

Formulation and Optimization of Ezetimibe Containing Solid Dispersions Using Kollidon VA64

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The solubility behaviour of drugs remains one of the most challenging aspects in formulation development. Many different methods have been tried over a long period for enhancing the solubility of poorly soluble drugs. Preparing a solid dispersion is one among the methods. Solid dispersions in water-soluble carriers have shown promising results as a means of enhancing the dissolution rate, thus improving bioavailability for most of hydrophobic drugs. The objective of the present study was to enhance the solubility and dissolution rate of a poorly water-soluble drug, ezetimibe. Solid dispersions were prepared by using Kollidon VA64 as carrier with different drug-to-carrier ratios. Dispersions with Kollidon VA64 were prepared by melt extrusion technique. These formulations were characterized for solid state properties by differential scanning calorimetry, X-ray powder diffraction and FTIR spectral studies. Formulations were further evaluated for dissolution and stability studies. The aqueous solubility of ezetimibe, in present formulations was improved by the presence of polymer. Solid-state characterization indicated that ezetimibe was present as amorphous material in formulation with kollidon VA64, due to efficient entrapment in polyer matrix. Ezetimibe in pure form has very slow dissolution rate, when compared with dispersions.

Key words: Ezetimibe, Kollidon VA64, Solid dispersions, Melt extrusion technique.

Ezetimib İçeren Katı Dispersiyonların Kollidon VA64 Kullanarak Formülasyonu ve Optimizasyonu

Etken maddenin çözünürlük özellikleri formülasyon geliştirmede en ilgi çekici konulardan biri olmaya devam etmektedir. Uzun zamandır, düşük çözünürlüklü maddelerin çözünürlüklerini artırmak için pek çok değişik metod denenmiştir. Katı dispersiyon hazırlanması bu metotlardan biridir. Suda çözünür taşıyıcılar içindeki katı dispersiyonlar artan çözünme hızı ile ve böylece de pek çok hidrofobik etken maddenin biyoyararlanımının iyileştirilmesiyle umut verici sonuçlar göstermiştir. Bu çalışmanın amacı, suda çözünürlüğü az olan ezetimibin çözünme hızı ve çözünürlüğünü artırmaktır. Katı dispersiyonlar taşıyıcı olarak Kollidon VA64'ün değişik etken madde-taşıyıcı oranları kullanılarak hazırlandı. Dispersiyonlar, melt ekstrüzyon tekniği ile hazırlandı. Bu formülasyonlar katı durum için diferansiyel taraöalı kalorimetre, X-ray toz difraksiyon ve FTIR spectral çalışmalarla karakterize edildi. Formülasyonlarda polimer varlığında ezetimib'in sudaki çözünürlüğü artırıldı. Katı durum karakterizasyonu, ezetimib'in Kollidon VA64 ile hazırlanan formülasyonlarda etkin şekilde polimer matrisin içine hapsoldüğü için amorf olduğunu gösterdi. Saf haldeki ezetimibin dispersiyonlarla karşılaştırıldığında çok düşük çözünme hızına sahipti.

Anahtar kelimeler: Ezetimib, Kollidon VA64, Katı dispersiyonlar, Melt ekstrüzyon tekniği

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INTRODUCTION

Aqueous solubility of the therapeutically active substance is a key property which governs dissolution, absorption and *in vivo* efficiency (1). To enhance the solubility of those drugs scientists over the world are inventing various approaches. Formulation approaches such as micronization, modification of crystal habits, complexation, using surfactants and cosolvents, solid dispersions, etc have been extensively studied. Chemical modifications such as prodrugs, salt formation, and polar group incorporation were also studied. A well established method to improve the solubility and bioavailability of poorly soluble drugs is solid dispersion technology (2-6). Solid dispersion refers to the dispersion of one or more active ingredients in an inert carrier matrix at solid state prepared by melting (fusion), solvent evaporation, solvent wetting, super critical fluid technology, lyophilization, melt extrusion etc. (7-10) Drugs in solid dispersion can exist in an amorphous form in polymeric carriers. Such a system improves the solubility and dissolution of a drug compared to the crystalline material (11).

Many of the said approaches were proved to be beneficial and produced good results but in few cases it lack commerciality because of various problems. The hot melt extrusion technology (HME) is the newer technology with an aim to produce solid dispersions with lower cost and is commercially feasible (12-14). HME involves passing the physical mixture of the drug-polymer blend through a series of heat zones through screw extruder. The screw consists of different regions for movement, mixing, kneading of the blend. This process softens the mass and help in efficient mixing of the drug and polymers giving a uniform dispersion of drug in the polymer. The screw extruder provides high shear stress and intense mixing and can therefore handle high drug loads thus proving advantageous in pharmaceutical industry.

In this study, solid dispersions of ezetimibe were prepared by melt extrusion method using

Kollidon VA64 as carrier. This method is suitable for thermostable drugs and for the polymers that possess high melting points. Since povidones are hygroscopic, it proves that these classes of carriers are highly hydrophilic, hence suitable for preparation of solid dispersions of crystalline drugs. PVPs possess hydrophilicity which improves wettability. These carriers have good solubility in a wide range of organic solvents (15-16). Solid dispersions bear most common disadvantage like instability of solid dispersion. This is because the drug tends to convert amorphous form of solid dispersion into crystalline form which leads to poor solubility and stability. The stability of the drug can be maintained by impregnating drug into the polymeric matrix. As Kollidon VA 64 aides in stabilizing the active ingredient in amorphous form, solubility is improved. Kollidon VA64 is vinylpyrrolidone – vinyl acetate copolymer soluble in water and alcohol. The main applications of Kollidon VA64 are soluble binder for granulation and as dry-binder in direct compression technology, as a film-forming agent in sprays and as pore-former in coating and taste-masking applications, as well as solubilizer in Hot Melt Extrusion processes.

