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RESEARCH ARTICLE

Physicochemical characterization and dissolution study of solid dispersions of diacerein with polyethylene glycol 6000

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Abstract

Objective: Diacerein (DCN) is a new anti-inflammatory analgesic and antipyretic drug developed specially for the treatment of osteoarthritis. DCN is a poorly water-soluble drug with relatively low bioavailability. Therefore, the purpose of this study was to enhance the solubility and dissolution of DCN by complexation with polyethylene glycol 6000 (PEG).

Methods: Solid dispersions (SDs) of DCN were prepared in weight ratios of 60:40, 40:60, 20:80, and 5:95 by the melting method using PEG as carrier. These SDs were characterized by differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), and Fourier transform infrared (FTIR) spectroscopy to ascertain whether there were any physicochemical interactions between drug and carrier that could affect dissolution. Solubility and dissolution studies were conducted with pure DCN, physical mixtures (PMs) and SDs.

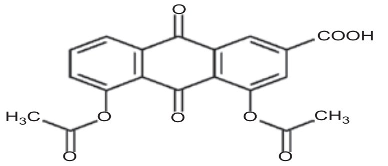
Results and discussion: Solubility studies indicated that PEG significantly increased the solubility of DCN in water. The Gibbs free energy (ΔG_{tr}°) values were negative, indicating the spontaneous nature of DCN solubilization. Phase solubility studies indicated complex with a possible stoichiometry of 1:1.

Conclusion: FTIR, DSC and PXRD studies indicate that there is no chemical interaction between DCN and PEG in solid state. In contrast to slow dissolution rate of pure DCN, the dispersion of drug in PEG considerably enhanced the dissolution rate. Even PMs of DCN prepared with PEG also showed better dissolution profiles compared with that of DCN, indicating the solubilization effect of PEG. Therefore, it is concluded that the preparation of SDs of DCN with PEG provides a promising way to increase its solubility and dissolution rate.

Keywords: Diacerein, polyethylene glycol, solid dispersion, solubility, dissolution

Introduction

Diacerein (DCN), chemically, 4,5-diacetoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid, is a chondroprotective agent used for the treatment of osteoarthritis (Oneil et al., 2006; Toegel et al., 2007). DCN is the di-acetylated derivative of rhein, a molecule with an anthraquinone ring, which is actually the active metabolite of DCN (Nicolas et al., 1998).



Chemical Structure of diacerein (DCN)

DCN is a poorly water-soluble drug with relatively low bioavailability. The poor solubility and wettability of DCN give rise to difficulties in pharmaceutical formulation meant for oral or parental use, which may lead to variation in bioavailability. To overcome these difficulties, increasing the aqueous solubility of DCN is an important goal. Because there is no report on the preparation and evaluation of DCN and polyethylene glycol (PEG) solid dispersions (SDs), in this investigation, SDs of DCN were prepared with PEG with the aim to improve its pharmaceutical properties (i.e. aqueous solubility and dissolution properties).

The poor dissolution characteristic of relatively insoluble drugs has long been a problem to the pharmaceutical industry, and it still remains so because the dissolution rate could be the rate-limiting process in the

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absorption of a drug from a solid dosage form. The solubility of a poorly water-soluble drug can be altered in many ways, such as (a) reducing particle size to increase the surface area; (b) using water-soluble carriers to form inclusion complexes; (c) solubilization in surfactant systems; (d) using pro-drugs and drug derivatization; (e) modification of drug crystal forms, and (f) addition of cosolvents. SD is one of such methods, and it involves a dispersion of one or more active ingredients in an inert carrier or matrix in solid state prepared by melting, dissolution in solvent or melting-solvent method (Leuner and Dressman, 2000). SD technique has been used to enhance the dissolution rate and bioavailability of poorly soluble drugs (Sekiguchi and Obi, 1961; Goldberg et al., 1965; Chiou and Regelman, 1971; Chen et al., 2004).

Among the carriers used in the formation of SDs, PEG is the most commonly used. It shows excellent water solubility and varies significantly in molecular weight, ranging from 200 to >300,000. PEG is often used as vehicle because of its low toxicity, low melting point, rapid solidification rate, high aqueous solubility, availability in various molecular weights, economic cost, and physiological tolerance. A particular advantage of PEGs for the formation of SDs is that they have good solubility in many organic solvents. The melting point of PEG is low in all cases, which is advantageous for manufacturing SDs. Additional attractive features of PEGs include their ability to solubilize some compounds and improve compound wettability. These and other properties make PEG a suitable vehicle in the formulation of dosage forms (Franco et al., 2001; Teresa et al., 2002; Susumu et al., 2005; Moreshwar et al., 2009). Therefore, in this study, PEG was chosen as a suitable polymer for the preparation of SDs.

Many methods are available for determining the physical nature of a SD. SDs can be characterized in the solid state by Fourier transform infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), powder X-ray diffraction (PXRD), etc.

The increase in dissolution rate for SDs can be attributed to a number of factors, which include reduction in particle size, absence of aggregation or agglomeration of fine crystallites of the drug, possible solubilization effect of the polymer, excellent wettability and dispersibility of the drug from SD and partial conversion of the drug into amorphous form (Moreshwar et al., 2009).

In this work, DCN-PEG SDs were studied with the objective of improving the dissolution rate of DCN. Fusion method was used to obtain SDs of DCN with PEG in different weight ratio. The drug–carrier interactions in the liquid and solid states were studied by using phase solubility analysis, dissolution studies, PXRD, FTIR, and DSC.

Materials and methods

Materials

DCN was supplied by Haustus Biotech Pvt. Ltd. (Himachal Pradesh, India), and PEG 6000 was purchased from S.D. Fine Chem. Ltd. (Mumbai, India). Triple distilled water was used throughout the experiments. All other chemicals were of reagent grade and used without further purification.

