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Studies in Dissolution Enhancement of Ezetimibe by Solid Dispersions in Combination with a Surface Adsorbent

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ABSTRACT

The aim of this investigation was to improve the dissolution properties of the water-insoluble drug ezetimibe (EZE) and potentially improve bioavailability. A combination of melt and adsorption techniques was employed for the preparation of solid dispersions. PEG 4000, PEG 6000, and Gelucire 44/14 were used as hydrophilic carriers, and lactose monohydrate was used as an adsorbent. Phase solubility curves are of A_L type, indicating a linear relationship between drug solubility and carrier concentration. Dissolution studies reveal an improvement of in vitro drug release. Mathematical modeling indicates that drug release data are best described by the Korsmeyer–Peppas model, with Fickian diffusion as the possible drug-release mechanism. Physicochemical characterization of solid dispersions by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD) suggests a reduction in drug crystallinity following dissolution enhancement. Hence, the present investigation reveals that the dissolution characteristics of EZE could be ameliorated in a solid dispersion.

INTRODUCTION

Out of several methods employed to enhance the dissolution characteristics of poorly water-soluble drugs, solid dispersion techniques have been widely reported by various researchers with encouraging results for different drugs. However, a solid dispersion system is somewhat limited by poor flow properties and poor stability. The processing variables of solid dispersions can be improved by the addition of adsorbent in the solid dispersion melt, thereby increasing the effective surface area of the drug leading to improved dissolution (*1*, *2*).

Various carriers have been used to prepare solid dispersion systems; among those, polyethylene glycols (PEG) and Gelucire 44/14 are employed in the present investigation. PEGs are used because of their low toxicity, high water solubility, low cost, and availability in a wide range of molecular weights. Gelucire 44/14 is a mixture of glycerol and PEG 1500 esters of long-chain fatty acids. The suffixes 44 and 14 refer to its melting point and its hydrophilic/lipophilic balance (HLB), respectively. PEG 4000, PEG 6000, and Gelucire 44/14 have been used successfully to improve the dissolution properties of poorly water-soluble drugs by preparing solid-dispersion systems (*3*–*5*). However, the solid dispersions prepared with these carriers are sticky and difficult to handle. Hence, they must be used in amalgamation with an adsorbent to improve their flow properties.

Ezetimibe (EZE), 1-(4–fluorophenyl) –3(R)-[3-(4–fluorophenyl) –3(S) hydroxy-propyl]-4(S)-(4-hydroxyphenyl)-2-azetidinone, is the first lipid-lowering drug that inhibits the intestinal uptake of cholesterol without affecting the absorption of fat-soluble nutrients. It is indicated as a monotherapy or in combination with statins for the treatment of hypercholesterolemia (*6*). EZE, being practically insoluble in water, exhibits a low dissolution profile in gastrointestinal fluids with variable bioavailability. Thus, researchers have investigated different approaches to ameliorate the dissolution characteristics of EZE (*7*–*9*) and optimize bioavailability with a less variable pharmacokinetic profile.

In the present investigation, an attempt was made to improve the dissolution properties of EZE by preparing free-flowing solid dispersions. A combination of solid dispersion and adsorption techniques was employed for the preparation of the solid systems, using lactose monohydrate as adsorbent. The prepared solid dispersions were characterized by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and powder X-ray diffraction (PXRD).

MATERIALS AND METHODS

Materials

EZE was kindly gifted by Mepro Pharmaceuticals Ltd. (Surendranagar, India). Gelucire 44/14 was a generous gift sample from Gattefosse Pvt. Ltd. (Mumbai, India). PEG 4000 and PEG 6000 were purchased from Sisco Research Lab Pvt. Ltd. (Mumbai, India). All reagents were of analytical grade. Double-distilled water was used throughout the work.

