Original Article

Improvement in the dissolution profile of diacerein using a surfactant-based solid dispersion technique

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ABSTRACT: In an attempt to improve the dissolution rate of poorly aqueous soluble diacerein (DCN), solid dispersions (SDs) were prepared with a surfactant Pluronic® F 127 (PXMR) at drug to polymer ratios of 1:0.5, 1:1.5, and 1:2.5 (w/w) by an ordinary melting technique. The interaction of DCN with PXMR in all solid binary systems was evaluated by thin layer chromatography (TLC), Fourier transform infrared spectrometry (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) studies. TLC indicated an absence of chemical interaction of DCN with PXMR whereas FTIR studies demonstrated an existence of strong hydrogen bonding between them. A uniform molecular dispersion of DCN was observed in DSC thermograms, and this finding was further supported by loss of the crystalline and irregular shape of DCN detected in SEM photomicrographs. Dissolution studies were promptly conducted to examine the release rate performance of DCN from all binary systems. The drug dissolution properties of binary systems improved significantly in comparison to crystalline DCN. The rate and extent of DCN release were observed to be strongly dependent on the proportion of PXMR present within the formulations.

Keywords: Diacerein, surfactant, Pluronic®, solid dispersion, dissolution profile

1. Introduction

Despite significant advancements in the science of drug delivery, solubilization of poorly aqueous soluble drugs still remains a challenging task for formulation experts in the pharmaceutical industry. The solubility of a drug is a prime determinant of its dissolution and consequently its oral bioavailability (*1,2*). Various formulation techniques have been employed to compensate for the poor aqueous solubility and slow dissolution rate of drugs. These include formulation of an amorphous solid form (*3*), microparticles (*4*), use of surfactants (*5*), inclusion complexation (*6*), and solid dispersion (*7-9*). Among these methods, solid molecular dispersions are one of the most widely used techniques to improve drug dissolution and solubility. The mechanisms of drug solubilization from solid dispersions involve reducing the particle size, increasing the surface area, reducing the crystallinity, and increasing the wettability of the drug with surrounding hydrophilic carriers to improve its dissolution rate (*10*).

In recent years, Pluronic® or poloxamer block copolymers have been used extensively in solid dispersion systems for solubilization of poorly water-soluble drugs (*11-13*). A high hydrophilic-lipophilic balance (HLB) value and low melting point means that they are best suited to a solid dispersion technique using melt granulation (*14*). The current article describes enhanced dissolution of poorly-water soluble diacerein (DCN) using a solid dispersion technique with Pluronic® F 127 (PXMR).

DCN, chemically 4,5-diacetoxy-9,10-dioxo-9,10-dihydroanthracene-2-carboxylic acid (Figure 1), is a non-steroidal anti-inflammatory drug and chondroprotective agent used in the treatment of osteoarthritis (*15,16*). DCN lacks cyclooxygenase inhibitory activity and hence has no effect on prostaglandin synthesis (*17-19*). It is a selective inhibitor of interleukin-1 with a protective

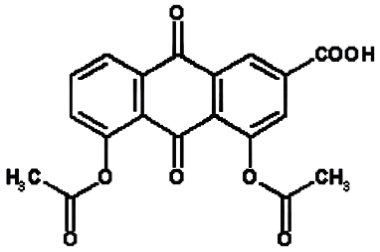

Figure 1. Chemical structure of diacerein.

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effect on granuloma-induced cartilage breakdown by its reduction of the concentration of proinflammatory cytokines (*20*,*21*). However, the poor aqueous solubility (it is practically insoluble) (*22*) and hence limited dissolution of DCN mean that only 35-56% (bioavailability) of the drug reaches the systemic circulation (*23*). Poor bioavailability of a drug often results in a limited therapeutic response. Therefore, the current study sought to improve the dissolution rate of DCN *via* a solid dispersion technique.

