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Preparation and physicochemical characterization of surfactant based solid dispersions of ezetimibe

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Received November 6, 2008, accepted November 10, 2008

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Pharmazie 64: 227–231 (2009) *doi: 10.1691/ph.2009.8331*

Solid dispersions of the poorly water-soluble drug ezetimibe were prepared with a surfactant, Pluronic® 188 in different ratios and characterized by FTIR, XRD, DSC and dissolution studies. The melting method was employed to prepare the solid dispersions whereas a physical mixture (1 : 3) was prepared by co-grinding the individual components in a mortar. Physical studies demonstrated a significant reduction in crystallinity with a possibility of presence of amorphous character of drug in the solid dispersions of ezetimibe. Among all binary systems studied, the 1 : 3 proportion of ezetimibe: Pluronic® 188 showed fastest dissolution rate (DE_{90}: 73.38% ± 3.95) suggesting optimum ratio of the surfactant used.

1. Introduction

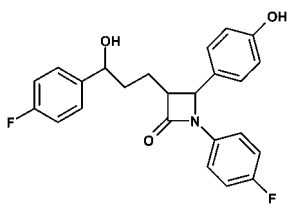
Solubilization of poorly aqueous soluble drug continues to be a challenging task for formulation experts. Poor aqueous solubility of a drug frequently results in poor dissolution which is a prime determinant of rate and extent of drug absorption (Proudfoot 1991). The drugs having low aqueous solubility often elicit poor therapeutic response because of limited oral bioavailability. An improvement in aqueous solubility/dissolution can overcome this problem. One of the possible ways to modify such physicochemical properties of drug molecules is to formulate them in a suitable hydrophilic carrier in the form of molecular dispersions usually referred as solid dispersion systems (Chiou and Riegelman 1971; Leuner and Dressman 2000; Serajuddin 1999). Recently, surfactant based solid dispersion systems have gained wide acceptance in drug delivery systems (Newa et al. 2007; Schott et al. 1982).

Surfactants are believed to alter physical properties of drugs such as hydrophobicity, surface charge, flocculation/dispersion, floatation and wetting. Because of these unique properties, surfactants have been proved to be excellent carriers for preparation of solid dispersion systems (Ghebremeske et al. 2007; Zhang and Somasundaran 2006; Sharma and Joshi 2007).

Pluronics® or pluronic block copolymers are nonionic surfactants widely used in pharmaceutical formulations for improving the solubility of poorly water-soluble drugs (Chen et al. 2004). Pluronic® consists of hydrophilic corona EO (ethylene oxide) and hydrophobic core PO (polypropylene oxide) blocks arranged in a triblock structure resulting in an amphiphilic copolymer. Their low melting point renders them suitable for melt granulation technique. Moreover, their ability to self aggregate thereby forming micelles and liquid crystalline phases is the added advantage for solubility enhancement of poorly water-soluble drugs via solid dispersion technique. For drug delivery purposes, hydrophobic drugs may be solubilized within the core of micelle or conjugated to the micelle-forming polymer (Singhare et al. 2005). Pluronics® are available in different grades such as Pluronic® 188 and Pluronic® 407 (Kabanov et al. 2002). These surfactants are also used in the pharmaceutical industry as solubilizing agents, detergents, defoaming agents, gelling agents, dispersing agents and emulsifying agents (Erlandsson 2002).

The solubilization of drug from solid dispersion systems is mainly mediated by the reduction in particle size, increase in the surface area and reduction in crystallinity that improves dissolution rate. Further, no energy is required to break up the crystal lattice of a drug during the dissolution process and drug solubility and wettability may be increased by surrounding hydrophilic carriers (Craig 2002).

Ezetimibe, 1-(4-fluorophenyl)-3(*R*)-[3-(4-fluorophenyl)-3(*S*)-hydroxypropyl]-4(*S*)-(4-hydroxyphenyl)-2-azetidinone is used as lipid lowering agent. It inhibits the absorption of cholesterol from the small intestine (Woodlinger 2005). The drug is practically insoluble in water (Vytorin Description RxList.com) which leads to its poor dissolution resulting in poor bioavailability (35–65%) which ultimately affects its therapeutic response.