Methods

Phase Solubility

Phase solubility studies were carried out as described by Higuchi and Connors (*10*). A quantity of EZE (about 10 mg) that exceeded its solubility was added to flasks containing 25 mL of solutions of different polymer

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concentrations in 0.05 M acetate buffer, pH 4.5. The suspensions were shaken in an environmental shaker (Tempo Instruments and Equipments Pvt. Ltd., Mumbai, India) at 37 °C for 24 h. The samples were filtered with Whatman filter paper (0.12 µm) and analyzed spectrophotometrically (UV-1700 Shimadzu, Japan) for dissolved drug at 232 nm. The apparent 1:1 stability constant was calculated from the phase solubility graph using

$$K_s = \frac{Slope}{S_o\,(1 - slope)}$$

where S_o is the solubility of EZE in the absence of polymer. Values of Gibb's free energy of transfer ($\Delta G°_{tr}$) of EZE from pure buffer media to polymer solution was calculated using

$$\Delta G°_{tr} = -2.303RT \log\left(\frac{S_o}{S_s}\right)$$

where S_o/S_s is the ratio of the solubility of EZE in buffer solution of polymer to that of the pure buffer media.

Preparation of Solid Dispersions and Physical Mixtures

Solid dispersions of EZE were prepared in 1:1, 1:2, and 1:3 (drug/carrier) ratios by a melt method. Each carrier was melted in a Petri dish on the water bath; drug was then dispersed in the molten carrier mass and cooled at room temperature. Lactose monohydrate was added to the molten mass during cooling. With the PEGs, lactose was added in a concentration of 50% of the carrier, and with Gelucire, it was added until the prepared solid dispersion was free flowing. This quantity was measured, and the ratio was about 1:10 carrier/lactose. The prepared solid dispersion were collected, sieved, and stored in desiccators until subsequent analysis. Physical mixtures of EZE with the carriers were prepared by blending the individual constituents. For ease of discussion, preparations are designated by abbreviations as shown in Table 1.

Determination of Drug Content

Drug content was determined by dissolving accurately weighed quantities of ternary systems of drug, carrier, and adsorbent in methanol. The solutions were filtered and diluted appropriately; samples were measured spectrophotometrically at 232 nm.

In Vitro Release Studies

In vitro release studies of EZE, solid dispersions, and physical mixtures were carried out in USP Apparatus 2 (Electrolab Dissolution Tester TDT-06P) at 50 rpm in 500 mL of 0.45% (w/v) SLS in 0.05 M acetate buffer (pH 4.5) at 37 °C (*11*). Dissolution studies were carried out with 10 mg of pure drug and an equivalent amount of preparations. Aliquots of 5 mL were withdrawn at specified time intervals of 5, 10, 20, 30, 40, 50, and 60 min and replaced with fresh media. The samples were filtered with Whatman filter paper (0.12 µm) and analyzed spectrophotometrically at 232 nm for the dissolved drug. The dissolution studies were carried out in triplicate.

Table 1. Designations for Drug–Carrier Preparations

Carrier	Ratio	Preparation Type	Code
PEG 4000	1:1	Solid Dispersion	F11
	1:2	Solid Dispersion	F12
	1:3	Solid Dispersion	F13
	1:3	Physical Mixture	PMF13
PEG 6000	1:1	Solid Dispersion	S11
	1:2	Solid Dispersion	S12
	1:3	Solid Dispersion	S13
	1:3	Physical Mixture	PMS13
Gelucire 44/14	1:1	Solid Dispersion	G11
	1:2	Solid Dispersion	G12
	1:3	Solid Dispersion	G13
	1:3	Physical Mixture	PMG13

Analysis of Drug Release

Dissolution profiles were compared using three parameters: DP_{10min} (percent drug released in 10 min), $\%DE_{20min}$ (percent dissolution efficiency at 20 min), and t_{50} (time required for 50% drug release). One-way analysis of variance (ANOVA) was applied to assess the differences in the results obtained. In vitro release data were fitted to various kinetic models (*12*, *13*) including zero-order, first-order, Higuchi, Korsmeyer–Peppas, and Hixson–Crowell cube-root model by employing regression analysis techniques to determine the probable drug–release mechanism.