The purpose of this work was to investigate the potential of Pluronic® F 127 (PXMR), a surfactant, for use as a solubilizing agent for DCN in solid dispersions. Solid dispersions (SDs) of DCN were prepared at DCN to PXMR ratios of 1:0.5, 1:1.5, and 1:2.5 (w/w) using a melting technique. Thin layer chromatography (TLC), Fourier transformation infrared spectroscopy (FTIR), differential scanning calorimetry (DSC), and scanning electron microscopy (SEM) were used to characterize the solid-state properties of pure DCN and its SD systems. All formulations including pure DCN were further evaluated for their dissolution performance in a phosphate buffer (pH 6.8).

2. Materials and Methods

2.1. *Materials*

DCN was donated by Glenmark Pharmaceuticals Ltd., Mumbai, India. Pluronic® F 127 (PXMR) (Lutrol) was donated by Signet Chem Lab, Mumbai, India. All reagents were of analytical grade. Double-distilled water was used throughout the experiment.

2.2. *Preparation of SDs*

SDs of DCN were prepared by a simple melting method. PXMR was melted at 60°C. DCN was added to the molten polymer, mixed well, and cooled to room temperature to obtain a solid mass. The solidified masses were crushed and passed through a 60-µ mesh sieve. The resulting SDs were stored in desiccators until further analysis.

2.3. *TLC*

TLC analysis was carried out using silica gel GF 254 (0.2 mm) glass plates with a solvent system of benzene: methanol (90:10, v/v) as a mobile phase to study any interaction between the drug and polymer. Spots were visualized by exposure to iodine vapors. The R_f values of pure drug and binary systems were calculated (*24*).

2.4. *FTIR*

FTIR spectra were obtained using a Perkin-Elmer Spectrum-one FTIR spectrometer (Shelton, CT, USA) spectrometer. The samples were prepared in KBr disks. The scanning range was kept from 4,000 to 450 cm^{-1}.

2.5. *DSC*

DSC measurements were carried out on a Mettler DSC 30S (Mettler Toledo, Leicester, UK) differential scanning calorimeter. Samples (5 mg) were placed in an aluminum pan and the experiment was carried out in a nitrogen atmosphere (flow rate 40 mL/min) at a scanning rate of 10°C/min in the range of 30-300°C.

2.6. *SEM*

Photomicrographs of DCN and its all binary systems were obtained by SEM (JSM-6360; JEOL Ltd., Tokyo, Japan). DCN or its formulations were mounted on double-sided adhesive tape and sputtered with gold. Scanning electron photographs were taken at an accelerating voltage of 15 kV and the micrographs obtained were examined at magnifications of ×50, × 100, ×200, ×500, and ×1,000.

2.7. *Drug content uniformity*

Drug content was determined by dissolving SDs equivalent to 5 mg of DCN in 10 mL of dimethyl formamide (DMF) and then adjusting the volume to 50 mL with distilled water. The solution was filtered through Whatman filter paper No. 41 and suitably diluted. Absorbance was measured at 258 nm using a double beam UV spectrophotometer (Model 1700; Shimadzu, Kyoto, Japan).

2.8. *Dissolution studies*

Dissolution rate studies of pure DCN and binary systems were conducted in 900 mL of phosphate buffer (pH 6.8) at 75 rpm maintained at 37 ± 0.5°C in a dissolution apparatus (Model Disso 2000 tablet dissolution test apparatus, LabIndia, Thane, India) using the paddle method. Fifty mg of DCN or an equivalent amount of SDs were added to dissolution medium and the samples were withdrawn at appropriate time intervals. The volume of dissolution medium was adjusted to 900 mL by replacing it with fresh medium. The samples were immediately filtered through a 0.45-µm membrane filter, suitably diluted, and then analyzed spectrophotometrically at 258 nm. The results of dissolution studies were statistically analyzed using ANOVA.

3. Results and Discussion

3.1. *Drug content uniformity*

Percentage drug content of the formulations was found

Table 1. % Drug content and R_f values of diacerein and solid dispersions

System	% Drug content*	R_f values
DCN	---	0.49
SD 1:0.5	96.45 ± 1.05	0.51
SD 1:1.5	97.68 ± 0.86	0.46
SD 1:1.5	98.27 ± 0.65	0.47

* Data are shown as mean ± S.D. (n = 3).
Abbreviations: DCN, diacerein; SD, solid dispersion.

to be in the range of 96.45 ± 1.05 (w/w) to 98.27 ± 0.65 (w/w) for all binary systems (Table 1).

