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Effect of binary and ternary solid dispersions prepared by fusion method on the dissolution of poorly water soluble diacerein

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Abstract

The poor solubility of drug substances in water and their low dissolution rate in aqueous G.I.T fluid often leads to insufficient bioavailability. The present investigation is an attempt to improve the solubility and dissolution rate of diacerein (a poorly soluble drug) by solid dispersion technique. Binary solid dispersions were made using PEG-4000 or PEG-6000 as carriers with varying drug: carrier ratios 1:1, 1:3 and 1:5. Also ternary solid dispersions were made using PEG-4000 and Pluronic F-68 at ratios 1:5:1, 1:5:2 and 1:5:3. Nine formulae were prepared and evaluated for saturated solubility, *in-vitro* drug release. Solid state characterization including DSC, FTIR, XRD and SEM is also carried out. All formulae showed marked significant improvement in the solubility and dissolution rate of the drug. The interaction studies showed no interaction between the drug and any of the used carriers. Formula SD9 (1:5:3; drug: PEG-4000: Pluronic F-68) showed the best dissolution profile with about 44.73% of the drug being released in the first 5 minutes and more than 79 % of the drug being released in the first 15 minutes. Also this formula showed the highest dissolution rate of 6.66 %/min. It was concluded that combination of PEG-4000 and Pluronic F-68 can be well utilized to improve the solubility of poorly soluble drugs.

Keywords: Diacerein, Solid dispersion, Polyethylene glycol, Physicochemical characterization; *In-vitro* dissolution.

Introduction

Discovering a way to increase the solubility of poorly water soluble drugs in order to improve their pharmaceutical and biological availability still remains one of the major technological problems.

The current status of scientific development having highly variable oral bioavailability due to low solubility and dissolution rate in the gastrointestinal absorption of many new drugs [1].

Even though there are many methods intended to solve the problem from which, the formulation of solid dispersion is one of the ideal methods of dissolution enhancement. The solid dispersions is a dispersion of one or more active ingredients in an inert carrier or matrix, prepared by the melting, solvent, or melting solvent method. Solid dispersions have been explored as potential delivery systems for many poorly soluble drugs such as griseofulvin, indomethacin and oxazepam [2].

The ability of solid dispersions to afford drug release as fine, dispersed particles has resulted in improvements in dissolution rates of poorly water soluble drugs which have also been reflected in increases in oral bioavailability [3]. A significant particle size reduction can be obtained by manufacturing solid dispersions and in many cases the drug is molecularly dispersed in the carrier. Conversion of the physicochemical state of the drug, e.g. from crystalline to amorphous as well as solubilization and supersaturation by the carrier, can cause an increase in the kinetic solubility and the dissolution rate [4].

Diacerein (chemically 4,5-diacetoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid) a non-steroidal anti-inflammatory having a chondroprotective action is used in the treatment of osteoarthritis [5,6].

Diacerein lacks cyclooxygenase inhibitory activity and hence has no effect on prostaglandin synthesis. It is a selective inhibitor of interleukin-1 with a protective effect on granuloma induced cartilage breakdown by its reduction of the concentration of pro inflammatory cytokines [7,8]. However, its poor aqueous solubility and hence limited dissolution makes the bioavailability of the drug to be 35-56% of the total dose (50mg) and thus it results in a limited therapeutic response [9,10].

The present work was conducted to improve the dissolution of diacerein using solid dispersion technique with PEGs. Pluronic F-68 (which is non-ionic amphiphilic surfactant) was used in some formulations in an attempt to increase drug wettability, solubility and hence drug dissolution.

Materials

Diacerein was obtained as a gift sample from (EVA pharm, Egypt), Polyethylene glycols grades 4000 and 6000 were purchased from Fluka (Switzerland) and Pluronic F-68 was purchased from Sigma-Aldrich (USA). All other chemicals and solvents were of analytical grades.

Phase solubility study

Phase solubility study was performed according to the method described by Higuchi and Connors [11]. Diacerein in excess amounts was added to 20 ml of different concentrations of PEG-4000 and PEG-6000 in glass stoppered flasks. The concentrations used were 0.05%, 0.1%, 0.15%, 0.2%, 0.25% and 3% w/v in phosphate buffer pH 7. Flasks were placed in thermostatically controlled shaking water bath (Memmert, France) for 72 hr at 37ºC. After equilibrium, aliquots were withdrawn then passed through a millipore filter (0.45 um Sartorious, AG Germany), then analyzed using a UV–visible spectrophotometer at 257 nm after suitable dilution. All the data were the average of three determinations.

The Gibb's free energy of transfer (ΔG°_{tr}) value provides information about whether the treatment is favorable or unfavorable for drug solubilization in aqueous medium. Negative Gibbs free energy values indicate improved dissolution [12-13]. Values of ΔG°_{tr} were calculated using the following equation:

$$\Delta G^{\circ}_{tr} = -2.303RT \text{ Log } \frac{S_o}{S_s} \qquad \text{Eq. 1}$$

Where S_o/S_s is the ratio of the solubility of diacerein in buffer solution of polymer to that of the pure buffer media. The value of gas constant (R) is 8.31 $J.K^{-1}.mol^{-1}$ and T is temperature in degree kelvin.

Table 1: Composition of different binary and ternary solid dispersion formulae.