The objective of this work was to enhance the dissolution rate of ezetimibe via solid dispersion technique using Pluronic® 188 as a hydrophilic carrier. The solid disper-

sion systems of ezetimibe were prepared with Pluronic 188 in 1 : 1, 1 : 2 and 1 : 3 ratios using the melting technique. Different ratios of the polymer were selected purely on random basis. Fourier transformation-infrared spectroscopy (FTIR), Powder X-Ray diffractometry (XRD) and Differential scanning calorimetry (DSC) were used to characterize the solid state properties of pure ezetimibe and its solid dispersion systems. The dissolution behavior of ezetimibe and all its binary systems were further investigated.

2. Investigations, results and discussion

2.1. Percentage drug content study

Percentage drug content of the formulations was found to be in the range of 96.94 ± 0.17 to 98.71 ± 0.14.

2.2. Fourier transformation infrared spectroscopy (FTIR)

Figure 1 illustrates the FTIR spectra of ezetimibe, Pluronic® 188 and solid dispersion systems. The IR spectrum of ezetimibe (Fig. 1A) is characterized by principal absorption peaks at 3264.41 cm^{-1} (broad, intermolecular hydrogen bonded, O−H strech), 2913.81 cm^{-1} (aromatic C−H strech), 2855.57 cm^{-1} (aliphatic C−H strech), 1879.87 cm^{-1} (weak combination and overtone band of ring), 1718.04 cm^{-1} (C=O of lactam), 1602.50 cm^{-1} (ring skeletal vibration band), 1509.34 cm^{-1} (ring C=C strech), 1445.82 and 1432.02 cm^{-1} (C−N strech), 1354.03 cm^{-1} (in plane O−H bend), 1221.51 cm^{-1} (C−F strech), 1118.21, 1103.09 and 1066.56 cm^{-1} (C−O strech of secondary alcohol) and 830.98 cm^{-1} (ring vibration due to para-disubstituted benzene).

The IR spectrum of physical mixture (Fig. 1C) appeared as a combination of peaks of ezetimibe and polymer with decreased peak intensity. However, some principal peaks at 2913.81 cm^{-1}, 2855.57 cm^{-1}, 1879.87 cm^{-1} of ezetimibe have been found to be absent in the physical mixture. IR spectra of all solid dispersions (Fig.s 1D, 1E and 1F) showed disappearance of most of the peaks of ezetimibe. The peaks at 3264.41 cm^{-1}, 2913.81 cm^{-1}, 2855.57 cm^{-1}, 1879.87 cm^{-1}, 1602.50 cm^{-1} and 1066.56 cm^{-1} completely disappeared in 1 : 1, 1 : 2 and 1 : 3 ezetimibe-Pluronic® 188 binary systems (Figs. 1D, 1E and 2F). However, the two principal absorption peaks of Pluronic® at 2892.54 cm^{-1} and 1114.64 cm^{-1} were consistent in all binary systems of ezetimibe and appeared with increasing intensity with increase in the proportion of the polymer. All peaks of ezetimibe were smoothened indicating strong physical interaction of ezetimibe with polymer. However, no additional peak was observed in all binary systems indicating absence of any chemical interaction between ezetimibe and polymer (Ford 1986).

2.3. X-ray powder diffractometry (XRD)

The XRD pattern of ezetimibe displayed (Fig. 2) intense and sharp peaks, indicating its crystalline nature. Pure ezetimibe showed sharp peaks at 18.98°, 18.30°, 21.45° and 22.44° (2θ) with peak intensities of 135, 86, 40 and 28 respectively. Peaks of ezetimibe with highest intensity (18.98°, 18.30°, 21.45° and 22.44°) disappeared in all binary systems (Figs. 2C, 2D, 2E and 2F). In the diffraction patterns of solid dispersion systems, a gradual decrease in