3.2. *TLC*

The TLC study indicated R_f values from 0.46-0.51 for all binary systems, which were almost identical to the R_f value for pure DCN (Table 1). This indicated that there was no chemical interaction between DCN and PXMR.

3.3. *FTIR*

FTIR investigations are mainly carried out to examine a molecular change in the drug due to its interaction with excipients (polymers) (*25,26*).

FTIR spectra of DCN, PXMR, and SDs are shown in Figure 2. The principal absorption peaks of DCN were observed at 3,300 cm^{-1} (O-H, stretch, broad, COOH), 3,069 cm^{-1} (C-H, stretch, aromatic), 2,935 cm^{-1} (C-H, stretch, aliphatic, sym), 1,770 cm^{-1} (C=O, stretch, ester), 1,679 cm^{-1} (C=O, stretch, COOH), 1,693 cm^{-1} (C=O, stretch, ketone), 1,593 cm^{-1} (C=C, stretch, aromatic), 1,450 cm^{-1} (C-O, stretch, COOH), 1,026 cm^{-1} (C-O, stretch, ester), 760 cm^{-1} (m substituted benzene), and 704 cm^{-1} (benzene) (*27*).

The FTIR spectrum of PXMR is characterized by principal absorption peaks at 3,485 cm^{-1} (O-H, stretch, broad), 2,884 cm^{-1} (C-H, stretch, aliphatic), 1,343 cm^{-1} (in-plane O-H bend) and 1,111 cm^{-1} (C-O stretch) (*27*), which consistently appeared in all of the binary systems of DCN.

All SD systems displayed frequency shifts and/or the disappearance of characteristic IR bands of either the drug or polymer, indicating alterations in the drug or polymer environment.

The principal absorption peaks of DCN at 3,300, 3,069, 1,693 and 2,935 cm^{-1} disappeared for all SDs. The peak at 1,770 cm^{-1} (C=O, stretch, ester) shifted to a slightly lower frequency at 1,769 cm^{-1} for all SDs whereas the peak at 1,679 cm^{-1} shifted to a slightly higher frequency at 1,680 cm^{-1} in a 1:1.5 SD. No frequency shift was observed for this peak in 1:0.5 and 1:2.5 SDs. The peak of PXMR at 3,485 cm^{-1} shifted to a lower frequency at 3,445, 3,447, and 3,433 cm^{-1} in 1:0.5, 1:1.5, and 1:2.5 SDs, respectively, revealing its involvement in hydrogen bonding with oxygen in the drug (*28*). The peak of PXMR at 2,884 cm^{-1} also shifted to 2,873, 2,886, and 2,872 cm^{-1} in 1:0.5, 1:1.5, and 1:2.5 SDs, respectively, indicating strong physical interaction between the polymer and drug. None of the binary systems of DCN-PXMR showed any new peaks, indicating the absence of chemical bond formation in those binary systems (*29*).

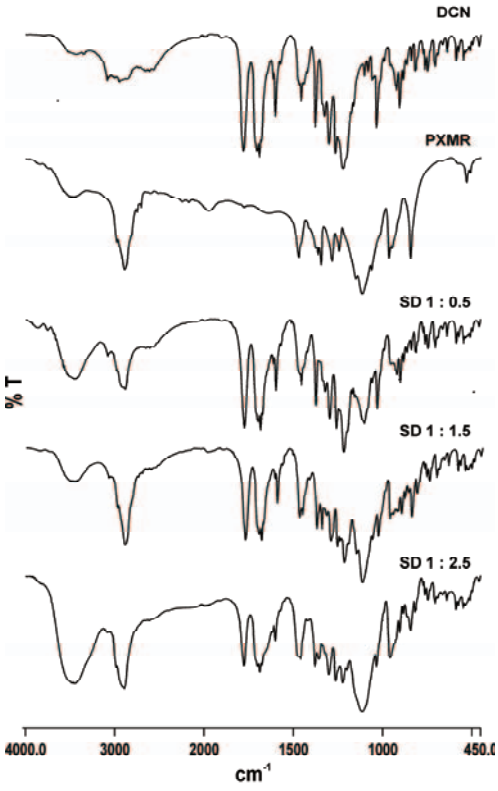

Figure 2. FTIR spectra of diacerein and all its binary systems with Pluronic® F 127. DCN, diacerein; PXMR, Pluronic® F 127; SD, solid dispersion.