Formula No.	Drug: Carrier	ratio
SD1	Diacerein:PEG-4000	1:1
SD2	Diacerein:PEG-4000	1:3
SD3	Diacerein:PEG-4000	1:5
SD4	Diacerein:PEG-6000	1:1
SD5	Diacerein:PEG-6000	1:3
SD6	Diacerein:PEG-6000	1:5
SD7	Diacerein:PEG-4000:Pluronic F68	1:5:1
SD8	Diacerein:PEG-4000:Pluronic F68	1:5:2
SD9	Diacerein:PEG-4000:Pluronic F68	1:5:3

Phase solubility diagrams were obtained by plotting the solubility of diacerein (mole/L), versus the concentrations of the polymers PEG-4000 and PEG-6000 used (%w/v) the results were presented in table 2 and figure 1. The complexation efficiency (C.E) as a parameter indicating the solubilization power of the polymers

Table 2: Values of complexation efficiency and stability constant of diacerein complexes with PEG-4000 and PEG-6000.

PEG-4000 conc. (%w/v)	Diacerein conc.(mole/L) Average ± S.D	ΔG°_{tr} kJ/mole at 37 C	PEG-6000 conc. (%w/v)	Diacerein conc.(mole/L) Average ± S.D	ΔG°_{tr} kJ/mole at 37 C
0	0.00011169 ± 0.042	0	0	0.00011169 ± 0.042	0
0.05	0.00014596 ± 0.021	-689.50	0.05	0.00012237 ± 0.093	-235.37
0.1	0.00016927 ± 0.011	-1071.24	0.1	0.0001554 ± 0.002	-850.89
0. 15	0.00020201 ± 0.014	-1526.89	0. 15	0.00017426 ± 0.011	-1146.17
0.2	0.00025363 ± 0.098	-2113.13	0.2	0.00018425 ± 0.077	-1289.79
0.25	0.00030399 ± 0.082	-2579.84	0.25	0.00021103 ± 0.090	-1639.42
0.3	0.00034922 ± 0.005	-2937.23	0.3	0.00022477 ± 0.088	-1801.89
0.4	0.00034784 ± 0.077	-2723.91	0.4	0.00022227 ± 0.022	-1637.72
0.5	0.00034686 ± 0.039	-2610.23	0.5	0.00021592 ± 0.012	-1462.38
0.6	0.00034478 ± 0.057	-2491.31	0.6	0.00021672 ± 0.085	-1274.23
[a]C.E = 0.0008			[a]C.E = 0.0004		
$^{b}K_{1:1}$ = 8.006 $mole^{-1}$			$^{b}K_{1:1}$ = 4.001 $mole^{-1}$		

[a]C.E: Complexation Efficiency, **$^{b}K_{1:1}$:** Stability Constant, **ΔG°_{tr}:** Gibbs free energy, **S.D:** Standard Deviation

towards the drug was calculated from the straight line of the phase solubility diagrams according to the equation (2):

$$C.E = S_o \cdot K_{1:1} = \frac{\quad}{\quad} \qquad \text{Eq. 2}$$

Where S_o represents the drug solubility in the absence of polymers, $K_{1:1}$ is the apparent stability constant, where $K_{1:1}$ = ——— [14].

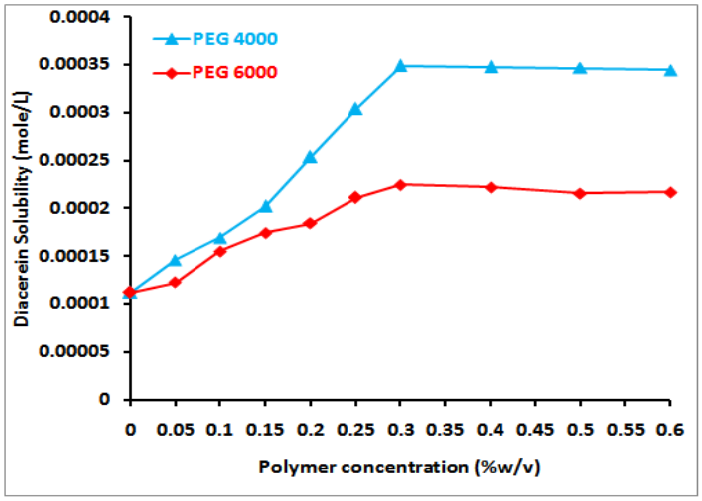

Figure 1: Phase solubility profiles for diacerein dispersion in solutions of PEG-4000 and PEG-6000.

Preparation of diacerein solid dispersions by fusion method

As shown in table (1), Binary diacerein solid dispersion formulae SD1 to SD6 were prepared with PEG-4000 and PEG-6000 as hydrophilic carriers in ratios of 1:1, 1:3 and 1:5. While in ternary solid dispersion formulae SD7 to SD9, Pluronic F-68 were incorporated along PEG-4000 in ratios 1:5:1, 1:5:2 and 1:5:3 (drug: PEG-4000: Pluronic F-68). Diacerein was added to the molten polymer(s) at 60 C while continuous stirring till homogenous mixture was obtained then cooled to room temperature to obtain a solid mass. The solidified mass was crushed and passed through sieve No.40 to get uniform sized particles. The obtained drug SDs were stored in desiccators till further analysis [15,16].

Evaluation of diacerein solid dispersions

Determination of saturated solubility

Saturated solubility of pure drug and its solid dispersions were conducted as follows: excess amount of pure drug or solid dispersions were added to 10 ml phosphate buffer pH 7.4 in glass tubes with a teflon caps in thermostatic shaker bath. After 72 hrs shaking period at 37 ± 0.5ºC, the solutions were filtered using a millipore filter (0.45 um Sartorious, AG Germany), suitably diluted and the absorbance was measured using spectrophotometer (Jasco V-530, Japan) at 257 nm. All experiments were repeated in triplicate and presented in table 3 and figure 2.