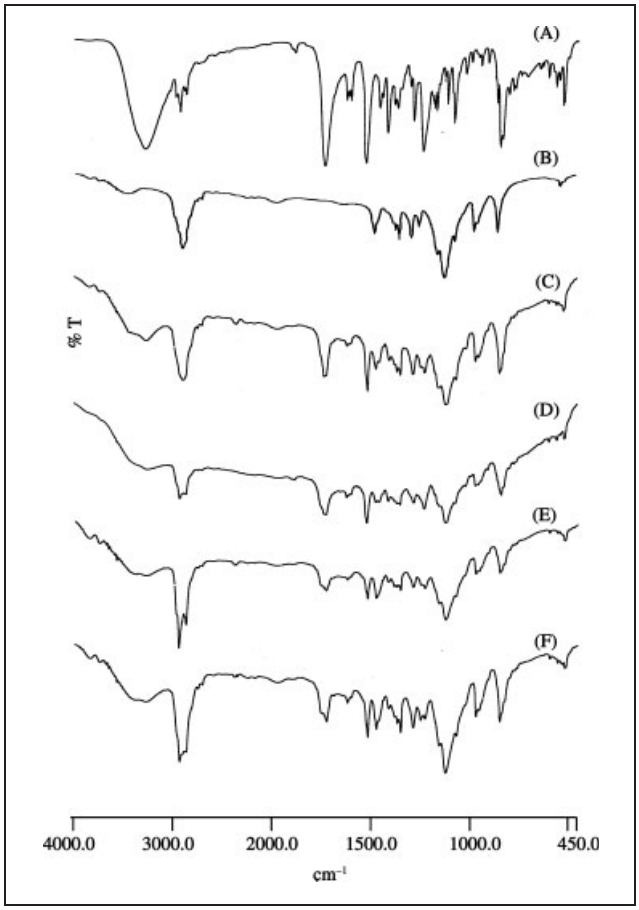


Fig. 1: FTIR spectra of ezetimibe-Pluronic® 188 binary systems: (A) ezetimibe; (B) Pluronic® 188; (C) physical mixture; (D) 1 : 1 solid dispersion; (E) 1 : 2 solid dispersion; (F) 1 : 3 solid dispersion

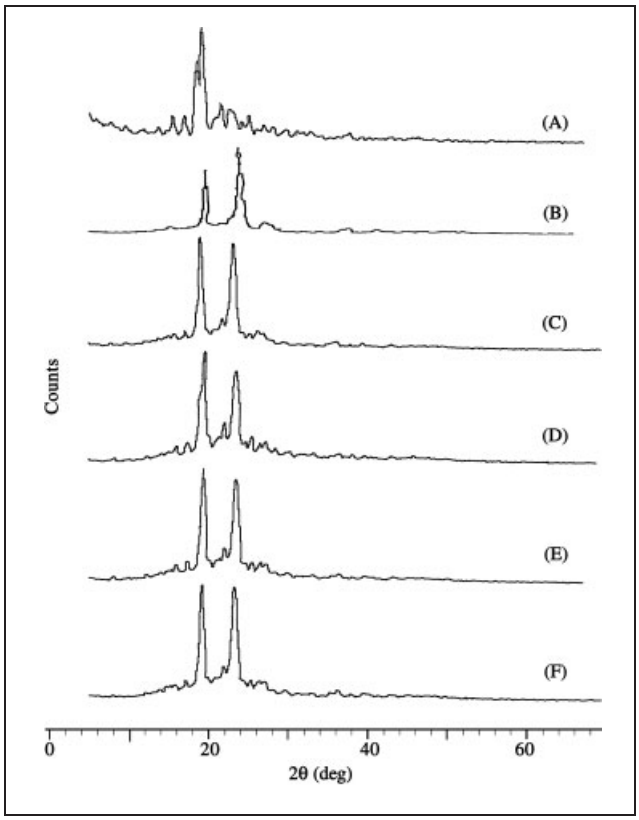


Fig. 2: XRD patterns of ezetimibe-Pluronic® 188 binary systems: (A) ezetimibe; (B) Pluronic® 188; (C) physical mixture; (D) 1 : 1 solid dispersion; (E) 1 : 2 solid dispersion; (F) 1 : 3 solid dispersion

the crystallinity was observed with increase in the polymer concentration (Figs. 2D, 2E and 2F). The relative decrease in crystallinity (RDC) value of physical mixture and all solid dispersions cannot be calculated as all intense peaks of ezetimibe have been completely disappeared. The disappearance of intense peaks of ezetimibe in all solid dispersion suggested loss of the crystallinity and possibility of presence of some amorphous entities of ezetimibe in this system (Ryan 1986).