Ezetimibe is a BCS class II drug. It is an anti hyperlipidemic drug and it helps in lowering the cholesterol (17-18). The melting point of ezetimibe is 164 -166 °C. It actually localizes at the brush borders of the villi in the small intestine region and prevent absorption of the cholesterol from the intestine. It binds to a carrier of cholesterol absorption, the Niemann-Pick C1-Like 1 (NPC1L1) protein on the gastrointestinal tract epithelial cells and in hepatocytes thus decreasing the LDL in the body leading to prevention of various life threatening diseases.

MATERIALS AND METHODS

Ezetimibe and Kollidon VA 64 were obtained as gift samples from Mylan Laboratories Ltd,

Hyderabad. All other chemicals and reagents used were of analytical reagent grade.

Preparation of solid dispersion

The solid dispersions of ezetimibe were prepared by hot melt extrusion technique using Kollidon VA64 as carrier. The compositions of various solid dispersions were given in Table 1.

screw feeder. The obtained mass is milled by using Quadra-co mill and passed through sieve # 120 to obtain finely divided solid dispersions. The prepared solid dispersions were subjected to drug content determination, solubility studies, and drug carrier interaction studies by DSC, XRD and IR spectral studies, dissolution and

Table 1. Compositions of various ezetimibe solid dispersions

Formulation code	Carrier	Ratios	Quantity (g)
SD1	Drug: Kollidon VA 64	1:2	10:20
SD2	Drug : Kollidon VA 64	1:3	10: 30
SD3	Drug: Kollidon VA 64	1:4	10: 40

The ezetimibe and Kollidon VA64 were weighed accurately in different ratios and passed through sieve #40 and blended in double cone blender for 10 minutes. These blends are then processed in the hot melt extruder instrument (Leistritz Hot Melt Extruder, Model – Nano 16). The temperatures of the heating zones are adjusted in such a manner that the drug and the polymer mix well and melt well to give a uniform solid dispersion. The melting point of the ezetimibe (164-170 °C) and Kollidon VA 64 (melting point 100-110 °C) were taken into consideration while setting the temperatures of the heating zones. Temperatures of 110-125-135-150 °C ($\pm 5-10$ °C) across the four heating zones and an rpm of 50 to 200 were maintained. Screw speed and temperature are most relevant process parameters in the extrusion. On increasing the screw speed and the residences time of material decreases and machine torque increases which are desirable parameters in extrusion. The extrusion parameters were given in Table 2. An rpm of 100 was found to be producing uniform and efficient solid dispersions. The screw rpm was given in Table 3. The torque was maintained by regulating the feed rate of the blend into the

stability studies.

Evaluation of solid dispersions

Solid dispersions prepared by hot melt extrusion technique were evaluated for particle size and flow properties. Particle size was determined by sieve analysis and flow properties of solid dispersions were determined by angle of repose and Carr's index.

Solubility studies

These studies were performed by taking the ezetimibe pure drug and ezetimibe solid dispersion theoretically equivalent to 10 mg of ezetimibe and added to 10 mL each of distilled water and buffer solutions. The pKa value of ezetimibe is 9.6. The samples were then subjected to incubated shaking at 100 rpm for 24 hrs at 36°C. The resultant solutions were collected and filtered through 0.45 μ membrane filters and analyzed spectrophotometrically at 232 nm after suitable dilutions. The studies were conducted in triplicate. The solubility of various dispersions was given in Table 4.

Characterization of Ezetimibe Solid Dispersions *Differential scanning calorimetry (DSC)*

Differential Scanning Calorimetry measurements were performed on ezetimibe, Kollidon VA64 and solid dispersion formulations using differential scanning calorimeter (METTLER TOLEDO with eSTAR software). The samples were placed in a sealed aluminium crucible and evaluated with a heating rate of 20 °C/min at a temperature range of 25-250 °C. The thermograms were

recorded and were shown in the Figure 1 and Figure 4.

X-Ray powder diffraction (XRD)

The powder crystallinity of the ezetimibe and the ezetimibe solid dispersions were determined using Bruker D8 Advance XRD with copper target instrument. The conditions were maintained at 40 Kv voltages, with 40 MA

Table 2. Table for extrusion parameters for preparing solid dispersions.

Sr. No	Formulation	Temperature in different zones				Extrudate temperature	Screw rpm
		1	2	3	4		
1	SD1	110	125	135	150	155	100
2	SD2	110	125	135	150	155	100
3	SD3	110	125	135	150	155	100

Table 3. Optimization of screw rpm for efficient mixing.