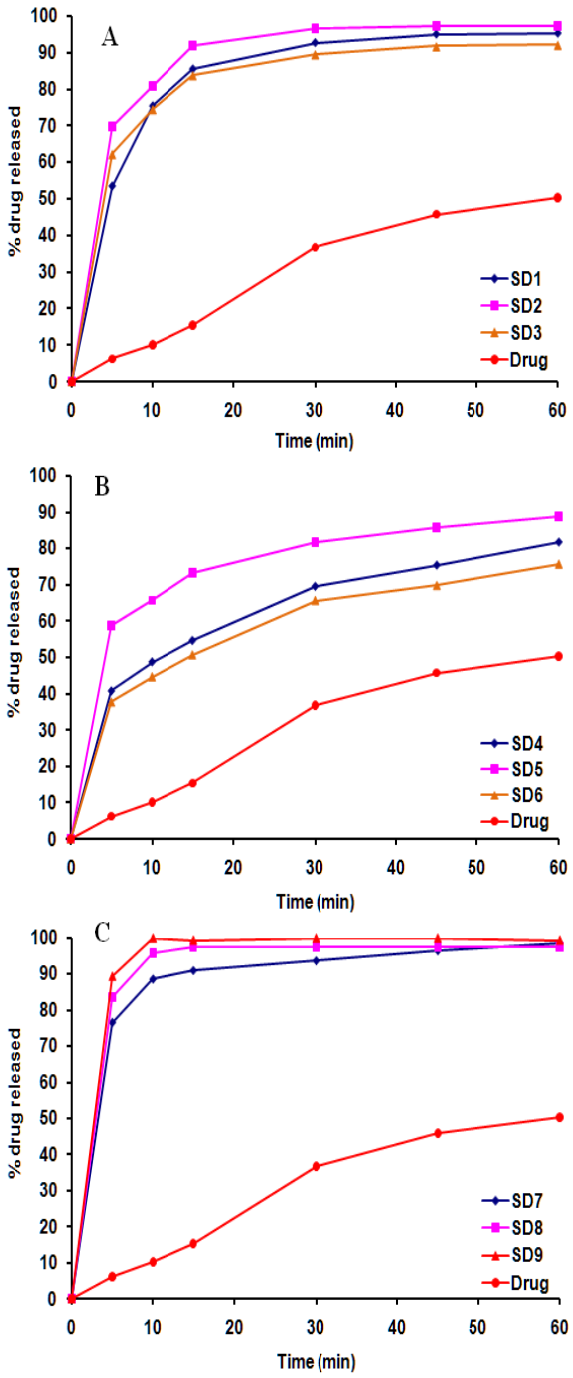

Figure 2: *In-vitro* drug release profile of diacerein solid dispersions SD1 to SD9 compared with pure drug.

Drug content analysis

Drug content was determined by dissolving an amount of 100 mg of drug SDs in 100 mL phosphate buffer pH 7.4. The solution was filtered, suitably diluted and the absorbance was measured spectrophotometrically at 257 nm. All experiments were repeated in triplicate and presented in table 3.

Table 3: Results of saturated solubility and percentage of drug content of diacerein in different solid dispersions formulae.

Formula No.	Saturated solubility (µg/ml) in distilled water (average ± S.D)	% increase in solubility	Drug content average (%) ± S.D
SD1	339.17 ± 0.23	688.94	99.23 ± 1.21
SD2	363.28 ± 0.67	745.04	99.52 ± 1.37
SD3	297.81 ± 0.92	592.74	97.13 ± 0.52
SD4	264.97 ± 1.33	516.35	101.83 ± 0.05
SD5	279.55 ± 0.54	550.69	99.17 ± 1.52
SD6	245.48 ± 0.34	471.03	98.89 ± 0.62
SD7	384.29 ± 0.61	794.49	98.63 ± 1.01
SD8	431.83 ± 0.45	904.49	101.13 ± 0.34
SD9	505.95 ± 0.38	1076.92	100.91 ± 0.69
Pure diacerein	42.99 ± 0.17		

[a]**C.E:** Complexation Efficiency, [b]$K_{1:1}$**:** Stability Constant, ΔG^{o}_{tr}**:** Gibbs free energy, **S.D:** Standard Deviation

In-vitro drug release

Pure drug (50 mg) and an amount of solid dispersion equivalent to 50 mg were sprinkled on the surface of the dissolution medium in a dissolution tester, apparatus II (Hanson Research, SR 8 Plus model, USA). Dissolution studies of diacerein were performed in 900 ml phosphate buffer of pH 7.4 and stirring speed of 100 r.p.m maintained at 37 ± 0.5 C. At appropriate time intervals, aliquots of 5 ml were withdrawn and measured spectrophotometrically at λ_{max} 257 nm. Experiments were carried out in triplicate.

Model Independent Approaches Dissolution efficiency (% DE)

Percent DE at 5 and 15 minutes were calculated for all formulae for comparison according to equation 3. The dissolution efficiency (DE) is defined as the area under the dissolution curve up to a certain time (t), expressed as a percentage of the area of the rectangle described by 100% dissolution in the same time.

Eq. 3

$$D.E. = \frac{\int_{o}^{t} y \times dt}{y_{100} \times t} \times 100\%$$

Initial dissolution rate (%/min)

To compare dissolution rate enhancement of diacerein from SDs formulae, Initial dissolution rate (IDR) was calculated as percentage dissolved of drug over the first 5 minutes per minute.