Preparation of SDs and physical mixtures

DCN:PEG SDs were prepared in the weight ratios 60:40 (SD1), 40:60 (SD2), 20:80 (SD3), and 5:95 (SD4) of DCN:PEG by fusion method. DCN and PEG in the required ratios were homogeneously mixed and fused in a porcelain dish over a calibrated hot plate (75–80°C). The fused mass was solidified immediately in a freezing mixture of ice and sodium chloride under constant stirring. The mass was pulverized and sifted through 100-mesh sieve and stored in a desiccator over fused calcium chloride.

DCN:PEG physical mixtures (PMs) were prepared in the ratios 60:40 (PM1), 40:60 (PM2), 20:80 (PM3), and 5:95 (PM4) of DCN:PEG by homogeneously mixing the ingredients and sifted through 100-mesh sieve.

Content uniformity analysis

Drug content of the SDs and PMs were evaluated (in methanol) spectrophotometrically (Perkin Elmer, New Delhi, India) at 258 nm. The absorbance was recorded against a blank solution of an equivalent amount of PEG in methanol.

Saturation solubility and phase solubility studies

Weighed amounts of DCN (pure drug), SDs, and PMs, each sample equivalent to 200 mg of drug, were separately introduced into 25-mL stoppered conical flasks containing 10 mL of distilled water. The sealed flasks were shaken on a water bath shaker for 72 h at 37°C. An aliquot was passed through 0.2-μm filter (Millipore, Bangalore, India), and the filtrate was suitably diluted and analyzed on a UV spectrophotometer (Perkin Elmer) at 258 nm. The samples were studied in triplicate for saturation solubility; the objective was to study the effect of PEG on the aqueous solubility of DCN.

The phase solubility studies were conducted as per the method reported by Higuchi and Connors (1965). Excess DCN was added separately into 25-mL stoppered conical flasks containing 10 mL of aqueous solution (4.2–25 mM) of PEG. The flasks were sealed and shaken on a water bath shaker at 37°C for 72 h. An aliquot was filtered through a membrane filter (0.2 μm, Millipore), and filtrate was suitably diluted and analyzed at 258 nm. All the data are the average of three determinations. The stability constant (K) was calculated from the plot of concentration of PEG vs. concentration of DCN.

Solubilization efficiency

The ratio of the solubility obtained with PMs or SDs to the intrinsic solubility (S_{int}) of the pure drug was calculated. These ratios were used to compare the relative solubilization efficiency of SDs with that of the PMs.

Dissolution of SDs and PMs

In vitro dissolution tests of the pure drug, powdered SDs, and PMs (equivalent to 0.1 g DCN) were performed in triplicate, using the dissolution apparatus (Electrolab, Mumbai, India) type II paddle method at 37 ± 0.5°C for 2 h, with a stirring rate of 50 rpm, in 900 mL of a dissolution medium of enzyme-free simulated intestinal fluid (pH 6.8 ± 0.1). Dissolution samples were collected at 5, 10, 15, 20, 30, 45, 60, and 120 min, with replacement of an equal volume of temperature-equilibrated dissolution medium. The samples were filtered through a 0.2-µm membrane filter, and the concentration of the drug was determined by UV spectrophotometry at 258 nm by taking equivalent PEG solution in temperature-equilibrated dissolution medium as blank. All samples were analyzed in triplicate, and release curves were plotted using calculated mean values of cumulative drug release.

Release profile comparison

The release profiles were compared with each other by calculating dissolution efficiencies (DEs) after 15, 30, and 60 min. Mean dissolution time ($MDT_{50\%}$) values were also calculated to compare the extent of improvement in the dissolution rate of DCN from different SDs and PMs. MDT reflects the time for the drug to dissolve and is the first statistical moment for the cumulative dissolution process that provides an accurate drug release rate (Reppas and Nicolaides, 2000). It is an accurate expression for drug release rate. A higher MDT value indicates a greater drug retarding ability (Vueba et al., 2004).

The obtained dissolution data of all samples were fitted into the equation to get the values of $MDT_{50\%}$.

$$\mathrm{MDT} = \sum_{i=1}^{n} t_{\mathrm{m}} \frac{M_t}{M_\infty}$$

where M_t is the fraction of dose released in time $t_m = (t_i + t_{i-1})/2$,

M_∞ corresponds to the loading dose,

i is the sample number,

n is the number of dissolution sample time, and

t_i is the time at the midpoint between i and i−1

A model-independent mathematical approach proposed by Moore and Flanner (1996) for calculating a similarity factor f_2 was used for comparing dissolution profiles of different samples. The similarity factor f_2 is a measure of similarity in the percentage dissolution between two dissolution curves and is defined using the following equation:

$$f_2 = 50\log\left\{\left[1+\left(\frac{1}{n}\right)\sum_{t=1}^{n} \mathrm{W_t}\left(\mathrm{R_t}-\mathrm{T_t}\right)^2\right]^{-0.5} \times 100\right\}$$

where n is the number of withdrawal points,

R_t is the percentage dissolved of reference at the time point t,

T_t is the percentage dissolved of test at the time point t, and

W_t is optional weight at time t (for the entire study, the value of W_t was assumed to be 1).

A value of 100% for the similarity factor (f_2) suggests that the test and reference profiles are identical. f_2 values between 50 and 100 indicate that the dissolution profiles are similar, whereas lower f_2 values imply an increase in dissimilarity between release profiles (Moore and Flanner, 1996; Patel et al., 2008).