2.4. Differential scanning calorimetry (DSC)

The DSC thermograms of ezetimibe and solid dispersions with Pluronic® 188 are presented in Fig. 3. The DSC thermograms of ezetimibe alone (Fig. 3A) showed two endothermic T_{max} values of 86.67 and 165.63 °C, corresponding to the melting point of two polymorphs of crystalline form of the drug ezetimibe (Judith et al. 2006). The DSC thermogram of Pluronic® 188 showed a sharp endothermic peak at 62.83 °C indicating the melting point of the polymer. In the DSC thermograms of solid dispersions 1 : 1 and 1 : 3 (Figs. 3D and 3F), the sharp melting point peaks of pure ezetimibe at 86.67 °C and 165.63 °C were invisible. The 1 : 2 solid dispersion showed the melting peak of drug at 83.55 °C which is of one of polymorphs of ezetimibe. This indicated that some crystalline ezetimibe still could be detected in this binary system. The characteristic features of ezetimibe polymorph peaks were lost in 1 : 1 and 1 : 3, and physical mixture demonstrating ezetimibe was molecularly dispersed (Kim et al. 2006) and perhaps no longer present as a crystalline material, but was converted into the amorphous form (Ruan et al. 2005).

The peak of polymer in binary systems; physical mixture, 1 : 1, 1 : 2 and 1 : 3 solid dispersions was found to be shifted to lower value; 58.26 °C, 48.61 °C, 49.39 °C and 45.76 °C respectively which might be because of solid–solid phase transition state occurred during melting of the polymer.

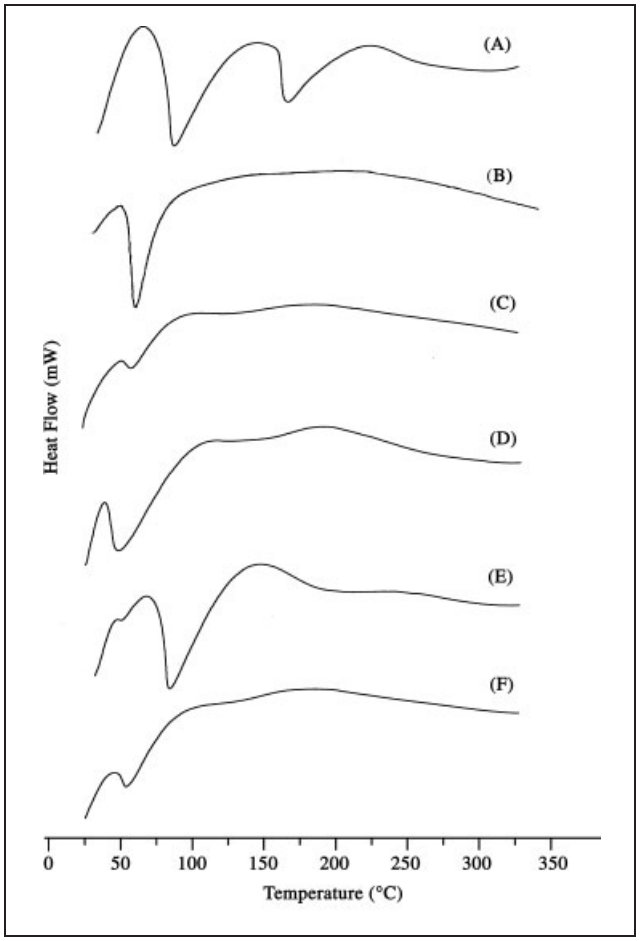


Fig. 3: DSC curves of single component and binary systems of ezetimibe and Pluronic® 188; (A) ezetimibe; (B) Pluronic® 188; (C) physical mixture; (D) 1 : 1 solid dispersion; (E) 1 : 2 solid dispersion; (F) 1 : 3 solid dispersion

2.5. Dissolution rate studies

The dissolution curves of pure ezetimibe and solid dispersions in 0.01 M sodium phosphate (pH 7.0) at 37 ± 0.5 °C are shown in Fig. 4. The release rate profiles were expressed as the percentage of drug released (vs.) time. It is evident that all binary systems have improved the dissolution rate of ezetimibe moderately, except 1 : 3 solid dispersion where the dissolution increment was found to be significant. The Table shows % drug dissolved in 5 min (DP_5), 15 min (DP_{15}), and 90 min (DP_{90}) for ezetimibe and its binary systems with Pluronic® 188. The dissolution efficiency values (DE_{90}) at 90 min have been calculated and compared statistically. The dissolution efficiency (DE) is defined as the area under dissolution curve upto the time t expressed as percentage of the area of rectangle described by 100% dissolution in the same time (Khan 1975).