Similarity factor (f_2) and Dis-similarity factor (f_1)

A model-independent, mathematical approach proposed by Moore and Flanner for calculating f_1 and f_2 was used for comparison among the dissolution profiles [17]. The f_2 and f_1 is a measure of similarity and dissimilarity factor respectively, between two dissolution profiles and is given by equations 4 and 5 respectively.

Eq. 4

$$f_2 = 50 \times \log\left\{\left[f_1 = \frac{\sum_{j=1}^{n} \left| R_j - T_j \right|}{\sum_{j=1}^{n} R_j} \times 100 \right]^{0}\right\}$$

In which n is the number of withdrawal points, Rj is the percentage dissolved of reference at the time point t, and Tj is the percentage dissolved of test at the time point t. A value of 100 for f 2 suggests that test and reference profiles are identical. Values between 50 and 100 indicate that the dissolution profiles are similar, where as smaller values imply an increase in dissimilarity. The difference factor (dis-similarity factor f1) measures the percent error between two profiles over all time points. The value of f1 is zero when the test and drug reference profiles are identical and increase proportionally with the dissimilarity between the two dissolution profiles.

Analysis of drug release data

In-vitro release data were fitted to various kinetic models 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 [18, 19].

Solid state characterization

Differential Scanning Calorimetry (DSC)

A differential scanning calorimeter (DSC 60, Shimadzu) was used to obtain the DSC curves of diacerein, polymers and some selected drug-SDs formulae. Five milligrams samples were placed in an aluminum pan and the experiment was carried out under nitrogen atmosphere at a flow rate of 40 mL/min and a scanning rate of 10 C/min in the range of 25-250 C.

FTIR Spectroscopy

IR spectrum of diacerein, polymers and solid dispersions were recorded using Shimadzu FT/IR 5300, IR spectrophotometer in scanning range 400 to 4000 cm^{-1}, by KBr disc method.

Powder X-Ray Diffractometry (PXRD)

The X-ray powder diffraction patterns were obtained by using Philips PW 1700 with Cu K alpha (Lambda) radiation and crystal monochromator, voltage of 45 mV and 20 Amp current. The diffraction patterns run at 2.4° /min over the 2θ range of 2-50º [20].

Scanning Electron Microscopy (SEM)

Photomicrographs of diacerein and some selected SD formulae were obtained by SEM (JSM-6360; JEOL Ltd., Japan). The powder were mounted on double-sided adhesive tape and sputtered with gold for 2 min using SPI sputter (USA). Scanning electron photographs were taken at an accelerating voltage of 15 kV.

Results and Discussion

Phase solubility study

The phase solubility profiles for diacerein in the used PEG-4000 and PEG-6000 buffered solutions are presented in figure 1 (Phase solubility profiles for diacerein dispersion in solutions of PEG-4000 and PEG-6000).

They displayed A_L type [21] equilibrium phase solubility diagrams for diacerein in both solutions, showing that diacerein solubility increases linearly as a function of PEG concentrations and soluble adsorption complexes were formed without occurrence of precipitation in the range of PEG concentrations used till 0.3% w/v of the polymer, thereby demonstrating that reaction became more favourable as concentration of polymer was increased. The enhancement in solubility might be due to hydrophilic nature of polymers and surface adsorption of drug on the polymer.

The stability constant was found to be 8.006 and 4.001 mol^{1} for PEG-4000 and PEG-6000 respectively. The complexation efficiency in case PEG-4000 was twofold that of PEG-6000. The results are in accordance with the well established formation of soluble complexes between water soluble polymeric carriers and poorly water soluble drugs [22-25].

An indication of the process of transfer of diacerein from pure water to the aqueous solution of PEG 6000 may be obtained from the values of Gibbs free energy change. Table 2 presents the values of Gibbs free energy (ΔG°_{tr}) associated with the aqueous solubility of diacerein in presence of PEG-4000 and PEG-6000.

The negative values of ΔG°_{tr} were observed at the treated concentrations of the polymers, which reflect the spontaneous nature of diacerein solubilization. Also, values decreased with increasing concentrations of polymer till 0.3% w/v, thereby demonstrating that reaction became more favourable as concentration of polymer was increased. Above 0.3% w/v reaction became un-favourable as concentration of polymer was increased. These values also indicated that the extent of improvement in solubility was more with PEG-4000 as compared with PEG-6000. Analogous results have been observed with other drugs and have been attributed to the formation of weak soluble complexes [18, 26-27].

Evaluation of diacerein solid dispersions

Determination of saturated solubility

Due to the ability to improve wettability and to solubilize some compounds, polyethylene glycols (PEG) have been widely used as carriers in SDs. Additional presence of self-emulsifying component (Pluronic F-68) improves the water solubility of the active ingredient. Moreover, it can also increase the dispersability of hydrophobic drug in the hydrophilic carrier during the process of solid dispersion formation. Therefore, higher amounts of molecularely dispersed substance are expected.

As shown in table 3, all the tested samples have an increase in drug solubility over diacerein. It might be due to either the reduction of the crystallinity of drug or the improved wetting of the drug particles. Improving the wettability of the hydrophobic drug crystals might also occur.

The order of dissolution enhancement with the prepared systems was: SD9 > SD8 > SD7 > SD2 > SD1 > SD3 > SD5 > SD4 > SD6 > pure drug The saturated solubility of the drug is increased with an increase in the concentration of carriers. Among the preparations of three carriers, formulae SD9 then SD8 gave the best results. Since the saturated solubility of diacerein from formula SD9 was 505.95 ug/ml versus 42.99 ug/ml of pure drug with 1076.92% increase in solubility, while formula SD8 showed diacerein solubility of 431.83 ug/ml versus 42.99 ug/ml of pure drug with 904.49% increase in solubility.

