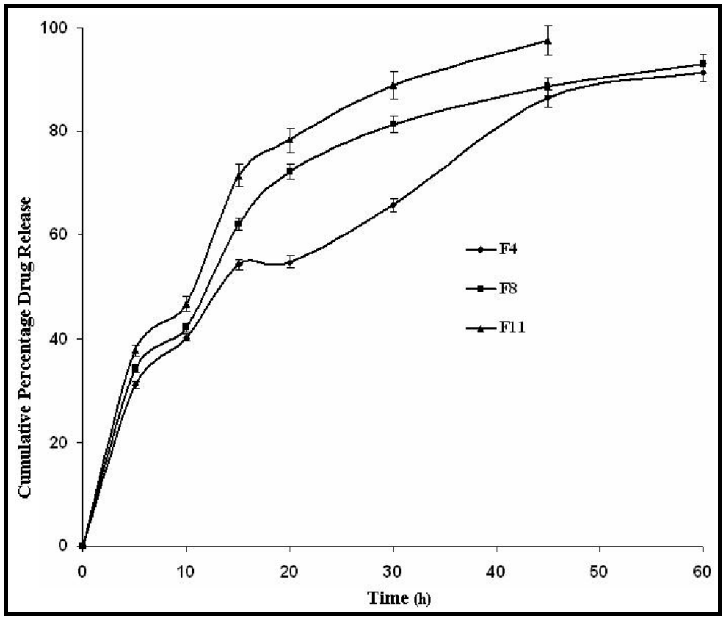

Figure 6. Dissolution studies of EZB Tablets containing EZB Solid Dispersions