Physical characterization of PMs and SDs

PXRD

The scanning PXRD patterns of DCN and PEG and their SDs and PMs were obtained on a X-ray diffractometer (X'PERT-PRO) under the following conditions: Ni-filtered Cu-Kα radiation; 45 kV voltage: 40 mA current, scan speed 2°/min in terms of 2θ angle. These PXRD were used to characterize the physical state of the drug in the SDs and PMs. Samples were scanned over a range of 2θ values from 5 to 50°, at a scan rate of 2.0°/ min.

DSC

DSC thermograms were recorded on a differential scanning calorimeter (NETZSCH - 204 F1, Phoenix, AZ). Samples were heated at a scanning rate of 10°C/min.

FTIR spectroscopy

A Perkin Elmer FTIR spectrophotometer (Type Spectrum RX 1) was used for the FTIR studies. The samples were ground and prepared as KBr discs (one part of sample to two parts of KBr) for analysis. The scan range was 4000–400 cm^{-1} at an instrument resolution of 2 cm^{-1}.

Results and discussion

Low standard deviation values in percent drug content ensured uniformity of drug content in each sample.

Content uniformity analysis

The contents of DCN in all the PMs and SDs were found to vary from 98.25 to 100.15% of the claimed amount of drug. Therefore, SDs of drug with PEG exhibit good content uniformity and hence can be exploited for the development of a quality formulation.

Interaction between DCN and PEG in SDs and PMs

An indication of the process of transfer of DCN from pure water to aqueous solution of PEG was obtained from the values of Gibbs free energy of transfer ($\Delta G_{tr}°$), and it was calculated using the following equation:

$$\Delta G_{\mathrm{tr}}{}° = -2.303RT\log\left(\frac{\mathrm{S_c}}{\mathrm{S_o}}\right)$$

where S_c/S_o is the ratio of molar solubility of DCN in aqueous solution of polymer to that in pure water

The values of $\Delta G_{tr}°$ are shown in Table 1. The $\Delta G_{tr}°$ values show whether or not the reaction condition is favorable for drug solubilization in the aqueous carrier solution. Negative $\Delta G_{tr}°$ values indicate favorable conditions. $\Delta G_{tr}°$ values were all negative at different PEG concentrations, indicating the spontaneous nature of DCN solubilization, and decreased with an increase in PEG concentration, demonstrating that the reaction became more favorable as the concentration of PEG increased (Patel et al., 2008).

Solubilization efficiency of PEG

The solubility enhancement (S_c/S_o) values obtained from the PMs and SDs for DCN are presented in Table 2. It is clear that PEG is a potent solubility enhancer. It can be seen that the solubility of PMs and SDs increases initially with increase in the concentration of PEG but then the solubility level decreases somewhat (Loftsson et al., 1996; Dabbagh and Taghipour, 2007; Kumar et al., 2008; Patil et al., 2010). At high polymer concentration, this may be due to an increase in the polymer–polymer intermolecular force of interaction, which decreases their ability to form drug complexes. From the results of saturated solubility study shown in Table 2, it was observed that all SDs showed more saturated solubility than their respective PMs.

It can be seen that substantial improvement in the solubility was obtained for SD3. Solubility increase of more than 8-fold was obtained for this SD.

The mechanisms for the solubility enhancement of SDs have been proposed by several investigators. It may be attributed to the reduction in the particle size, decrease in the crystallinity of the drug and/or the presence of drug in the water-soluble carrier in molecular form. The greater solubility of drug from the PM than the pure drug can be attributed to the wetting of hydrophobic surface of DCN due to solubilization of the water-soluble carrier (Ahmed et al., 2010).

Table 1. Gibbs free energy of transfer ($\Delta G_{tr}°$) of DCN from pure water to aqueous solutions of PEG.

Concentration of PEG (moles/L)	$\Delta G_{tr}°$ (J/mole)
0.0042	–1512.30
0.00833	–2217.43
0.0125	–3225.66
0.0166	–3773.91
0.0208	–4205.47
0.025	–4462.26

Complexation constant with PEG from the phase solubility

The solubility of pure DCN in triple distilled water was 0.099 mM. The solubility increased linearly in the presence of PEG (Figure 1), with a slope less than unity suggesting the formation of 1:1 complexes (Ahuja et al., 2007; Singh et al., 2009; Gorajana et al., 2010).

Therefore, assuming 1:1 complex formation between the drug and polymer, the stability constant was calculated from the slope of the plot between molar solubility of drug and concentration of PEG (straight line with R^2 0.9935) using the following equation:

$$K_{st} = \text{slope} / S_o(1 - \text{slope})$$

where S_o is the intrinsic solubility of the drug alone.

It is evident from the data that the solubility of DCN was enhanced significantly by PEG and that the solubility increased in a linear fashion as a function of PEG concentration resulting in A_N type of phase solubility diagram (Higuchi and Conners, 1965). The stability constant K_{st} was calculated to be 196.7 M^{-1}.

Dissolution studies

For comparative analysis of all the formulations, %DE values at two times, representing the early and late phase of dissolution study, were computed. The %DE values in the initial time period of dissolution study (e.g. $\%DE_{5\ min}$) provide comparative information for fast-releasing formulations, whereas $\%DE_{30\ min}$ values furnish relative information about both fast- and slow-

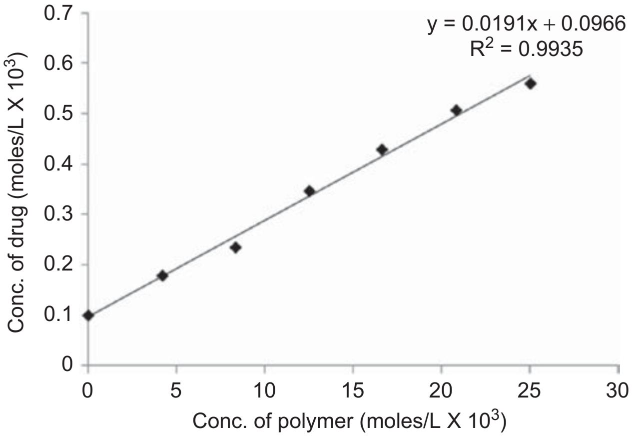

Figure 1. Phase solubility of DCN in aqueous solution of PEG.