It is better to note that, the increase in ratio of Pluronic F68 in formulae resulted in an increase in solubility of diacerein and this could be explained on the basis of micellar solubilization or by increasing the steric hindrance among the particles [27].

Also it is noted that the formulae containing PEG-4000 showed higher solubility than that prepared with PEG-6000 and this may be explained by decreased dispersibility and higher viscosity of PEG-6000 than PEG-4000.

Drug content

Percentage drug content of the formulations was found to be in the range of 97.13 ± 0.52 to 101.83 ± 0.05 as shown in table (3).

In-vitro drug release

The present study confirmed the advantage of improved aqueous solubility of diacerein in its binary and ternary solid dispersions form, with better dissolution characteristics.

Different mechanisms have been suggested for enhanced dissolution of drug from solid dispersion, these include: (a) molecular dispersions, after carrier dissolution the drug is molecularly dispersed in the dissolution medium, a high surface area is formed, resulting in an increased dissolution rate and consequently improved bioavailability [28-29], (b) a strong contribution to the enhancement of drug solubility is related to the drug wettability and improved wetting may lead to reduced agglomeration and increased surface area [30-31], (c) the increased porosity of solid dispersion particles also hastens the drug release profile [32-33], (d) the enhancement of drug release can usually be achieved using the drug in its amorphous state, because no energy is required to break up the crystal lattice during the dissolution process [34-36], and/or (e) drugs are presented as supersaturated solutions after system dissolution, and it is speculated that, if drugs precipitate, it is as a metastable polymorphic form with higher solubility than the most stable crystal form [29, 37-38].

Figure 2 (A, B and C) (In-vitro drug release profile of diacerein solid dispersions SD1 to SD9 compared with pure drug) shows the dissolution profiles of pure diacerein and its binary and ternary solid dispersion mixtures.

Model Independent Approaches

The calculated $\%DE_{5min,}$ $\%DE_{15min}$ and IDR values are presented in table 4. The average percentage release of pure drug was 50.24% in 60 min and it is obvious from $\%DE_{15min}$ of 8.03 and IDR of 1.03 %/min that the dissolution of pure diacerein is poor and slow and this was attributed to the hydrophobicity of the drug.

Formulation of diacerein as binary solid dispersion with either PEG-4000 or PEG-6000 resulted in significant enhancement of diacerein dissolution and this is clear from the values of $\%DE_{5min,}$ $\%DE_{15min}$ and IDR compared to the pure drug (table 4). The results obtained revealed that all binary and ternary solid dispersions of diacerein have faster dissolution than pure diacerein. Of note is the fact that the extent of enhanced dissolution depended on the concentration of the polymer used in the solid dispersion, increasing the polymer

Table 4: Dissolution parameters obtained from dissolution data of different binary and ternary solid dispersion formulae.

	Dissolution Parameters				
Formula No.	**% DE_{5min}**	**% DE_{15min}**	**IDR (%/min)**	f_2	f_1
Drug	3.12 ± 0.01	8.03 ± 0.22	1.03 ± 0.06		
SD1	26.73 ± 0.12	57.18 ± 1.01	5.73 ± 0.02	14.17 ± 0.02	202.40 ± 2.12
SD2	34.83 ± 0.09	65.43 ± 0.05	6.12 ± 0.06	11.97 ± 0.05	224.12 ± 2.03
SD3	31.08 ± 0.14	59.48 ± 0.92	5.58 ± 0.11	14.40 ± 0.23	200.18 ± 1.98
SD4	20.42 ± 0.08	39.02 ± 0.24	3.65 ± 0.25	24.66 ± 0.24	125.93 ± 1.65
SD5	29.42 ± 0.08	53.75 ± 0.36	4.88 ± 0.36	17.20 ± 0.26	176.38 ± 1.11
SD6	18.87 ± 0.13	35.95 ± 0.86	3.38 ± 0.22	27.57 ± 0.91	109.63 ± 2.05
SD7	38.27 ± 0.05	70.20 ± 0.88	6.06 ± 0.81	11.19 ± 0.15	231.38 ± 1.87
SD8	41.71 ± 0.02	75.96 ± 0.47	6.49 ± 0.44	9.51 ± 0.36	249.12 ± 1.63
SD9	44.73 ± 0.05	79.73 ± 0.96	6.66 ± 0.33	8.68 ± 0.66	258.03 ± 1.95

%$DE_{5\ min}$: Percent dissolution efficiency at 5 minutes, **%$DE_{15\ min}$:** Percent dissolution efficiency at 15 minutes, **IDR:** Initial dissolution rate, f_2: Similarity factor, f_1: Dis-similarity factor.

concentration leaded to increasing the drug release until certain concentration above which the drug release was decreased.

Formulae prepared with PEG-4000 showed higher dissolution rates than those prepared with PEG-6000 and this may be explained on the basis of PEG-4000 produced less viscous dispersion and the rapid diffusion of the dissolved drug molecules.

The best results among solid dispersion formulae were ternary solid dispersions obtained with PEG-4000 in combination with Pluronic F-68 in ratios of 1:5:3, 1:5:2 and 1:5:1 (drug: PEG-4000: Pluronic F-68) respectively. The drug release was extremely improved with these combinations. Increasing the Pluronic F-68 ratio in the ternary mixture resulted in more increase in drug dissolution as it is clear from the calculated dissolution parameters. The rapid dissolution obtained in case of the ternary system can be thus explained on the basis that both polymers enhance the dissolution by different mechanisms which provide a chance for synergism upon combination.