3.4. *DSC*

DSC thermograms of DCN and its corresponding binary systems with PXMR are shown in Figure 3. As shown in the figure, DCN displayed a sharp endothermic T_{max} of 256.14°C, corresponding to the melting point of the crystalline form of DCN. In contrast, PXMR showed a sharp endotherm at 57.40°C, indicating the melting point of the polymer, followed by a broad exotherm at 249.39 °C, indicating recrystallization or transfer of heat (energy) to surrounding molecules gained in the melting process.

A very broad endotherm 246.51°C was observed in the DSC thermogram of 1:0.5 SD, indicating the presence of some traces of crystalline DCN. A significant reduction in the intensity of the sharp peak of DCN was noted in 1:1.5 (240.30°C) and 1:2.5 (234.85°C) SDs. With dispersions, peak temperatures shifted to lower temperatures than with the drug alone, indicating a loss of the characteristic features of DCN peaks in these dispersions (*30,31*). This phenomenon might be attributed to complete molecular dispersion

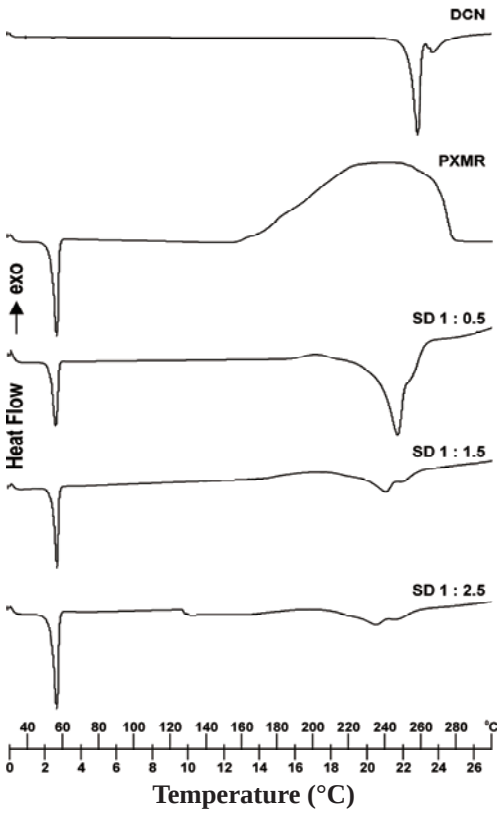

Figure 3. DSC thermograms of diacerein, Pluronic® F 127, and solid dispersions. DCN, diacerein; PXMR, Pluronic® F 127; SD, solid dispersion.