Table 2. Solubility enhancements for DCN in PMs and SDs.

Product	Solubility in Water at 37°C (μg/mL)(Mean ± SD)	S_c/S_o (S_o = 36.60 ± 0.977 μg/mL)
PM1	76.32 ± 4.022	2.08
PM2	94.71 ± 1.03	2.59
PM3	125.28 ± 1.95	3.42
PM4	130.57 ± 5.28	3.56
SD1	95.40 ± 1.034	2.60
SD2	136.78 ± 4.045	3.73
SD3	347.70 ± 6.218	9.5
SD4	296.55 ± 4.643	8.10

releasing formulations. $DP_{5\ min}$ (percent drug dissolved in 5 min), $DP_{30\ min}$ (percent drug dissolved in 30 min), $DP_{120\ min}$ (percent drug dissolved in 120 min), $DE_{5\ min}$ (dissolution efficiency in 5 min), $DE_{30\ min}$ (dissolution efficiency in 30 min), $MDT_{50\%}$, and $t_{50\%}$ (time to dissolve 50% drug) values for different samples are reported in Table 3. *In vitro* dissolution profiles of pure DCN and its PMs and SDs with PEG over a period of 2 h are shown in Figure 2.

MDT value is to characterize drug release rate from a dosage form and indicated drug release accelerating efficiency of the polymer (Table 3). A lower value of MDT indicates a higher drug accelerating ability and vice-versa. The obtained values of $MDT_{50\%}$ for all samples are presented in Table 3. The $MDT_{50\%}$ of pure DCN was high (>17.04 min). This value decreased to a greater extent after preparing its SDs and PMs with PEG. SD4 showed the lowest $MDT_{50\%}$ (≈2.48 min).

From data presented in Table 3 and Figure 2, it is evident that the dissolution rate of pure DCN is low ($DP_{5\ min}$, 7.34%; $DP_{30\ min}$, 25.66%; $t_{50\%}$, > 2 h; $\%DE_{5\ min}$, 3.75; $\%DE_{30\ min}$, 13.50). From Table 3 and Figure 2, it is also evident that SDs of DCN with PEG significantly enhanced the dissolution rate of DCN within 2 h compared with PMs and pure drug. The value of $\%DE_{5\ min}$ for pure drug (3.75) was enhanced from miniscule (11.90 for PM4) to high (21.15 for SD4). Similarly, the $\%DE_{30\ min}$ values reveal the lower dissolution improvement with PM4 (29.03) compared with SD4 (37.55) at the same carrier level (95% w/w) (Ahuja et al., 2007).

Analogous to $\%DE_{5\ min}$ values, the value of $RDr_{5\ min}$ is less in PM (3.10) compared with SD (5.32) for the same carrier level (95%). Lower $\%DE_{5\ min}$ and $RDr_{5\ min}$ values observed with the PMs represent slower dissolution in the initial time periods.

This enhancement of dissolution of DCN from drug–carrier systems can be ascribed to several factors. Chaulang et al. (2008), Ford (1986), and Martinez-Oharriz et al. (2002) reviewed the mechanism of dissolution rate improvement from SD. Lack of crystallinity, i.e. amorphization, increased wettability and dispersibility and particle size reduction considered to be important factors for dissolution rate enhancement. In PMs, dry mixing of drug with a hydrophilic carrier results in increase in wetting and increased surface available for dissolution by reducing interfacial tension between hydrophobic drug

Table 3. Different dissolution parameters of pure DCN and its PMs and SDs.

	Dissolution Parameters							
Formulation	DP_{5min} (Mean ± SD)	DP_{30min} (Mean ± SD)	DP_{120min} (Mean ± SD)	$\%DE_{5min}$	$\%DE_{30min}$	$t_{50\%}$ (min)	$MDT_{50\%}$	RDr_5
DCN	7.34 ± 0.21	25.66 ± 0.41	46.09 ± 0.48	3.75	13.50	>120	>17.04	—
PM1	10.34 ± 0.01	35.44 ± 1.25	55.62 ± 1.89	5.30	19.04	≈90	≈13.02	1.40
PM2	13.97 ± 0.27	44.68 ± 2.28	59.22 ± 3.05	7.20	24.56	≈60	≈8.41	1.90
PM3	17.32 ± 0.17	50.67 ± 3.33	73.29 ± 3.57	8.97	28.34	≈30	≈4.98	2.36
PM4	22.76 ± 1.04	51.73 ± 3.93	66.34 ± 2.83	11.90	29.03	20–30	≈4.20	3.10
SD1	17.28 ± 0.12	43.26 ± 3.13	66.41 ± 11.17	8.95	23.70	≈45	≈7.12	2.35
SD2	21.61 ± 0.96	54.84 ± 6.21	73.64 ± 8.08	11.28	31.11	20–30	≈5.3	2.94
SD3	35.59 ± 0.62	66.84 ± 3.71	97.43 ± 1.22	19.13	39.51	≈15	≈2.53	4.85
SD4	39.01 ± 3.04	64.15 ± 4.76	86.47 ± 3.76	21.15	37.55	10–15	≈2.48	5.32