The binary systems of ezetimibe showed faster dissolution than pure drug alone. The % release of ezetimibe was 46.65 ± 3.7 from physical mixture within 5 min (DP_5) whereas it was 47.85 ± 3.8, 47.94 ± 4.2 and 55.97 ± 4.2 from 1 : 1, 1 : 2 and 1 : 3 solid dispersion systems respectively within 5 min (DP_5). The release of ezetimibe from pure drug was 37.68 ± 3.8 within 5 min. The 1 : 3 solid dispersion system of ezetimibe with Pluronic® 188 significantly improved the dissolution rate of pure drug. Thus the 1 : 3 ratio of ezetimibe : Pluronic® solid dispersion displayed superior performance to its corresponding other ratios in enhancing dissolution rate of pure drug (DE_{90}: 73.38 ± 3.95, $p < 0.001$), indicating almost complete release of drug from solid dispersion (DP_{90}: 99.51 ± 3.9). The dissolution (DP values) increment from 1 : 3 solid dis-

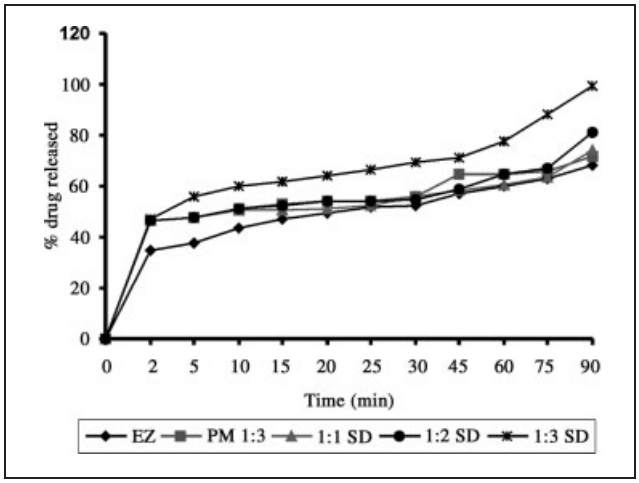


Fig. 4: The dissolution curves of ezetimibe – Pluronic® 188 system at 37 °C ± 0.5 °C.
EZ: ezetimibe; PM: physical mixture; SD: solid dispersion

Table: Dissolution data of pure ezetimibe and its various binary systems with Pluronic® 188 in 0.01 M sodium phosphate (pH 7.0) at 37 ± 0.5 °C

System	DP_5* ± S.D.	DP_{15}* ± S.D.	DP_{90}* ± S.D.	DE_{90}* ± S.D.
Ezetimibe	37.68 ± 3.8	47.11 ± 3.7	68.43 ± 3.7	54.09 ± 3.00
PM (1 : 3)	46.65 ± 3.7	53.04 ± 4.5	72.01 ± 4.2	61.34 ± 6.09
1 : 1 SD	47.85 ± 3.8	50.83 ± 4.5	74.00 ± 4.8	57.56 ± 4.16
1 : 2 SD	47.94 ± 4.2	52.14 ± 3.7	81.41 ± 3.1	59.82 ± 3.84
1 : 3 SD	55.97 ± 4.2	61.68 ± 4.3	99.51 ± 3.9	73.38 ± 3.95†

* Indicates mean of three readings (n = 3); S.D.: Standard deviation; SD: Solid dispersion; DP: % drug dissolved; DE: dissolution efficiency; † indicates p value compared to pure ezetimibe ($p < 0.01$) i.e. significant.

persion was consistent upto 90 min. However, the corresponding lower ratios (1 : 1 and 1 : 2) have improved the dissolution rate of ezetimibe moderately but not significantly. From these results it could be concluded that increase in weight fraction of polymer resulted in more rapid dissolution (Corrigan et al. 1985). Previous studies have reported the dissolution of ezetimibe with β-cyclodextrin and hydroxypropyl-β-cyclodextrin which shows a 50% release of ezetimibe in 34 and 16 min respectively (Patel et al. 2008). In the present investigation, the Pluronic® 188 binary system (1 : 3) released the same amount of drug in 5 min demonstrating its advantage over cyclodextrins. Thus, Pluronic® 188 could be considered as a proper choice for dissolution enhancement of ezetimibe.

The dissolution rate increase for the physical mixture was possibly due to close contact of the drug with hydrophilic polymer, brought about by dry mixing process. This might have increased wettability and dispersibility of drug resulting in increased dissolution of ezetimibe (Mooter et al. 1998).

The rapid dissolution of ezetimibe from solid dispersions may be attributed to decrease in the crystallinity of drug and its molecular and colloidal dispersion in hydrophilic carrier matrix. As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of very fine particles for quick dissolution (Geneidi et al. 1978; Save and Venkitachalam 1992).