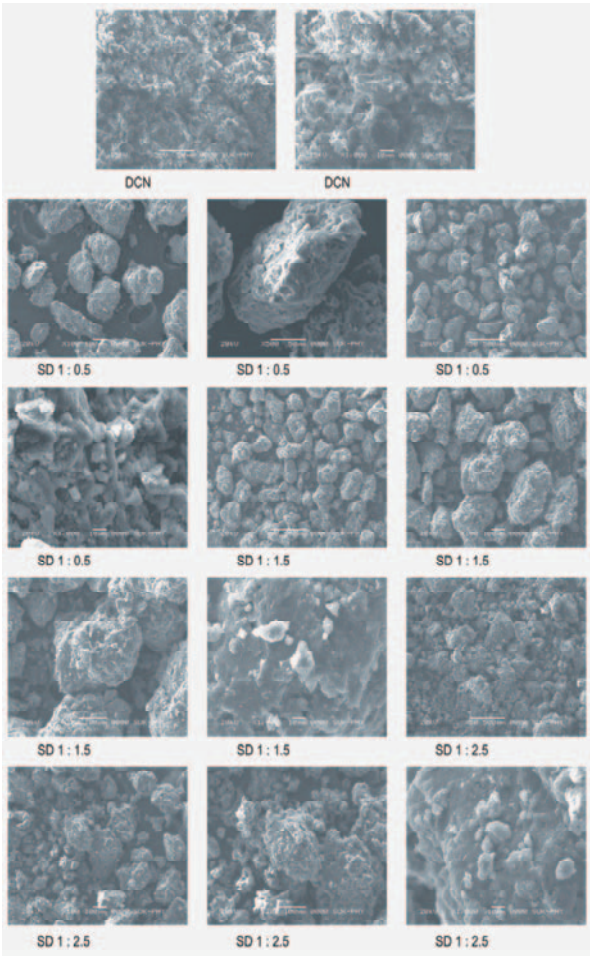

Figure 4. Scanning electron microphotographs of diacerein and solid dispersion particles. DCN, diacerein; SD, solid dispersion.

and possibly indicate the presence of an amorphous DCN in these binary systems (*32-35*). In all of the formulations, a decreased melting point peak for DCN was observed, and this might be attributed to solid-solid phase transition or the transfer of heat energy (from polymer to drug molecules) released after initial melting of the polymer. The peak for the polymer in all of the binary systems consistently appeared in the range of 55.65-56.75°C, which indicated the absence of any chemical interaction between the drug and polymer during the thermal process.

3.5. *SEM*

SEM microphotographs of pure DCN and its SDs are shown in Figure 4. Pure DCN consisted of some large irregular crystals with fine particles. A marked loss of the crystalline and irregular shape was detected in SEM photomicrographs of SDs as smooth patches of polymer covered the surface of the drug. SDs appeared as irregular particles in which the original morphological features of both the drug and polymer disappeared and tiny aggregates of amorphous pieces of irregular size were present (*35*). 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's improved dissolution rate as was observed with SD particles (*36*,*37*).

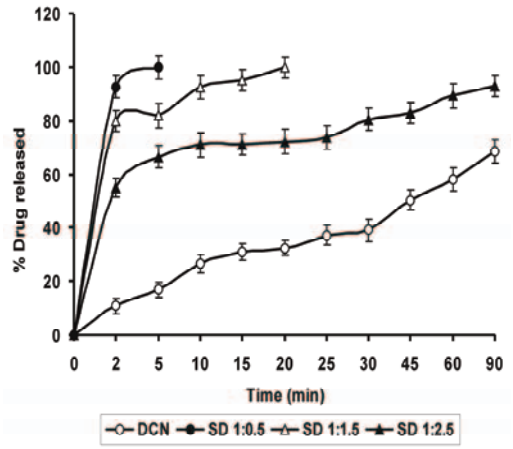

Figure 5. Dissolution curves of diacerein alone and all its solid binary systems. DCN, diacerein; SD, solid dispersion.

3.6. *Dissolution rate studies*

The dissolution curves of DCN alone and SDs in phosphate buffer (pH 6.8) are shown in Figure 5. The release rate profiles are expressed as the percentage of drug released over (*vs.*) time. All binary systems have an improved rate of DCN dissolution. Table 2 shows

Table 2. Dissolution profile of diacerein and its solid binary systems with Pluronic® F 127 in phosphate buffer (pH 6.8) at 37 ± 0.5°C

System	DP_2*	DP_5	DP_{15}*	DP_{90}*	DE_5*
DCN	10.8 ± 2.7	16.9 ± 2.9	31.1 ± 3.1	68.6 ± 4.3	10.5 ± 2.2
1:0.5 SD	92.7 ± 4.2	100.0 ± 4.4	–	–	77.4 ± 3.4**
1:1.5 SD	79.8 ± 3.9	81.9 ± 4.6	95.1 ± 4.8	–	64.5 ± 3.3**
1:2.5 SD	55.1 ± 3.5	66.4 ± 4.1	71.2 ± 3.9	93.0 ± 4.0	47.5 ± 3.0**