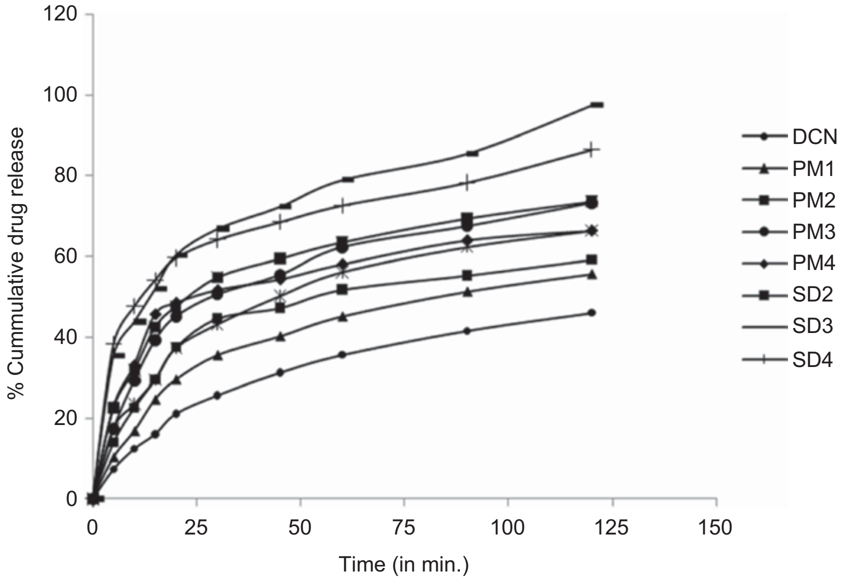

Figure 2. Dissolution profile of physical mixtures and solid dispersions of DCN.

and dissolution media. During dissolution studies, it is noted that drug–carrier PMs sink immediately to the bottom of dissolution vessel as SDs do, whereas pure drug keeps floating on the surface for a longer time interval (Van den Mooter et al., 1998). The increased dissolution rate observed in this case may thus be contributed by several factors, such as solubilization effect, conversion to amorphous state, and improved wettability of DCN, which is supported by DSC and X-ray diffraction (XRD) study.

Comparisons between the release profiles of DCN from different samples were made by similarity factor f_2. Calculated f_2 values are presented in Table 4. From this table, it is evident that the release profile of DCN from all samples (i.e. SDs and PMs) with reference to pure drug was dissimilar (Moore and Flanner, 1996). The release profiles of DCN from SDs and PMs having same percent drug were also dissimilar.

PXRD studies

PXRD was performed to elucidate the physical structure of the drug in the SD formulation. The PXRD patterns of pure DCN, PEG, PMs, and the SDs are shown in Figure 3. The powder X-ray diffractogram of pure DCN powder from 5 to 50° 2θ (Figure 3A) showed numerous distinctive peaks at 2θ degree of 5.18, 10.51, 17.35, 21.06, 21.44, 21.90, 25.06, 27.88, 30.85, and 31.21 that indicated a high crystallinity. PEG also exhibited crystallinity, as indicated by distinctive peaks at 2θ degree of 19.25, 23.05, 23.38, and 23.67 (Figure 3B). The PXRD patterns of DCN SDs in PEG, containing varying concentrations of DCN (Figure 3), showed the characteristic peaks of both PEG and DCN, but the height of the characteristic peaks of DCN gradually decreased with decreasing DCN concentration. Furthermore, no new peaks could be observed, suggesting the absence of any chemical interaction between the drug and the carrier. The height of the characteristic peaks of DCN was remarkably reduced in case of SD4. This indicates that DCN at low concentrations may have converted to a metastable amorphous form or may have dissolved in the matrix system to form a solid solution, or may exist in a microcrystalline form in the matrix system.

These PXRD patterns obtained were compared with those of PMs containing the same proportions of DCN. All the principal peaks from PEG and DCN were present in their PMs and SDs, although with lower intensity. From these observations, we can deduce that the crystalline nature of the drug was still maintained, but the relative reduction of diffraction intensity of DCN peaks in PEG suggests that the quality of the crystals was remarkably reduced. The peaks present were also shifted from their position in the PMs and SDs. However, in SDs, these peaks were seen with remarkably decreased intensity compared with the corresponding PMs. Relative reduction of diffraction intensity and shifting of peaks in SDs *vis-a`-vis* PMs suggests the presence of some physical interaction between the drug and the carrier. However, the positions of various peaks in the PMs and SDs were the same and superimposable, which again rules out the possibility of well-defined chemical interaction and new compound formation between these two components. Similar behaviour was shown by SDs of nifedipine in Pluronic F68 and Gelucire 50/13 1:1 ratio (Vippagunta et al., 2002), UC-781 in PEG 6000 (Damian et al., 2000), and etoricoxib in PEG (Suhagia et al., 2006).

FTIR spectroscopy

FTIR spectroscopy was used to further characterize possible interactions between the drug and the carrier in the solid state.

The spectrum of DCN showed one characteristic broad OH stretching band of COOH group at 3300–2300 cm^{-1}. Two carbonyl stretching peaks appear as a strong band at 1768 cm^{-1} (ester groups) and 1679 cm^{-1} (keto group merged with acid group) (Figure 4B). The PEG spectrum showed important peaks at 3465 cm^{-1} (a broad band because of OH stretch), at 1110 cm^{-1} (C–O–C stretch) and at 2887 cm^{-1} (CH stretch) (Figure 4A). From the chemical structures, hydrogen bonding could be expected between the hydroxyl group of PEG and carbonyl functions of DCN and hydrogen bonding between hydrogen atom of the COOH of DCN and one of the ion pairs of the oxygen atom in PEG, this could not be demonstrated.