S.No	Temperature in different zones (°C)				Extrudate temp. (°C)	Screw rpm	Remarks
	1	2	3	4			
1	110	125	135	150	155	50	Glassy material
2	110	125	135	150	155	100	Glassy material
3	110	125	135	150	155	150	Translucent material
4	110	125	135	150	155	200	Opaque material

Table 4. Solubility studies of ezetimibe formulations (solubility in µg/mL)

pH	Pure Drug	SD1	SD2	SD3
1.2	3.35 ± 0.11	23.11±0.11	33.96±0.14	54.48±0.17
4.5	5.43±0.12	25.31±0.13	35.07±0.12	57.72±0.11
6.8	4.32±0.11	23.09±0.12	31.84±0.18	54.26±0.15
7.4	4.29±0.13	22.83±0.18	33.54±0.17	53.93±0.14
Water	2.26±0.09	22.62±0.11	30.68±0.17	50.97±0.15

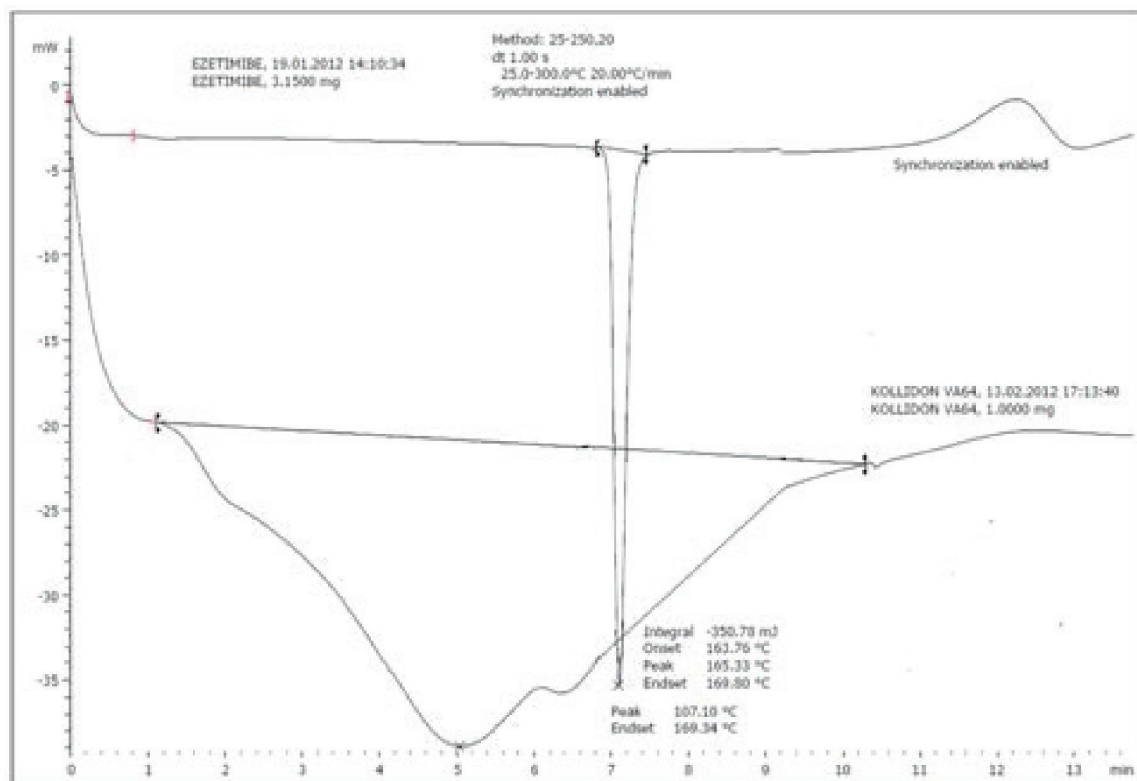


Figure 1. DSC thermogram of ezetimibe pure drug and Kollidon VA64

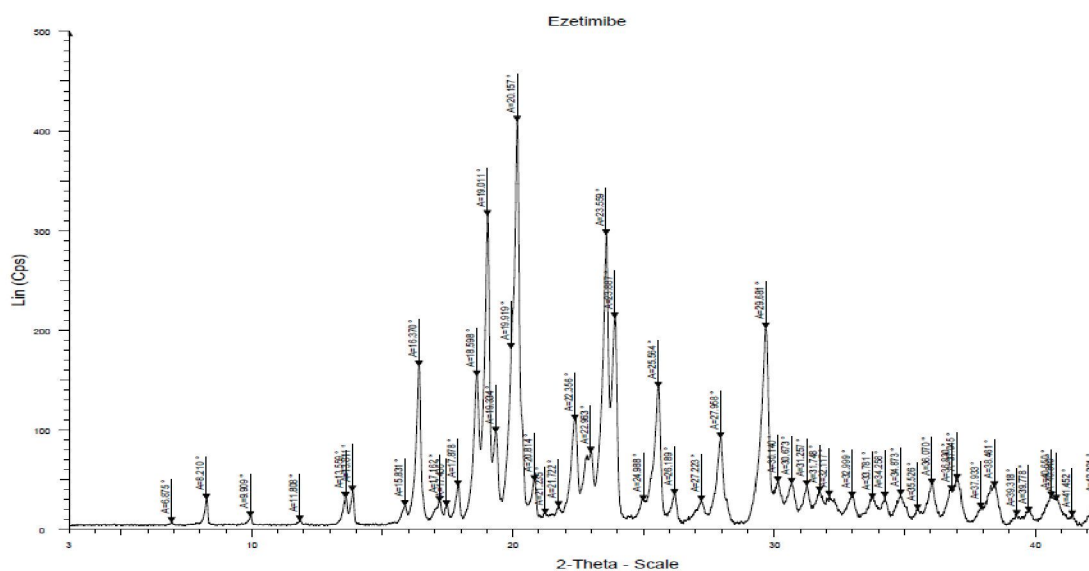


Figure 2. Powder X-Ray diffraction study of ezetimibe.