Characterization Studies

Fourier Transform Infrared Spectroscopy

Fourier transform infrared (FTIR) spectroscopy was carried out to identify the possible interactions between the drug and hydrophilic carriers in prepared solid systems. Samples of EZE, carriers, and their preparations were characterized by FTIR spectroscopy (Shimadzu 8400, Japan) using the potassium bromide (KBr) pellet method. The scanning range was 4000–400 cm^{-1} at a resolution of 1 cm^{-1}. An average of 20 scans was taken.

Differential Scanning Calorimetry

Differential scanning calorimetry (DSC) of pure EZE, carriers, and all preparations was done using a Shimadzu DSC 60 TSW 60 (Japan). Accurately weighed samples were crimped in aluminum pans and heated from 30 to 250 °C at a heating rate of 10 °C/min in air atmosphere. An empty sealed aluminum pan was used as reference.

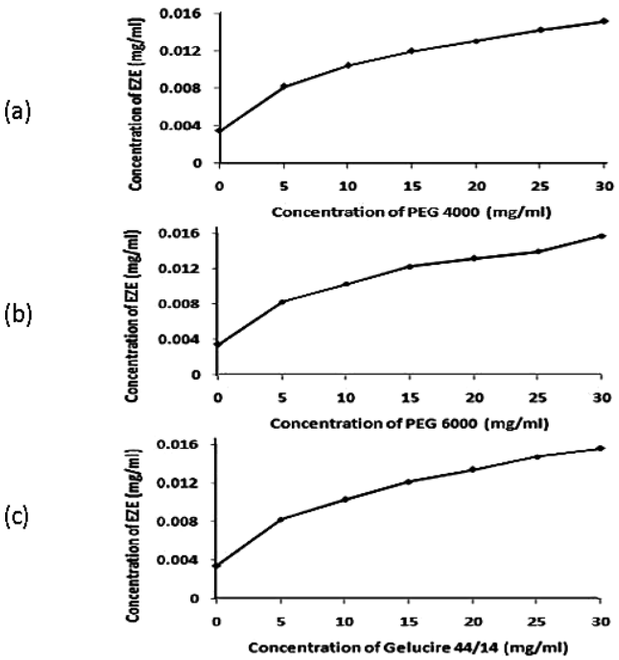

Figure 1. Phase solubility curves of EZE with (a) PEG 4000, (b) PEG 6000, and (c) Gelucire 44/14.

Powder X-ray Diffraction

Powder X-Ray diffraction (PXRD) patterns of pure EZE, carriers, and solid systems of EZE with hydrophilic carriers were recorded using a powder X-ray diffractometer (Phillips X-Pert MPD, The Netherlands) with a copper tube anode over the interval 1–40° $2\theta^{-1}$. The operational parameters were as follows: generator tension (voltage) of 45 kV; generator current of 40 mA; scan step time of 9 sec^{-1}, and scan step size of 0.008° (2θ).

RESULTS AND DISCUSSION

Phase Solubility Studies

Phase solubility curves are shown in Figure 1. Drug solubility increased with an increase in carrier concentration. Analogous results have been observed with other drugs and have been attributed to the formation of weak soluble complexes (*12*, *14*, *15*). Various parameters calculated from the phase solubility studies are shown in Table 2. The stability constants for 1:1 drug–carrier interactions were 103.59 and 106.47 mL/gm for PEGs and Gelucire 44/14, respectively, indicating weaker interactions among drug and carriers. The curves obtained were of A_L type with the resultant slopes less than unity (*10*). Further, as shown in Table 3, the values of Gibb's free energy of transfer, $\Delta G°_{tr}$, were negative indicating a spontaneous solubilization process of EZE in each polymer solution.