Comparing the spectra of PMs and SDs of DCN with PEG (Figure 4), no difference was shown in the position and trend of the absorption bands. Hence, provided the evidence for the absence of any chemical incompatibility between PEG with DCN under investigation, the spectra can be simply regarded as the superposition of those of DCN and PEG. The incorporation of DCN into PEG did not modify their peaks positions and trends. These results

Table 4. Similarity factor (f_2) for the release profile of DCN from SDs and PMs with PEG.

Sample	DIC	PM1	PM2	PM3	PM4	SD1	SD2	SD3	SD4
DIC	—	59.05	42.20	31.72	31.52	38.42	29.42	19.88	21.55
PM1	—	—	60.27	41.29	40.59	52.55	37.78	24.83	26.86
PM2	—	—	—	51.54	50.63	69.22	46.51	29.09	31.67
PM3	—	—	—	—	66.98	58.94	73.96	38.20	41.50
PM4	—	—	—	—	—	54.15	68.00	37.38	42.28
SD1	—	—	—	—	—	—	51.86	31.74	34.27
SD2	—	—	—	—	—	—	—	41.67	46.18
SD3	—	—	—	—	—	—	—	—	63.10

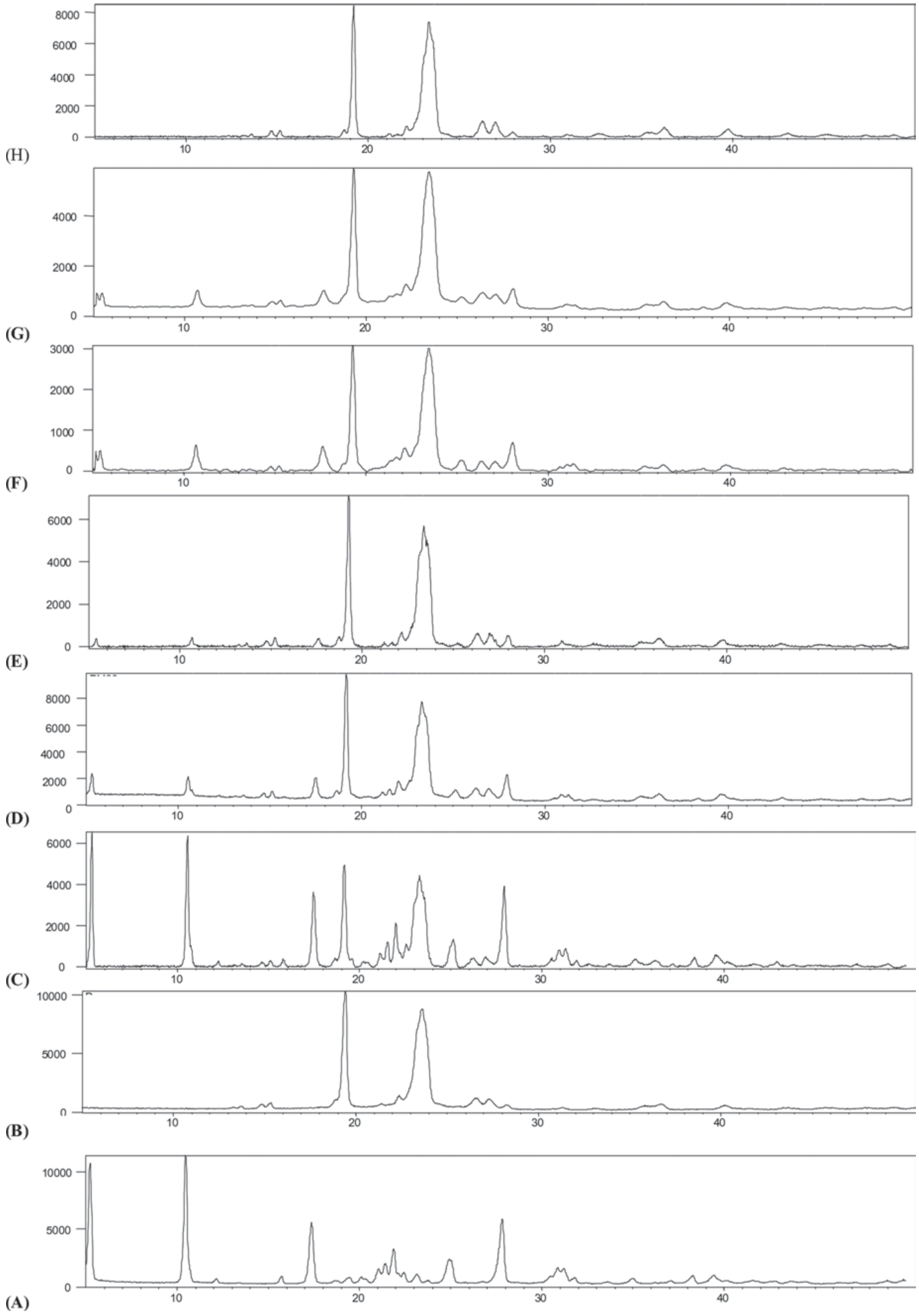

Figure 3. Powder X-ray diffractograms of DCN (A), PEG (B), PM1 (C), PM3 (D), PM4 (E), SD1 (F), SD3 (G), and SD4 (H).