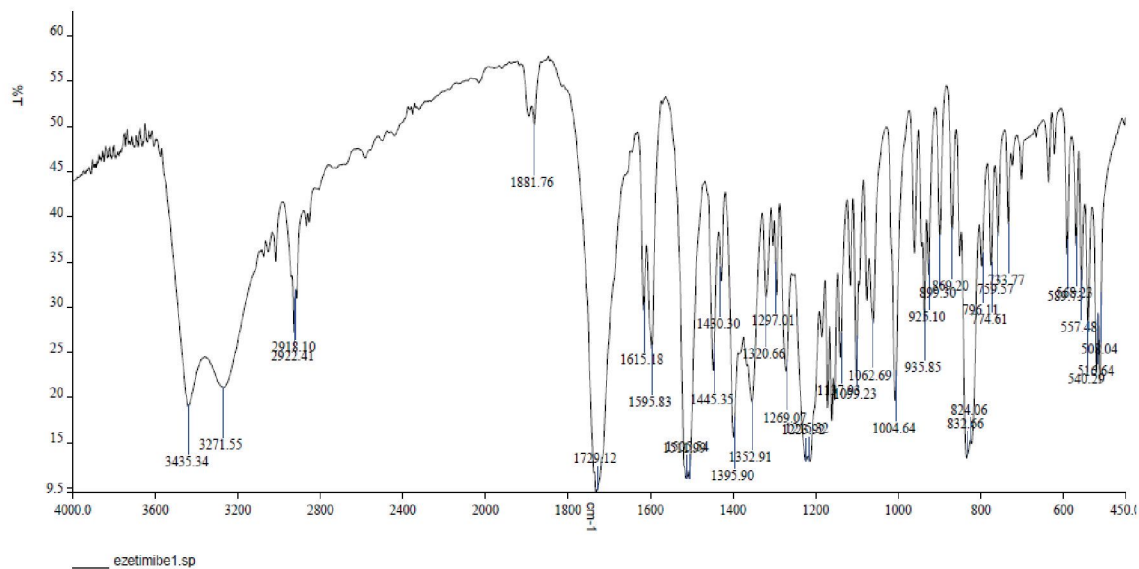


Figure 3. FTIR Spectra of the ezetimibe pure drug

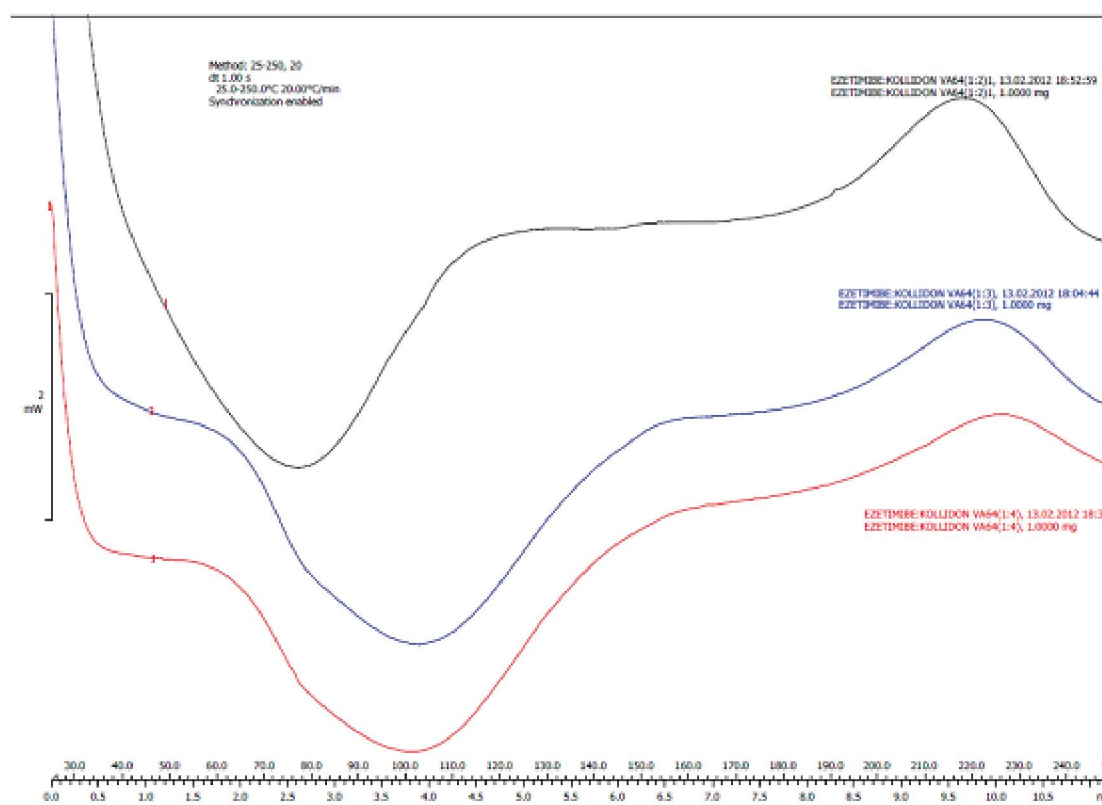


Figure 4. DSC thermograms of SD1, SD2, SD3 formulations.