Table 2. Solubility Parameters of EZE Obtained from Various Carriers at 37 °C

Carrier	Slope	Stability constant (mL gm^{-1})	r^2
PEG 4000	3.6×10^{-4}	103.59	0.9041
PEG 6000	3.6×10^{-4}	103.59	0.9102
Gelucire 44/14	3.7×10^{-4}	106.47	0.9201

Table 3. Gibb's Free Energy of Transfer, $\Delta G°_{tr}$, for Solubilization Process of EZE in Buffer Solutions of Various Carriers

Carrier Conc. (mg/mL)	$\Delta G°_{tr}$ kJ/mole at 37 °C		
	PEG 4000	PEG 6000	Gelucire 44/14
5	-0.959	-0.974	-0.968
10	-1.231	-1.216	-1.216
15	-1.388	-1.412	-1.401
20	-1.485	-1.493	-1.510
25	-1.578	-1.556	-1.619
30	-1.649	-1.689	-1.680

Percentage Drug Content

Percentage drug content was in the range of 94.37 ± 0.81% to 99.15 ± 0.48%. All determinations are mean ± SD ($n = 3$).

In Vitro Release Studies

The dissolution curves of EZE, solid dispersions, and physical mixtures with PEG 4000, PEG 6000, and Gelucire 44/14 are shown in Figure 2. The dissolution rate of EZE was improved with the solid dispersions as compared with pure drug. Table 4 demonstrates various dissolution parameters computed from the release data. According to these results, the dissolution characteristics of EZE in all ternary systems showed significant improvement ($p < 0.05$). The order of dissolution enhancement with the prepared systems was PEG 6000 > Gelucire 44/14 > PEG 4000. The dissolution rate increased with an increase in the concentration of carriers. Among the preparations of three carriers, batch S13 gave the best results. Enhancement in the dissolution properties of EZE with PEGs might be attributed to the formation of solid solutions and their better wettability (*3*, *4*). The emulsifying action of Gelucire (*16*, *17*) might be responsible for the improvement in drug release properties from the prepared solid dispersions. Apart from the mechanisms of the individual carriers, the presence of lactose might have also contributed to the better dissolution characteristics of EZE in solid dispersions. The probable mechanism might be the increase in surface area of the free-flowing system (*1*). The dissolution rate of EZE in the physical mixture also improved but to a lesser extent than for the respective solid dispersions. The probable reason for the improvement in the dissolution rate in the physical mixture was the local solubilizing action of the carriers (*18*).