The formula SD9 (1:5:3; drug: PEG-4000: Pluronic F-68) showed the best dissolution profile with about 44.73% of the drug being released in the first 5 minutes and more than 79 % of the drug being released in the first 15 minutes. Also this formula showed the highest dissolution rate of 6.66 %/min.

Improved wettability of the hydrophobic drug by amphiphilic compounds is another alternative mechanism. Amphiphilic molecules can modify the surface properties of particles which will result in a reduction of the contact angle with water or by formation of hydrophilic film around the particles [39]. The enhanced dissolution of diacerein from PEG solid dispersion was mainly attributed to the formation of microcrystalline dispersion of the drug [25].

The effect of Pluronic F-68 on the drug dissolution may be attributed to the enhanced wettability. Eutectic mixture formation was also suggested for Pluronic F-68 solid dispersion with other drugs [40].

Concerning the similarity factor (f_2) and dis-similarity factor (f_1) values in table (4), it is clear that all the prepared binary and ternary solid dispersion mixtures showed significant different dissolution profiles from that of pure diacerein. SD9 showed f_2 and f_1 of 8.68 and 258.03 respectively.

Analysis of drug release data

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 and based on the R^2, the model that best fit the drug release data was first order model for formulae SD1-SD2 and SD8-SD9. While Korsmeyer–Peppas is the best fitting model for SD3-SD7 with the values of diffusional exponent (n) of less than 0.45, indicating Fickian diffusional phenomena [13,18].

Table 5: Kinetic analysis of release data of different binary and ternary solid dispersion formulae.

		Diacerein SDs formulae									
Model	**Parameter**	**Drug**	**SD1**	**SD2**	**SD3**	**SD4**	**SD5**	**SD6**	**SD7**	**SD8**	**SD9**
Zero order	**K**	0.950	2.192	2.272	2.129	1.732	1.992	1.609	2.283	2.361	2.387
	R^2	0.9783	0.7224	0.6515	0.6831	0.8524	0.7296	0.8517	0.6085	0.5518	0.508
First	**K**	0.013	0.140	0.203	0.152	0.049	0.111	0.039	0.260	0.352	0.454
	R^2	0.9908	0.9978	0.9953	0.9891	0.9575	0.9668	0.9458	0.9957	0.9997	0.999
Higuchi	**K**	6.074	15.580	16.352	15.250	11.997	14.152	11.139	16.526	17.022	17.514
	R^2	0.9679	0.8911	0.8413	0.8640	0.9662	0.8931	0.9659	0.8052	0.7471	0.726
Krosmyer-Peppas	**K**	2.094	46.667	61.163	53.136	25.659	45.640	23.643	70.033	80.750	89.320
	n	0.793	0.188	0.123	0.144	0.285	0.166	0.287	0.086	0.056	0.031
	R^2	0.9864	0.9849	0.9936	0.9944	0.9994	0.9992	0.9985	0.9977	0.9965	0.997
Hixson-Crowell	**K**	0.004	0.025	0.026	0.025	0.013	0.023	0.010	0.026	0.026	0.027
	R^2	0.9882	0.9465	0.8968	0.9150	0.9392	0.9219	0.9226	0.8558	0.8075	0.784
Predicted Model		First	First	First	Kros-myer	Kros-myer	Kros-myer	Kros-myer	Kros-myer	First	First

Differential scanning calorimetry data

DSC thermograms of pure diacerein and its binary solid dispersion formula SD3 using PEG-4000 (1:5) and ternary solid dispersion formula SD9 using PEG-4000 and Pluronic F-68 (1:5:3) are shown in figure 3 (DSC thermograms of (A) pure diacerein, (B) pure PEG-4000, (C) pure Pluronic F-68, (D) binary solid dispersion formula SD3 and (E) ternary solid dispersion formula SD9). As shown in this figure, diacerein showed a sharp endothermic peak at 255.14 C, corresponding to the melting point of the crystalline form of diacerein. In contrast, PEG-4000 showed a sharp endothermic peak at 51.09 C, indicating the melting point of the polymer, while, Pluronic F-68 showed a sharp melting endothermic peak at 49.26 C. A broad endothermic peak was observed in the DSC thermogram of SD3 at 240.51 C, indicating the presence of some traces of crystalline diacerein.

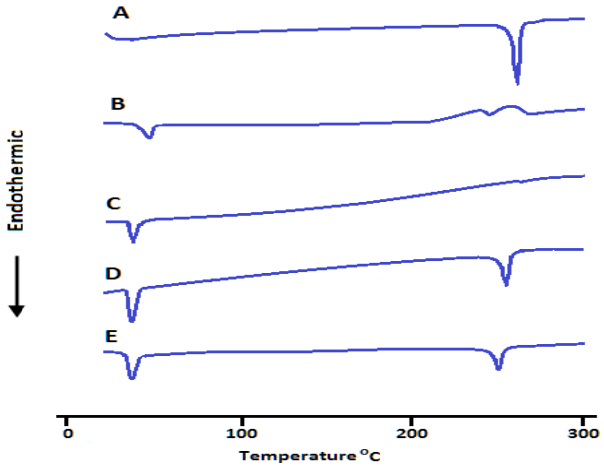

Figure 3: DSC thermograms of (A) pure diacerein, (B) pure PEG-4000, (C) pure Pluronic F-68, (D) binary solid dispersion formula SD3 and (E) ternary solid dispersion formula SD9

A significant reduction in the intensity of the sharp peak of diacerein was noted in DSC thermogram of SD9, where broad endothermic peak was observed 238.30 C. With dispersions, peak temperatures shifted to lower temperatures than with the drug alone, indicating a loss of the characteristic features of diacerein peaks in these dispersions [41]. This phenomenon might be attributed to complete molecular dispersionand possibly indicate the presence of an amorphous diacerein in these systems [42-43].