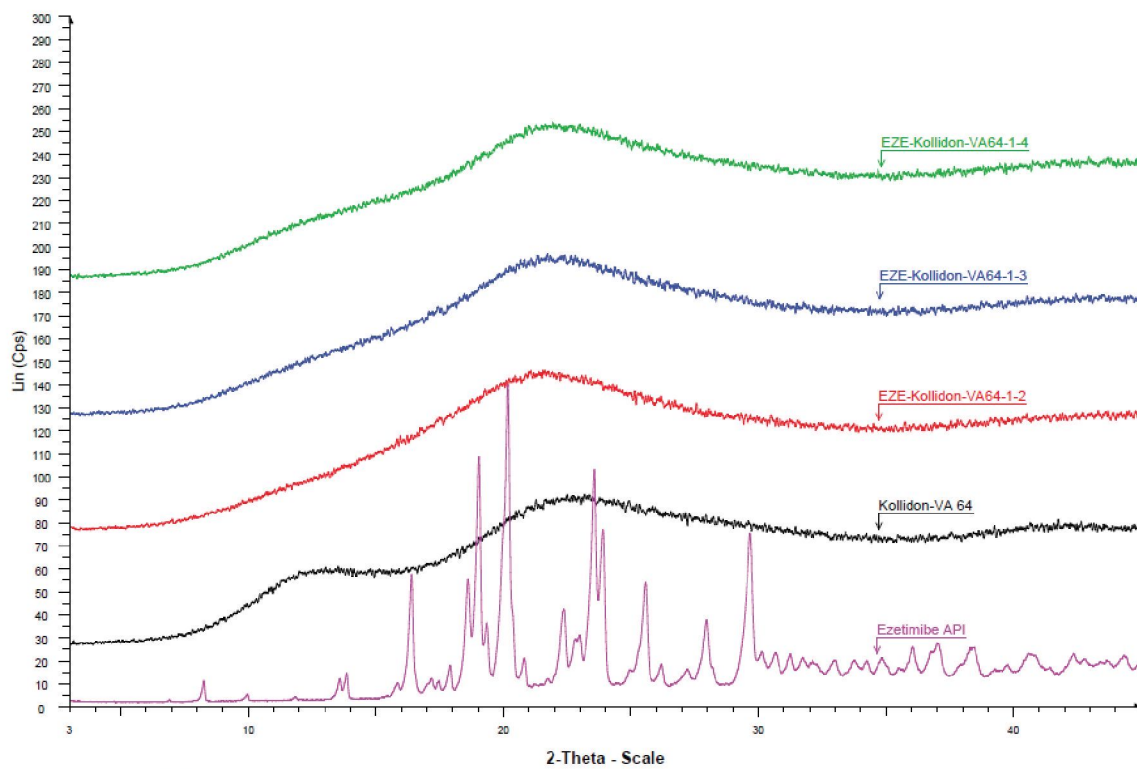


Figure 5. PXR D data of ezetimibe drug and solid dispersions.

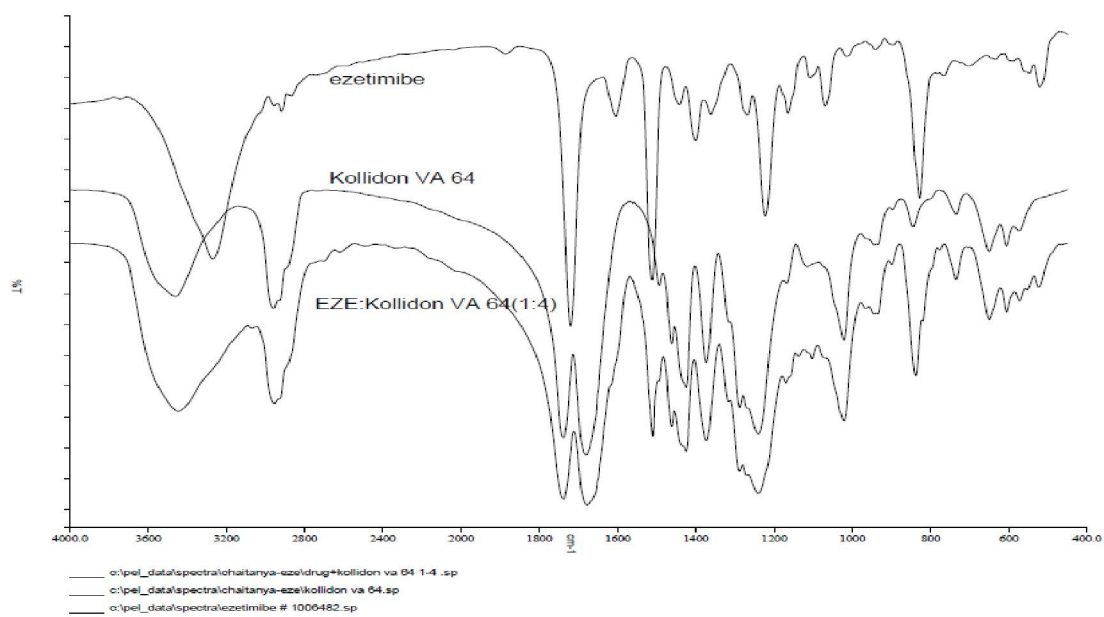


Figure 6. FTIR spectra of ezetimibe pure drug, Kollidon VA64 and solid dispersion (SD3).

current at room temperature. The scanning rate employed was 0.1° /sec over a range of 2θ values from 3° to 45° . The diffractograms were shown as Figure 2 and Figure 5.