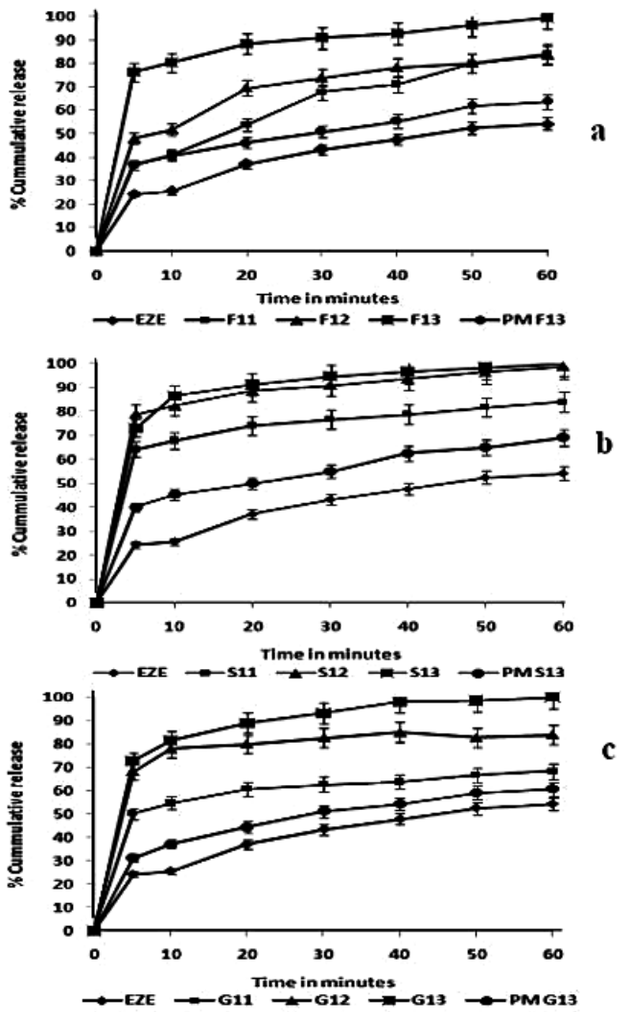

Figure 2. In vitro dissolution release profiles of EZE, solid dispersions, and physical mixtures of (a) PEG 4000, (b) PEG 6000, and (c) Gelcuire 44/14.

Table 5 lists the regression parameters obtained after fitting the dissolution release data to various kinetic models. Data fitting was done up to 90% of drug release. In general, the model that best fit the drug release data was Korsmeyer–Peppas. Results were based on the r^2 and residual sum of squares (SSR) values. Overall, the values of diffusional exponent *n*, obtained from the slopes of the fitted Korsmeyer–Peppas model, were less than 0.45, indicating Fickian diffusional phenomena (*12*, *19*).

Characterization Studies

To investigate the mechanism of improved dissolution properties of EZE in the prepared solid dispersions, systems of each polymer (F13, S13, and G13) were characterized by the following studies.

Fourier Transform Infrared Spectroscopy

Analysis by FTIR spectroscopy was carried out to assess any possible interaction between drug and hydrophilic carriers. Figure 3 depicts the FTIR spectra of drug, carrier, and the formulations with different carriers. The spectrum of pure EZE (Figure 3a) shows characteristic peaks at 3369.5 cm^{-1} (O–H stretch), 2919.3 cm^{-1} (C–H stretch), 1886.8 cm^{-1} (lactone ring C=O stretch), 1722.2 cm^{-1} (C=O stretch), 1604.6 cm^{-1} (C=C stretch), 1443.9 cm^{-1} (C–N stretch), 1398.6 and 1268.9 cm^{-1} (C–F stretch), 1222.0 cm^{-1} (C–O stretch), and 828.8 cm^{-1} (ring vibration of para-disubstituted benzene).

FTIR spectra of the polyethylene glycols, PEG 4000 (Figure 3c) and PEG 6000 (Figure 3e), show the same characteristic peaks because of their similar molecular structures. The spectra show peaks at 2950–2750 cm^{-1} (C–H stretch), 1468.84 cm^{-1} for PEG 4000 and 1470.77 cm^{-1} for PEG 6000 (C–H bending), and 1350–1000 cm^{-1} (C–O stretching).

FTIR spectra of Gelucire 44/14 (Figure 3g) show characteristic peaks at 2896.14 and 2856.67 cm^{-1} (C–H stretch), 1741.78 cm^{-1} (C=O stretch), 1464.98 cm^{-1} (C–H bending), and 1356.97, 1277.98, and 1117.79 cm^{-1} (C–O stretching).

FTIR spectra of solid dispersions F13, S13, and G13 (Figures 3b, 3d, and 3f, respectively) show no substantial shifting of the position of the functional groups. The peaks are only broadened, indicating no major interaction between EZE and hydrophilic carriers (*12*). Although hydrogen bonding could be expected between the hydrogen atom of the OH– group of EZE and the lone electron pairs of the carrier oxygen atoms, this could not be demonstrated (*3*, *4*).