FTIR spectroscopy data

FTIR investigations are mainly carried out to examine a molecular change in the drug due to its interaction with the used excipients [44, 45]. FTIR spectra of diacerein, PEG-4000, Pluronic F-68 and SD3 and SD9 are shown in figure 4 (FTIR spectra of (A) pure diacerein, (B) pure PEG-4000, (C) pure Pluronic F-68, (D) binary solid dispersion formula SD3 and (E) ternary solid dispersion formula SD9).

The principal absorption bands of diacerein were observed at 3421 cm^{-1} (O-H, stretch, broad, COOH), 3066 cm^{-1} (C-H, stretch, aromatic), 2935 cm^{-1} (C-H, stretch, aliphatic, sym), 1770 cm^{-1} (C=O, stretch, ester), 1678 cm^{-1} (C=O, stretch, COOH), 1693 cm^{-1} (C=O, stretch, ketone), 1593 cm^{-1} (C=C, stretch, aromatic), 1450 cm^{-1} (C-O, stretch, COOH), 1026 cm^{-1} (C-O, stretch, ester) and 704 cm^{-1} (benzene) [46].

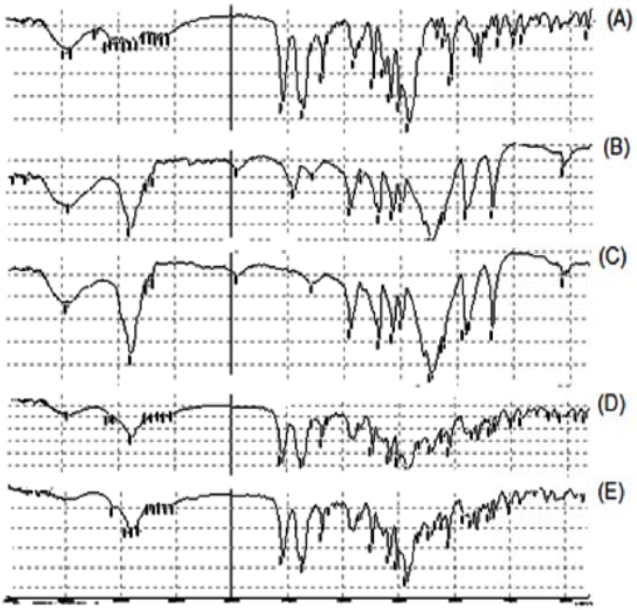

Figure 4: FTIR spectra of (A) pure diacerein, (B) pure PEG-4000, (C) pure Pluronic F-68, (D) binary solid dispersion formula SD3 and (E) ternary solid dispersion formula SD9.

The FTIR spectrum of PEG-4000 is characterized by principal absorption bands at 3421 cm^{-1} (O-H, stretch, broad), 2889 cm^{-1} (C-H, stretch, aliphatic).which consistently appeared in SD of diacerein. The FTIR spectrum of Pluronic F-68 is characterized by principal absorption bands at 3444 cm^{-1} (O-H, stretch, broad), 2885 cm^{-1} (C-H, stretch, aliphatic), 1342 cm^{-1} (in-plane O-H bend) and 1111 cm^{-1} (C-O stretch), which consistently appeared in SD of diacerein.

The FTIR spectra of SD3 and SD9 show the characteristic bands of the drug may be with decreased in intensity and this may be attributed to the dilution factor of the mixture by the carrier. There were no new bands observed in the spectrum, which confirms that no new chemical bonds were formed between the drug and the excipients.

Powder X-ray diffractometry

The diffraction patterns of pure diacerein, binary solid dispersion formula SD3 and ternary solid dispersion formula SD9 are shown in figure 5 (X- Ray Diffractograms of (A) pure diacerein, (B) binary solid dispersion formula SD3 and (C) ternary solid dispersion formula SD9).

The diffraction patterns of pure diacerein shows sharp peaks indicating the crystalline state of pure diacerein (figure 5A).
The binary solid dispersion formula SD3 and ternary solid dispersion formula SD9 are exhibit characteristics diffraction peaks of diacerein but of reduced intensity indicating decreased drug crystallinity consequently increased the drug solubility (figure 5 B and C).