Fourier transform infrared spectroscopy (FTIR)

The FTIR spectra of ezetimibe, Kollidon VA64 and solid dispersion formulations were obtained by using Bruker FTIR spectrophotometer to study the interaction between drug and carrier in solid dispersions.

The samples were prepared in KBr discs (2mg sample in 200mg KBr) and the sampling range was $400 - 4000\text{ cm}^{-1}$ and the resolution was 4cm^{-1} . The FTIR spectra were shown in Figure 3 and Figure 6.

Drug content

Solid dispersions theoretically equivalent to 10 mg of drug were taken and dissolved in methanol and filtered using $0.45\ \mu$ membrane filters. Then the filtrate was suitably diluted with buffer and drug content was analyzed against blank by UV spectrophotometer at 232 nm. The concentration of drug present in solid dispersion is compared with that of standard solution containing 10 mg of pure drug. The percentage of drug present in the solid dispersions was calculated with respect to standard concentration and the values were given in the Table 5.

Table 5. Drug content of ezetimibe in various solid dispersions

Drug/ solid dispersions	% drug content
SD1	99.62
SD2	99.76
SD3	99.73

In vitro dissolution studies

Dissolution rate studies of pure ezetimibe and ezetimibe solid dispersions were performed in

ELECTROLAB 8 stage dissolution test apparatus with rotating paddles at 50 rpm employing 500ml of pH 4.5, 0.05M acetate buffer (19) and the temperature was maintained at $37 \pm 0.5^{\circ}\text{C}$ throughout the experiment. 5 ml of the samples were withdrawn at various time intervals. The absorbance of the samples was measured at 232 nm for determining the amount of drug release at various intervals. Each time the equal volume of buffer was added for maintaining the constant volume of dissolution medium. The dissolution studies were carried out in triplicate. Based upon the data obtained from the dissolution studies the *in vitro* kinetic modeling parameters such as T 50, zero order and first order rate constants for solid dispersions were determined. The dissolution parameters were given in Table 6.

Stability studies

Among the prepared solid dispersions the formulation SD3 was further subjected to accelerated stability studies up to six months at 40°C with 75% RH. The formulation SD3 was selected for the stability studies based on the *in vitro* dissolution profile. The samples were withdrawn after one month and analyzed by PXRD and FTIR.

RESULTS AND DISCUSSION

In the present investigation an attempt was made to improve the solubility and dissolution rate of Ezetimibe. Ezetimibe solid dispersions were prepared by melt extrusion method using hot melt extruder with Kollidon VA64 as carrier. All the dispersions were prepared under similar conditions to avoid batch to batch variation. The dispersions were found to be uniform in their characteristics. All the solid dispersions were in the size range of $172 \pm 3 - 179 \pm 2\ \mu\text{m}$. The angle of repose values and the Carr's index values of all the solid dispersions were in the range of $13.2 - 38.2^{\circ}$ and $9.4 - 15.1\%$ respectively. All the solid dispersions prepared by this method were found to be stable with good flow characteristics.

Table 6. Dissolution parameters of ezetimibe solid dispersions in buffer solution

S.No	SD	% Drug released at 90 min	T ₅₀ (min)	Zero Order Rate constant K	R ² (Zero order curve)	First Order Rate Constant K (min ⁻¹)	R ² (First order curve)
1	PD	23.82	>50	0.184	0.8422	0.011	0.8444
2	SD1	91.63	19	1.006	0.8114	0.017	0.9914
3	SD2	95.32	14	0.766	0.8822	0.012	0.9899
4	SD3	98.56	10	0.864	0.8152	0.012	0.9753

Solubility measurement

Initially saturated solubility studies were performed for the Ezetimibe pure drug and also for the solid dispersions by using different buffer media. The solubility studies indicated that, the acetate buffer having pH 4.5 was found to be ideal dissolution media. The pure drug ezetimibe and its respective solid dispersions have exhibited very high solubility in pH 4.5 acetate buffer than the other buffer media. The drug content in various solid dispersions prepared was estimated spectrophotometrically by measuring the absorbance at 232 nm. All the solid dispersions were found to have excellent entrapment of drug in the carrier. The ezetimibe drug content in all the dispersions were found to be in the range of 99.6 to 99.76 %.

Characterization of solid dispersions.

The physical state of ezetimibe in the solid dispersions was characterized by DSC, XRD and FTIR spectral studies. The DSC thermograms of ezetimibe alone showed endothermic peak at 164-170 °C, corresponding to its melting point. The DSC thermogram of Kollidon VA64 have shown endothermic peak at 107 °C. No sharp endothermic peak of Ezetimibe was observed in solid dispersions prepared with Kollidon VA64 indicating that Ezetimibe was efficiently dispersed at molecular level. However, the peak of Kollidon VA64 in those solid dispersions were found to be shifted to lower values, indicated the solid-solid phase transition. This was further

supported by XRD. The DSC thermograms of ezetimibe and other solid dispersions were given as Figures 1 and 4.

The XRD patterns of ezetimibe, Kollidon VA64 and solid dispersions were shown in Figure 2 and 5. The powder diffraction patterns of pure ezetimibe showed characteristic high diffraction peaks. The diffraction patterns of Kollidon VA64 showed only few peaks with very weak intensities indicating the amorphous nature. On the other hand the XRD patterns of the solid dispersions showed decreased intensity of the peaks indicating amorphous nature of the drug in solid dispersions and are considered to be the reason for the dissolution and solubility enhancement.