The other factors that might have played an important role in enhancing the dissolution rate are greater hydrophilicity and surfactant property of polymer, increased wettability and dispersibility and particle size reduction of drug (Ford 1986). The greater hydrophilicity and surfactant property of Pluronic® 188 result in greater wetting and increases surface available for dissolution by reducing interfacial tension between hydrophobic drug and dissolution media. During dissolution experiments, drug carrier systems sank immediately, whereas pure drug floated on the surface of dissolution medium for a longer period of time.

3. Experimental

3.1. Materials

Ezetimibe was supplied by Ajanta Pharmaceuticals Ltd., Mumbai, India as a gift sample. Lutrol (Pluronic®) 188 was gift sample from Signet Chem Lab, Mumbai, India.All the reagents were of analytical grade. Double distilled water was used throughout the experiment.

3.2. Preparation of physical mixture

Physical mixture was prepared by grinding ezetimibe and hydrophilic polymer in a mortar in the ratio of 1 : 3 (ezetimibe : polymer).

3.3. Preparation of solid dispersions by melting method

Solid dispersions of ezetimibe were prepared by the melting method. Pluronic® was melted at 60 °C. Ezetimibe was added to the molten polymer, which was then mixed well and cooled to room temperature to obtain the solid mass. The solidified masses were crushed, pulverized and passed through sieve number 60. The resulting solid dispersions were stored in desiccators until used for further studies.

3.4. Fourier transformation infrared spectroscopy (FTIR)

Infrared spectra were obtained using a Perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, CT, USA) spectrometer using KBr disks. The samples were previously ground and mixed thoroughly with KBr. The KBr disks were prepared by compressing the powder. The scanning range was kept from 4000 to 450 cm^{-1} and the accumulations were 4.

3.5. X-ray powder diffractometry (XRD)

The XRD patterns of ezetimibe, Pluronic® 188 and solid dispersions were recorded by a Philips Analytic X-Ray – PW 3710 (Philips, Almelo, The Netherlands) diffractometer with tube anode Cu over the interval 5–70°/2θ. The operation data were as follows: generator tension (voltage) 40 kV, generator current 30 mA, and scanning speed 2°/min.

3.6. Differential scanning calorimetry (DSC)

DSC measurements were performed on a TA SDT 2960 DSC differential scanning calorimeter (TA instruments, New Castle, Delaware, USA). The accurately weighed sample was placed in an aluminum pan. An empty aluminum pan was used as reference. The experiment was carried out in nitrogen atmosphere (flow rate 100 ml/min) at scanning rate of 10 °C/min in the range of 0–350 °C.

3.7. Percentage drug content study

Drug content was determined by dissolving solid dispersions equivalent to 5 mg of drug in a small quantity of methanol. The volume was adjusted to 50 ml with methanol. The solution was filtered through Whatman filter paper no. 41, suitably diluted and absorbance was measured at 231 nm using double beam UV spectrophotometer. (Shimadzu 1700, Japan).

3.8. Dissolution studies

The dissolution rate studies of ezetimibe alone, physical mixture and solid dispersions were performed in triplicate in a dissolution apparatus (Lab India, Model Disso 2000 Tablet dissolution test apparatus, Mumbai, India) using the paddle method (USP Type II). Dissolution studies were carried out using 900 ml of 0.01 M sodium phosphate (pH 7.0) at 37 ± 0.5 °C at 50 rpm (U.S. Food and drug administration). 10 mg of ezetimibe or its equivalent amount of solid dispersion was added to 900 ml of 0.01 M sodium phosphate (pH 7.0). Samples of 5 ml were withdrawn at time intervals of 2, 5, 10, 15, 20, 25, 30, 45, 60 and 90 min. The volume of dissolution medium was adjusted to 900 ml by replacing each 5 ml aliquot withdrawn with 5 ml of fresh 0.01 M sodium phosphate (pH 7.0). The solutions were immediately filtered through a 0.45 μm membrane filter, suitably diluted and the concentrations of ezetimibe in samples were determined spectrophotometrically at 231 nm. The results of dissolution studies were statistically validated using ANOVA.

Acknowledgements: The authors are thankful to Shivaji University, Kolhapur, Maharashtra, India for providing FTIR, XRD and DSC facilities. Authors are very much thankful to Principal, Govt. College of Pharmacy, Karad, Maharashtra, India for providing laboratory facilities and constant encouragement.

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