Table 4. Dissolution Parameters for EZE and Various Solid Dispersion Systems

Sr. no.	Samples	DP_{10min} ± SD	$\%DE_{20min}$ ± SD	$t_{50\%}$ ± SD
1	EZE	25.57 ± 0.09	24.94 ± 0.11	44.75 ± 0.23
2	F11	41.22 ± 0.28	38.09 ± 0.13	16.96 ± 0.16
3	F12	51.86 ± 0.46	48.87 ± 0.01	7.53 ± 0.16
4	F13	80.50 ± 0.56	71.35 ± 0.19	3.29 ± 0.01
5	S11	67.81 ± 0.28	59.98 ± 0.36	3.97 ± 0.04
6	S12	82.37 ± 0.18	72.70 ± 0.12	3.16 ± 0.03
7	S13	86.39 ± 0.56	73.42 ± 0.40	3.38 ± 0.08
8	G11	54.69 ± 0.47	48.22 ± 0.41	5.2 ± 0.35
9	G12	77.88 ± 0.38	66.16 ± 0.21	3.67 ± 0.04
10	G13	81.40 ± 0.66	70.87 ± 0.41	3.42 ± 0.02

DP_{10min}: percent drug dissolved at 10 min.
$\%DE_{20min}$: percent dissolution efficiency at particular time.
$t_{50\%}$: time required for 50% drug release.
SD: standard deviation, n = 3.

Differential Scanning Calorimetry

DSC curves of pure EZE, polymers, and ternary systems are shown in Figure 4. DSC thermogram of EZE (Figure 4a)

Table 5. Statistical Parameters of Various Formulations Obtained after Fitting In Vitro Release Data to Various Kinetic Models

	Mathematical Models for Drug Release Kinetics														
	Zero-order			First-order			Higuchi			Korsemeyer–Peppas			Hixson–Crowell		
Samples	Slope	r^2	SSR	Slope	r^2	SSR	Slope	r^2	SSR	Slope	r^2	SSR	Slope	r^2	SSR
EZE	0.76	0.83	391.34	-0.01	0.91	290.88	6.83	0.97	60.62	0.35	0.96	18.08	0.02	0.88	319.22
F11	1.17	0.84	873.11	-0.03	0.97	410.56	10.48	0.97	122.26	0.35	0.98	32.37	0.03	0.94	545.81
F12	1.04	0.67	1763.40	-0.03	0.88	1288.30	9.94	0.84	582.29	0.24	0.97	35.78	0.03	0.82	1402.90
F13	2.26	0.51	2816.10	-0.07	0.77	2486.10	16.03	0.79	1190.10	0.10	0.99	1.93	0.07	0.67	2455.30
S11	0.86	0.47	2783.70	-0.02	0.71	2603.60	8.88	0.72	1447.20	0.11	0.99	2.26	0.02	0.62	2597.70
S12	2.22	0.48	3030.10	-0.07	0.72	2847.20	15.94	0.77	1348.70	0.08	0.99	0.86	0.07	0.62	2734.50
S13	3.93	0.62	2028.10	-0.11	0.84	1402.60	21.21	0.89	616.13	0.16	0.92	15.81	0.12	0.76	1461.10
G11	0.72	0.48	1788.10	-0.01	0.63	1683.10	7.32	0.74	896.64	0.12	0.98	2.82	0.02	0.58	1689.40
G12	0.81	0.38	3588.20	-0.02	0.53	3655.70	8.76	0.64	2056.70	0.08	0.85	29.64	0.02	0.47	3504.40
G13	2.37	0.56	2603.10	-0.08	0.85	1994.60	16.56	0.83	996.40	0.14	0.99	1.46	0.08	0.75	2107.40

SSR: residual sum of squares.

show an endothermic peak at 165.27 °C corresponding to the melting point of EZE (ΔH = -283.67 mJ gm^{-1}). Endothermic peaks at 56.16, 58.40, and 41.31 °C in the thermograms of PEG 4000 (Figure 4d), PEG 6000 (Figure 4f), and Gelucire 44/14 (Figure 4h), respectively, indicate the melting points of the polymers. The DSC curve of lactose monohydrate (Figure 4b) shows an endothermic peak at 152.14 °C from the loss of hydration water and a melting endothermic peak with decomposition at 221.96 °C.