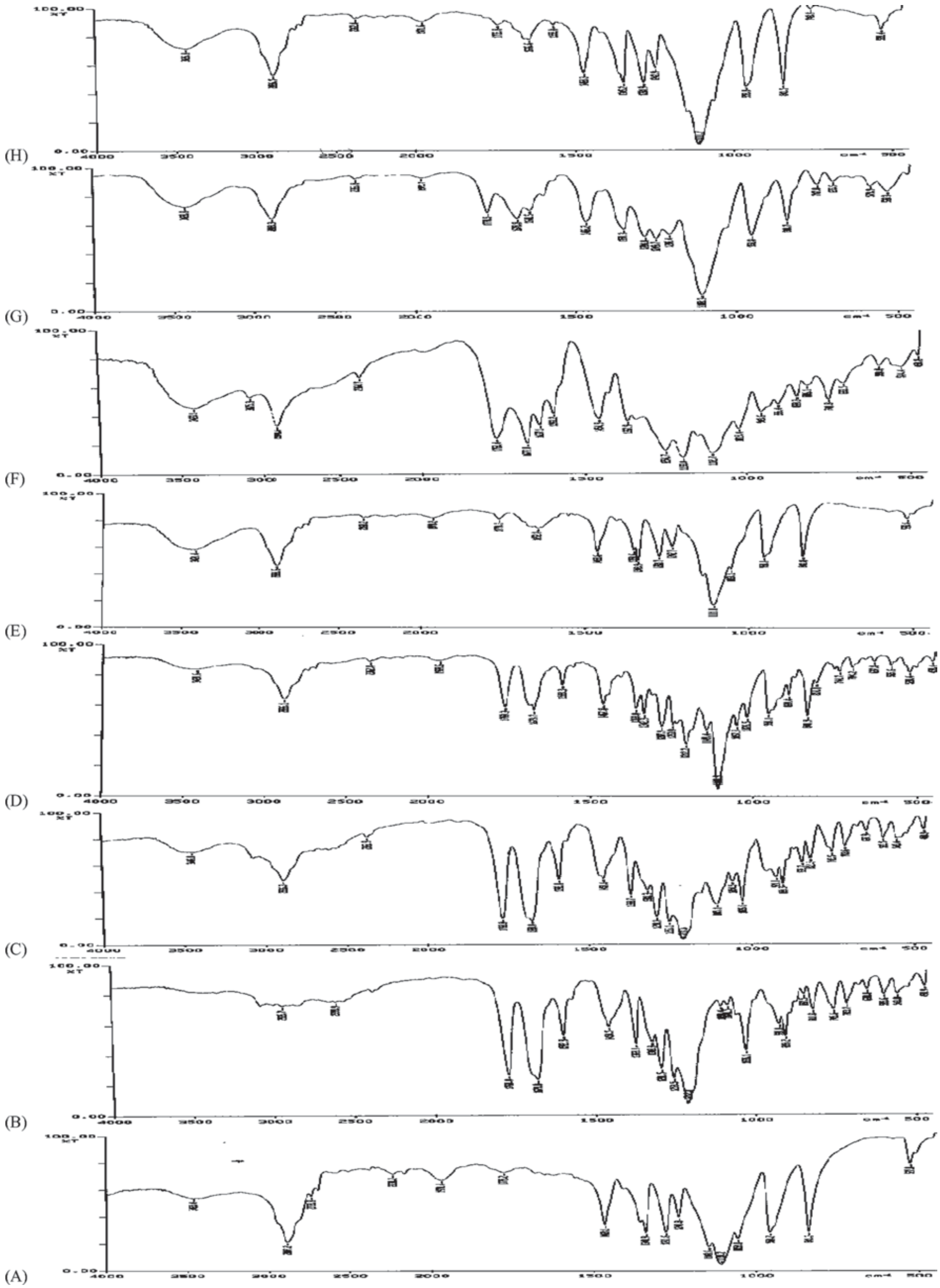

Figure 4. FTIR spectra of PEG (A), DCN (B), PM1 (C), PM3 (D), PM4 (E), SD1 (F), SD3 (G), and SD4 (H).