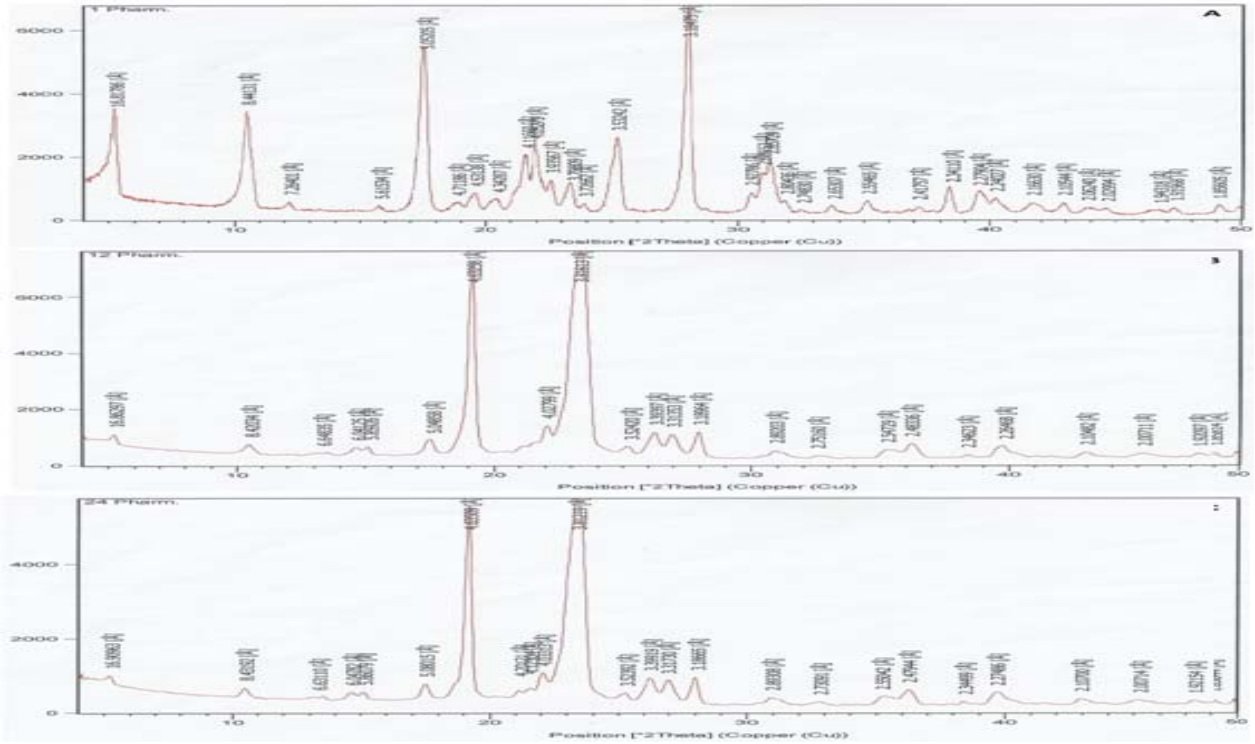

Figure 5: X- Ray Diffractograms of (A) pure diacerein, (B) binary solid dispersion formula SD3 and (C) ternary solid dispersion formula SD9

Scanning electron microscopy

SEM microphotographs of pure diacerein and its binary and ternary solid dispersion formulae are shown in figure 6 (SEM photographs of (A) pure diacerein, (B) binary solid dispersion formula SD3 and (C) ternary solid dispersion formula SD9). Pure diacerein consisted of some large irregular crystals with fine particles. A marked loss of the crystalline and irregular shape was detected in SEM photomicrographs of its binary and ternary solid dispersion formulae. SDs appeared as irregular particles in which the fine particles of the drug deposited on the surface of the polymer. Therefore, the reduced particle size, increased surface area, and the close contact between the hydrophilic carrier and the drug might be responsible for the drug improved dissolution rate as was observed with SD particles.

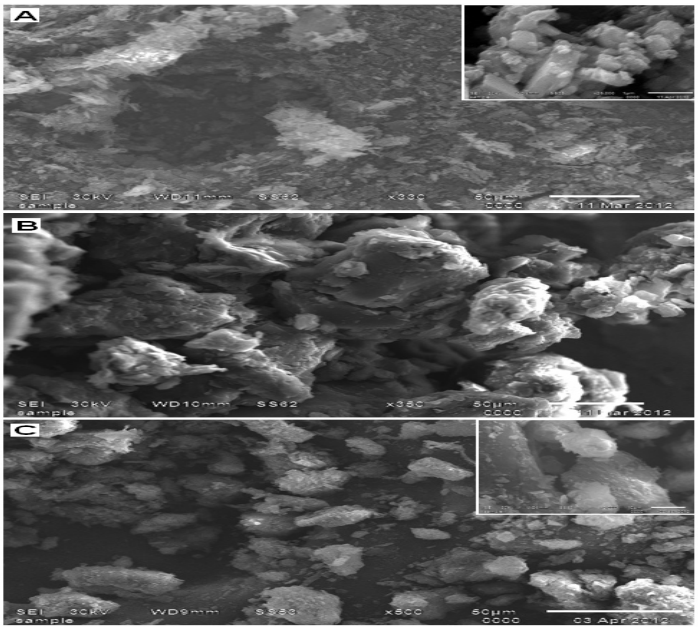

Figure 6: SEM photographs of (A) pure diacerein, (B) binary solid dispersion formula SD3 and (C) ternary solid dispersion formula SD9.

Conclusion

The present investigation revealed that the combination of PEG-4000 and Pluronic F-68 is a proper choice as a carrier to enhance the dissolution of diacerein from SDs. Among the ratios used, a ternary SD with a 1:5:3 (drug: PEG-4000: Pluronic F-68) ratio was found to be optimal because of its superior performance in enhancing the dissolution of diacerein. The physicochemical characterization of solid dispersion shows that there is no chemical interaction between drug and polymers. The XRD pattern revealed that the drug crystallinity decreased in solid dispersion as compared to drug consequently the drug solubility increased. Therefore, it can be concluded that the aqueous solubility of poorly soluble drugs can be significantly improved by utilizing the solid dispersion technique.

Authors' contributions

1) Randa M. Zaki had made substantial contributions to conception and design and in acquisition of data.
2) Adel A. Ali had been involved in design, analysis, interpretation of data and in drafting the manuscript and revising it critically for important intellectual content; and
3) Shahira F. El Menshawi and Ahmed abdel Bary had given final approval of the version to be published.

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