In thermograms of solid dispersions (Figures 4c, 4e, and 4g), the sharp melting peak of pure EZE was not visible, which might be because of complete dissolution of EZE in the melted polymer (*1*, *20*, *21*). DSC spectra of PEG 4000, PEG 6000, and Gelucire 44/14 show the dehydration peaks of lactose monohydrate at 148.17, 148.23, and 152.02 °C and decomposition peaks at 213.77, 215.09, and 221.54 °C,

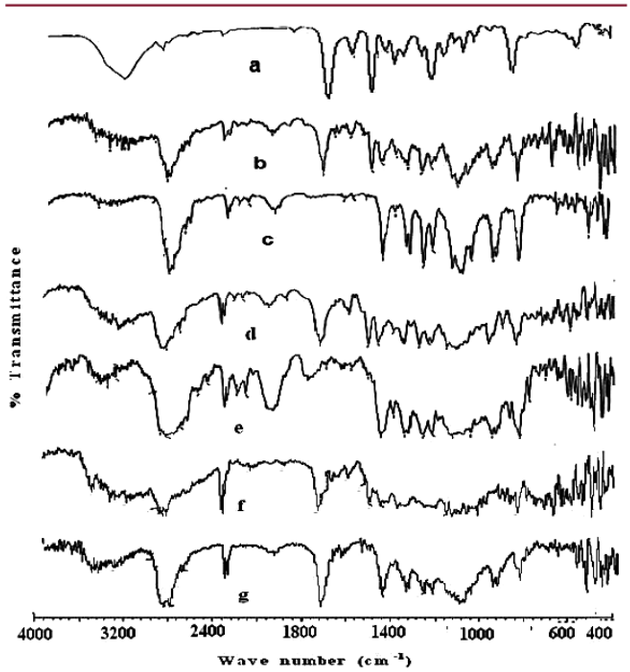

Figure 3. FTIR spectra of (a) EZE, (b) F13, (c) PEG 4000, (d) S13, (e) PEG 6000, (f) G13, and (g) Gelucire 44/14.

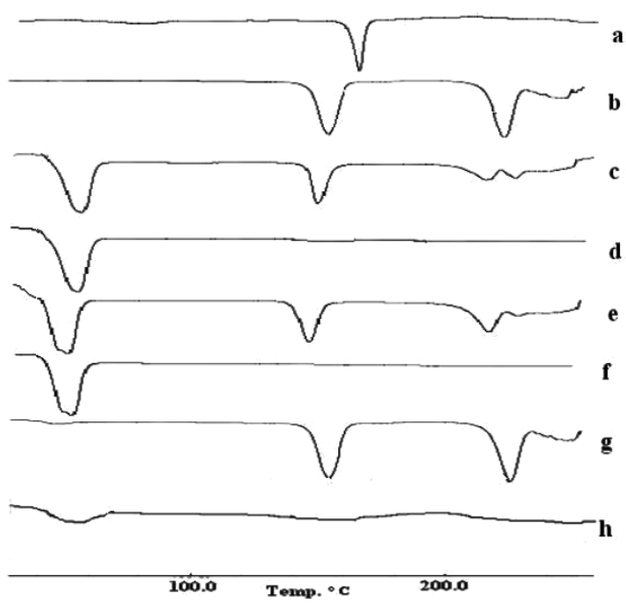

Figure 4. DSC thermograms of (a) EZE, (b) lactose monohydrate, (c) F13, (d) PEG 4000, (e) S13, (f) PEG 6000, (g) G13, and (h) Gelucire 44/14.