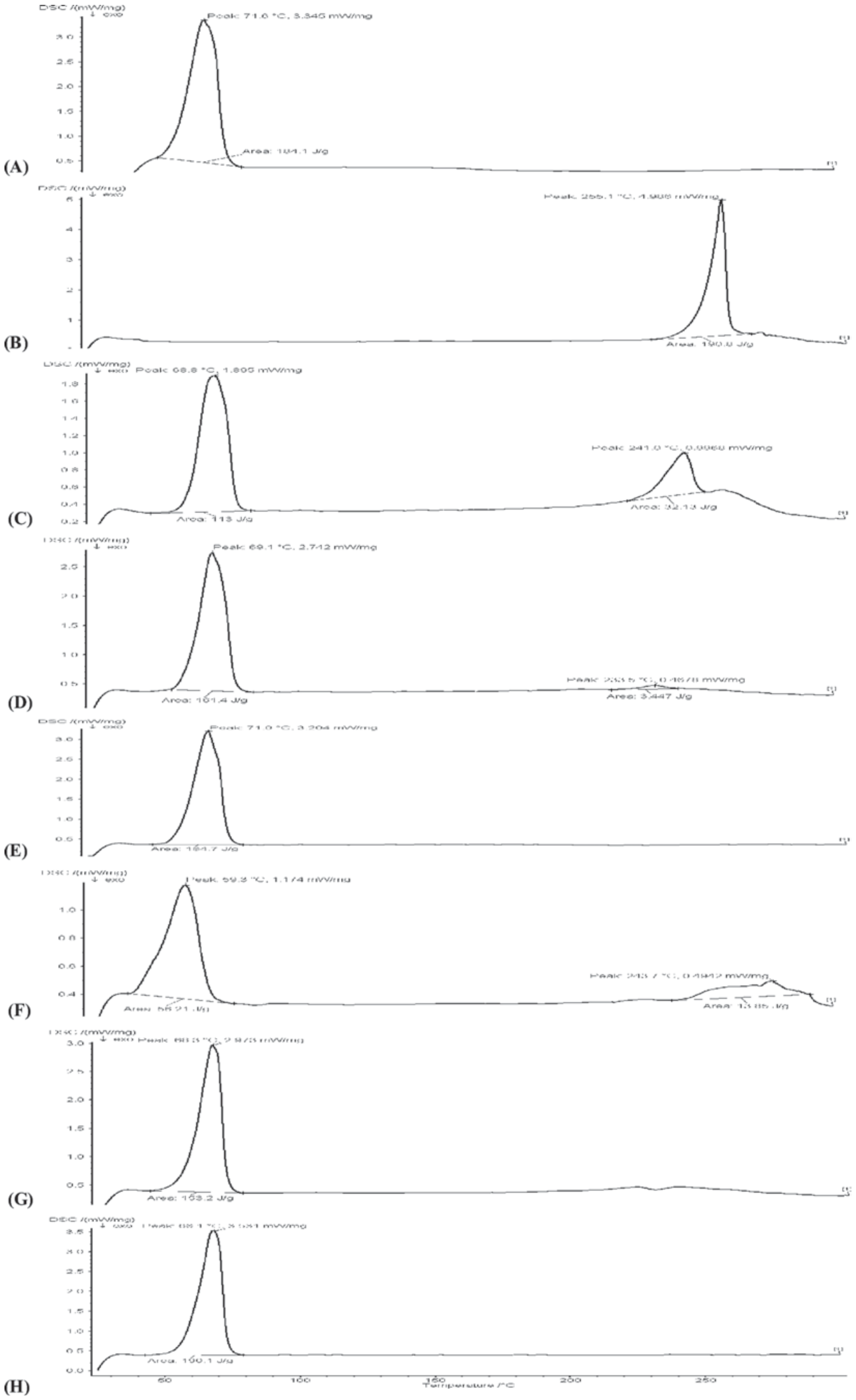

Figure 5. DSC thermograms of PEG (A), DCN (B), PM1 (C), PM3 (D), PM4 (E), SD1 (F), SD3 (G), and SD4 (H).

further indicate the absence of a well-defined interaction between DCN and PEG as already confirmed from the x-ray diffraction study (Loftsson et al., 1996; Valizadeh et al., 2004).

DSC

The DSC thermograms for pure DCN and PEG and their PMs and SDs are shown in Figure 5. DCN showed a melting peak at 255°C with an enthalpy of fusion (ΔH) of 190.8 J/g. The DSC scan of PEG showed a single sharp endotherm at 71°C because of its melting with an enthalpy of fusion (ΔH) of 184.1 J/g. DSC thermograms of all the PMs and SDs (Figure 5), except PM4 and SD4, showed the melting peak of both the drug and the PEG with a depression in the melting point of DCN.

In PM4 and SD4 samples, the thermopeaks suggested that the drug is completely soluble in the liquid phase with PEG 6000. This indicates that DCN is no longer present as a crystalline material when its concentration does not exceed 5% w/w, but it is converted into the amorphous state (Van den Mooter et al., 1998), which was also confirmed by XRD results. As the proportion of DCN was increased, the endothermic peak corresponding to the drug started to appear and gradually shifted toward the melting of pure drug. The characteristic features of the DCN peak, e.g. sharpness, were lost, and the peaks were broad. The broadening and disappearance of the endothermic peaks of DCN at a low concentration can probably be due to dissolution of DCN crystals in the PEG melt.

SDs showed almost the same thermal behaviour as their PMs of the same composition, suggesting the absence of a well-defined chemical interaction between DCN and PEG, whereas absence or shifting toward the lower melting temperature of the drug peak in SDs and PMs in DSC study indicates the possibilities of some physical interactions between DCN and PEG. The enthalpy of fusion of DCN decreased depending on the amount of the drug in the composition. The decrease of the enthalpy of fusion of DCN in the presence of PEG was the result of the solubilizing effect of PEG; only that part of the drug which was in excess showed a melting peak. As the concentration of drug was increased, the enthalpy of fusion also increased because there was an excess of solid drug. The incorporation of DCN into PEG resulted in a change in the peak temperature (T_m) of the endotherms displayed by the carrier from 71.6°C (pure PEG) to 68.8°C (40% w/w PEG) in PMs, and in SDs, from 71.6°C (pure PEG) to 59.3°C (40% w/w PEG), indicating that the presence of the drug affects the lattice energy of the crystalline polymer. This result is in agreement with the report of Damian et al. (2000), who observed similar type of behaviour by the PMs and SDs of UC-781 with PEG 6000 in their DSC studies.

Conclusion

Phase solubility studies showed a solubilizing effect by the carrier. The negative free energy variation, which accompanied the DCN dissolution process in PEG aqueous solutions, was found to be due to a favorable negative enthalpy variation. The study clearly shows that addition of PEG to DCN improves its dissolution rate. The results of solid-state studies reveal the absence of any chemical decomposition and of a well-defined chemical interaction between the drug and the carrier, indicating compatibility between PEG and DCN. No hydrogen bonding interaction between PEG and DCN could be detected by FTIR studies. The absence of an endothermic peak of DCN in the DSC thermograms of SDs at low concentration of drug shows the conversion of DCN from a crystalline to an amorphous state. The qualitative PXRD results clearly indicate that DCN is present predominantly in the crystalline state in the polymeric matrix at higher drug concentration, whereas absence of some peaks, shifting of peaks, or decrease in the intensity of the peaks in PXRD at low concentration of drug shows that a large proportion of the drug may have been converted into an amorphous form. Therefore, it can be concluded that the preparation of SDs of DCN with PEG provides a promising way to increase its solubility and dissolution rate by decreasing the crystallinity of the drug in addition to the wetting and solubilizing effect of the carrier.

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Declaration of interest

The authors declared no conflict of interest.

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