* Data are shown as mean ± S.D. (n = 3). ** Significant difference compared to pure DCN ($p < 0.001$), *i.e.*, significant.
Abbreviations: DCN, diacerein; SD, solid dispersion; DP, % drug dissolved; DE, dissolution efficiency.

the % drug dissolved at 2 min (DP_2), 5 min (DP_5), 15 min (DP_{15}), and 90 min (DP_{90}) for all formulations. The dissolution efficiency values (DE_5) at 5 min were statistically analyzed using ANOVA. The results obtained revealed that all binary systems of DCN with PXMR have faster dissolution than DCN alone. The increase in the dissolution rate of DCN was 8.6-, 7.4-, and 5.1-fold greater from 1:0.5, 1:1.5, and 1:2.5 SDs, respectively, within the same period of time.

Statistical analysis (ANOVA) of DE_5 values of DCN and its formulations revealed a significant difference between the dissolution profile of pure DCN and all its binary systems with PXMR ($p < 0.001$). The 1:0.5 ratio of DCN:PXMR SD had the greatest dissolution of DCN among all the binary systems evaluated, indicating almost complete release of the drug from the SD (DP_5: 100.0 ± 4.4). An SD with a 1:1.5 ratio of DCN:PXMR had complete release of the drug within 20 min (DP_{20}: 100.0 ± 3.9). However, the release of the pure drug was incomplete even at 90 min. Of note is the fact that the extent of enhanced dissolution depended on the concentration of the polymer used in the SD, a finding that was evidenced by retardation of drug release from 1:1.5 and 1:2.5 SDs. This might be because of altered rheological characteristics and gelling properties of PXMR at higher concentrations (*38*). Results indicated that the polymer's surfactant properties, and not the amorphization or reduction in crystallinity of DCN in SDs, played greater role in enhancing the dissolution of DCN. Therefore, a 1:0.5 ratio of SD was found to be optimal for enhancing the dissolution of DCN.

The rapid dissolution of DCN from SDs was attributed to a reduction in the crystallinity of the drug due to its colloidal dispersion in a polymer matrix. As a hydrophilic carrier dissolves, an insoluble drug is exposed to dissolution medium in the form of very fine particles, leading to rapid dissolution (*39,40*). PXMR copolymers exist in solution as unimers but self-assemble into micelles. At concentrations above the CMC, the hydrophobic propylene oxide (PO) core can incorporate water-insoluble molecules, resulting in increased solubility of the drug molecule. In addition, the greater hydrophilicity and surface properties of PXMR and increased wettability, dispersibility, and reduced particle size of the drug might contribute to the enhanced dissolution of DCN (*29,41*). Further, reports have indicated that the solubility of poorly water-soluble indomethacin (*11*) and insulin (*42-44*) has been significantly improved with PXMR. The aqueous solubility of piroxicam was enhanced 11-fold by PXMR in an SD (*12*). The faster and complete dissolution of nifedipine has been achieved from SDs incorporating PXMR (*45*). Nifedipine is also reportedly converted to an amorphous form in crystalline PXMR, enhancing its dissolution (*36*). Thus, the results obtained here were in full agreement with those already reported. In conclusion, the greater hydrophilicity and surfactant properties of PXMR result in a reduction in interfacial tension between the hydrophobic drug and dissolution medium, leading to greater wetting of the drug and surface availability for rapid dissolution.

4. Conclusion

The present investigation revealed that PXMR (Pluronic® F 127) is a proper choice as a carrier to enhance the dissolution of DCN from SDs. Among the ratios used, an SD with a 1:0.5 ratio was found to be optimal because of its superior performance in enhancing the dissolution of DCN. In contrast, higher concentrations of PXMR in SDs retarded the release of the drug. This indicated that an increase in the weight fraction of polymer did not offer any advantage in terms of enhancing dissolution. These results led to the conclusion that solid oral dosage forms of DCN with PXMR can be formulated with a high dissolution rate, faster onset of action, and improved bioavailability.

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