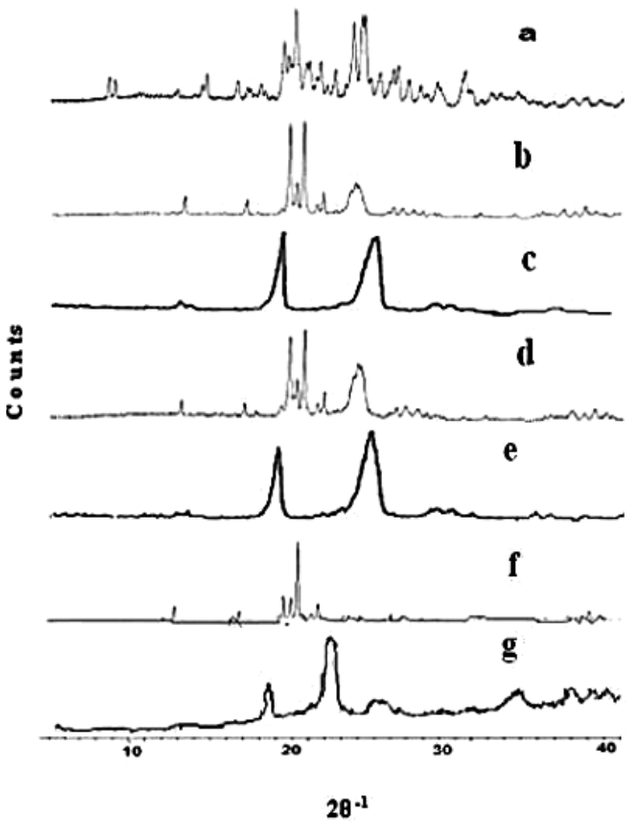

Figure 5. PXRD diffractograms of (a) EZE, (b) F13, (c) PEG 4000, (d) S13, (e) PEG 6000, (f) G13, and (g) Gelucire 44/14.

respectively. The dehydration peak of lactose monohydrate in PEG systems does not appear as a sharp peak and was shifted to a lower temperature; analogous results are reported with solid dispersions of other drugs (*1*, *22*).

Powder X-ray Diffraction

PXRD patterns of pure EZE, polymers, and of binary systems are shown in Figure 5. The powder X-ray diffractogram of EZE (Figure 5a) shows sharp peaks at diffraction angles (2θ) of 7.88°, 13.87°, 18.63°, 19.35°, 20.16°, 21.67°, 22.90°, 23.59°, 25.29°, and 29.71°, indicating its crystalline nature. PEG 4000 (Figure 5c) exhibits a distinct pattern with diffraction peaks at (2θ) 19.51° and 22.54°. PEG 6000 (Figure 5e) shows diffraction peaks at (2θ) 18.68° and 23.51°. Gelucire (Figure 5g) shows diffraction peaks at (2θ) 17.52° and 23.16°.

Diffraction patterns of solid dispersions (Figures 5b, 5d, and 5f) show the characteristic peaks of both EZE and polymers, but the intensity and number of drug peaks are reduced, indicating a decrease in drug crystallinity. The diffraction peak of lactose monohydrate at 20° is observed in the diffractograms of the solid dispersions; this finding is similar to that reported by other investigator (*23*). Thus, a decrease in drug crystallinity might be responsible for the improvement in dissolution of EZE.

CONCLUSIONS

Solid dispersion along with an adsorption technique that employs a water-soluble adsorbent can be used to enhance the dissolution of EZE, which may result from the combined effect of hydrophilic carriers and increased surface area. The Korsmeyer–Peppas model properly describes the dissolution data, possibly suggesting Fickian diffusion as the mechanism of drug release. Solid-state characterization studies revealed a partial loss of drug crystallinity of EZE, a potential source of dissolution enhancement. However, other factors such as particle size reduction, increased surface area, and improved wettability due to hydrophilic polymers represent other potential mechanisms. The clinical utility of enhanced release should be tested by an assessment of EZE bioavailability in humans.

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