In order to investigate the possible interaction of the drug with carrier FTIR analysis was performed. Figure 6 shows the FTIR spectra of pure ezetimibe, Kollidon VA64 and ezetimibe solid dispersion (SD3). FTIR spectra of ezetimibe shows strong absorption peaks at 3,500cm⁻¹ and 2,920 cm⁻¹ indicating presence of phenolic aryl amino group and alkane group respectively while, peaks at 1720 cm⁻¹, 1600 cm⁻¹, 1500 cm⁻¹ may be assigned to Carbonyl, amino group and 1-4 substituted aromatic group. A very broad band was observed at 3500 cm⁻¹ that in solid dispersion which was due to the presence of water confirming the broad endotherm observed in DSC studies (20). Along with the broad peaks from Kollidon VA64 at 3500 cm⁻¹ and 2900 cm⁻¹ the FTIR spectra of solid dispersion

still showed the peaks at same position of the drug. Hence the FTIR spectrum of the solid dispersion is seemed to be only a summation of drug and Kollidon VA64. This indicates that there was no major interactions between the functional moieties of drug molecule with the excipients incorporated in the formulation of solid dispersions.

of drug release from all the solid dispersions follows first order. Solid dispersions prepared by melt extrusion method were found to be suitable in increasing the dissolution rate of poorly soluble drug ezetimibe. The rapid dissolution of Ezetimibe from solid dispersions may be attributed to decrease in crystallinity of

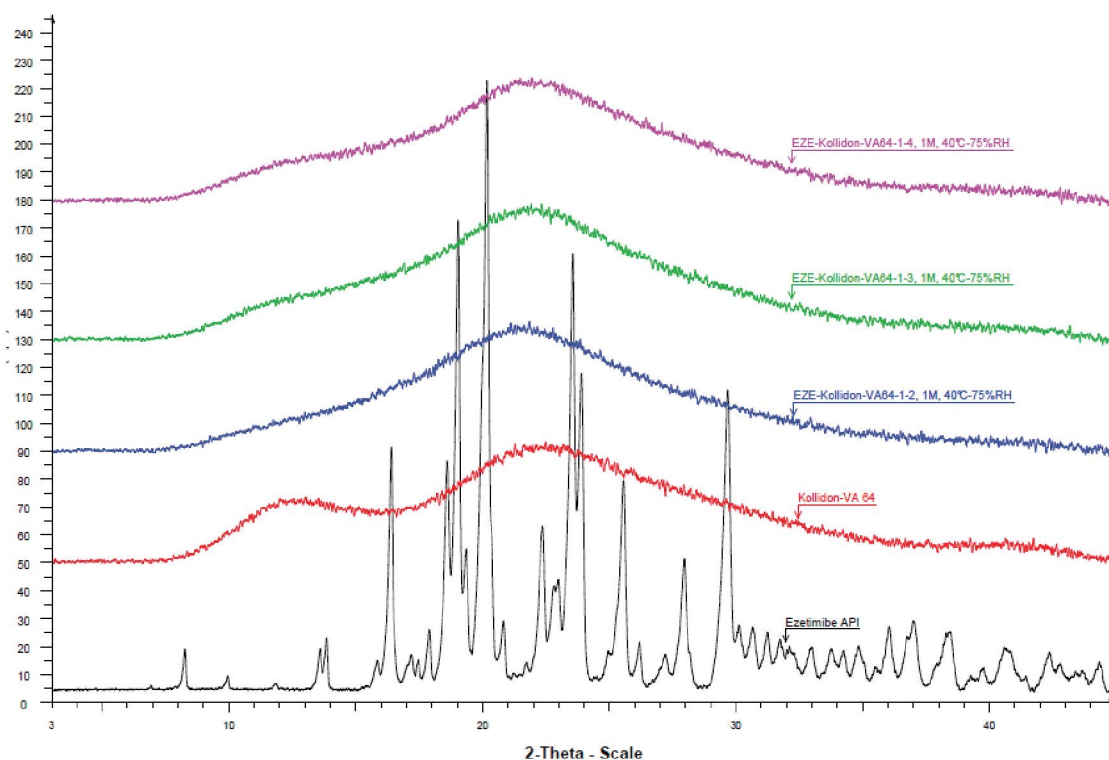


Figure 7. PXRD Stability data of the solid dispersions and ezetimibe pure drug

Dissolution studies

The dissolution studies of Ezetimibe as pure drug and its solid dispersions were performed in pH 4.5 acetate buffer by using paddle method. The dissolution studies were carried out in triplicate. The dissolution rate of all the solid dispersions was found to be rapid when compared to pure ezetimibe (Figure 9). The T50, T90 and rate constants (K) values of the dispersions indicated their rapid drug dissolution than that of pure drug. The kinetics

of drug and its molecular and colloidal dispersions in hydrophilic carrier. As soluble carrier dissolves, the insoluble drug gets exposed to dissolution medium in the form of fine particles for quick and faster dissolution. It was found that solid dispersions containing Kollidon VA 64 in the ratios of 1:4 prepared by melt extrusion method has shown faster dissolution rates than other dispersions.

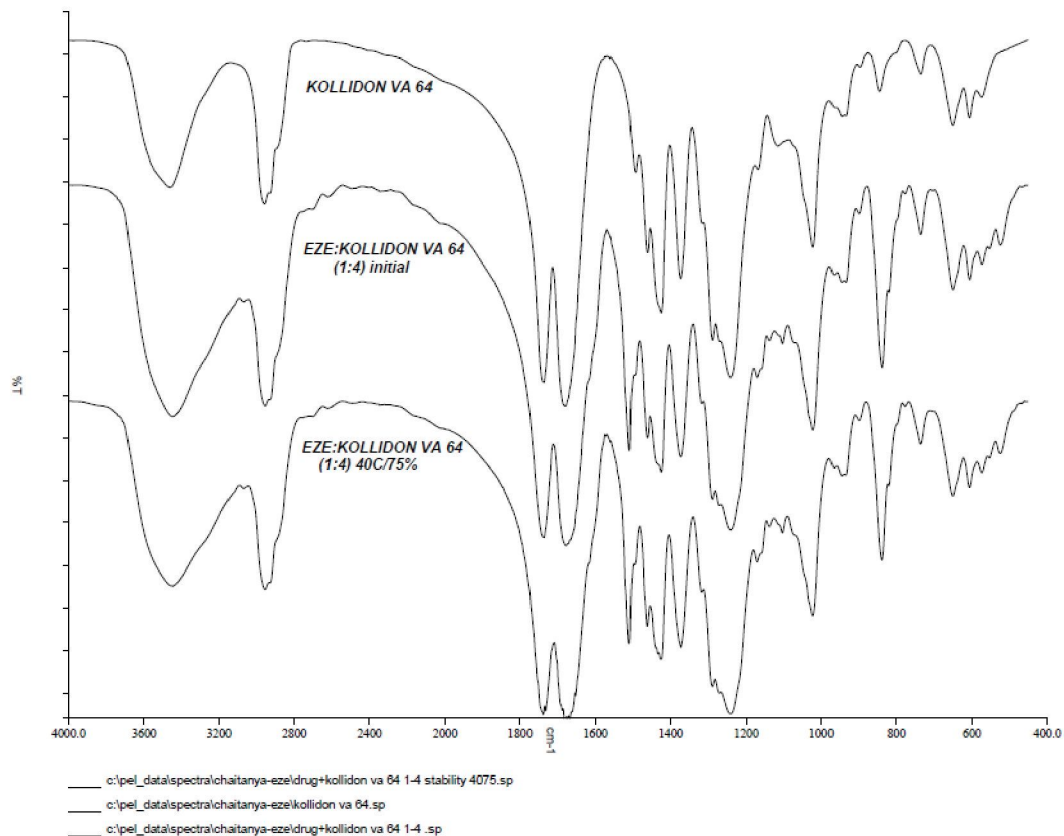


Figure 8. FTIR Stability data of the solid dispersions SD3 and Kollidon VA64.

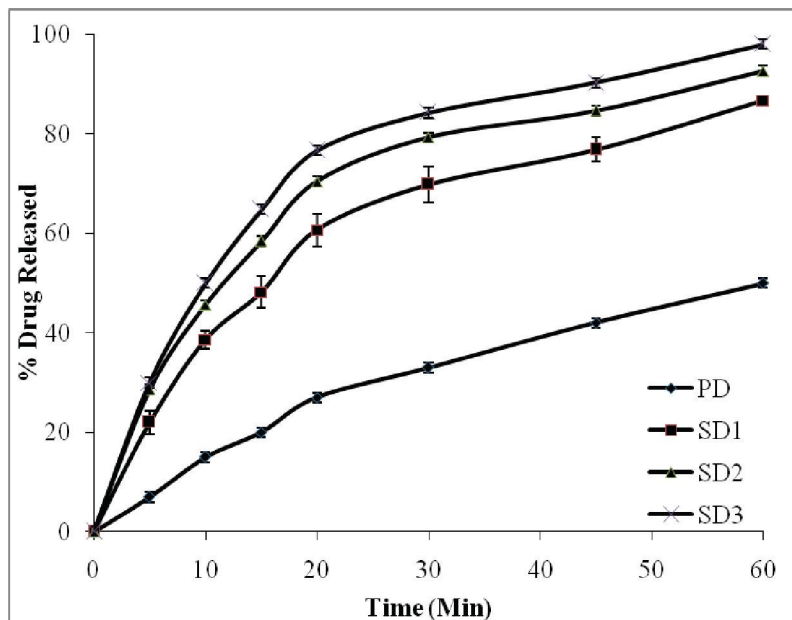


Figure 9. In vitro dissolution profiles of SD1, SD2 and SD3 & pure ezetimibe.

Stability studies

The solid dispersions were further evaluated for accelerated stability studies at 40 °C/75% RH for a period of 6 months. The solid dispersions were stored in HDPE containers throughout the study. Ezetimibe found to be present in amorphous form in all the three formulations which was observed in PXRD diffractograms (Figure 7) and FTIR (Figure 8) recorded after 6 months. It was observed that povidones with high molecular weight exhibit high viscosity which decreases the molecular mobility hence prevents recrystallization.

CONCLUSION

The present research showed the suitability of Kollidon VA64 as a carrier for the preparation of ezetimibe solid dispersions by hot melt extrusion process. The release characteristics of poorly water soluble drug, ezetimibe from solid dispersion containing Kollidon VA 64 k was found to give rapid dissolution profiles than their respective counterpart. Based on the above results solid dispersions prepared by hot melt extrusion process were found to be ideal for improving the dissolution rate and bioavailability of poorly soluble drug ezetimibe.

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