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EFFECT OF WATER SOLUBLE CARRIER ON DISSOLUTION PROFILES OF DICLOFENAC SODIUM

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Abstract: Pharmaceutical aviailability of diclofenac sodium from solid dispersions of PEG 6000 have been studied in comparison to those of the corresponding physical mixtures and pure diclofenac sodium. The diclofenac sodium is poorly water soluble drug. The properties of diclofenac sodium-PEG 6000 solid dispersions have been determined by the methods of differential scanning calorimetry (DSC), X-ray diffraction and scanning electron microscopy (SEM). The effect of PEG 6000 on the solubility of selected diclofenac sodium dispersions has been studied. The solubility of diclofenac sodium from its solid dispersion has been found to increase in the presence of PEG 6000.

Keywords: solid dispersion, diclofenac sodium, PEG 6000, solubility

Rheumatic diseases have been for a long time an important medical problem. The treatment of these diseases is based to a significant degree on nonsteroidal anti-inflammatory drugs (NSAIDs). From among them sodium diclofenac is known to show one of the strongest anti-inflammatory and pain killing effects. It has also relaxant effect on smooth muscle and reduces the concentration of uric acid in the blood. Its pharmacological activity is related to inhibition of formation of prostaglandins by the influence on the activity of COX-1 and COX-2 enzymes (1, 2).

Physicochemical and pharmacological properties of sodium diclofenac have been studied by many authors. Much attention has been also paid to development of new forms of this drug that would have better bioavailability and reduced side effects. Many studies have been undertaken to improve water solubility of sodium diclofenac as high water solubility is one of the most important features improving pharmaceutical availability of drugs (3-8).

One of the promising strategies has been formation of solid dispersions. Improvement of water solubility of drugs leads to a possibility of getting a desired therapeutic effect for a decreased dose of a drug and to limitation of its undesired side effects.

EXPERIMENTAL

Material

Diclofenac sodium (Sigma), polyethylene glycol 6000 (PEG 6000) (Merck), ethanol 95% (Polmos S.A.)

Measuring equipment

X-ray diffractometer Bruker D8 Advance; differential scanning calorimeter DSC-50 Shimadzu, scanning electron microscopy (SEM) Hitachi S-3000N.

Methods

Solid dispersions preparation

The solid dispersions were obtained by the method of evaporation (solid dispersion I) and melting method (solid dispersion II). The active substance was added to PEG 6000 molten in water bath and the mixture was stirred till solidification or PEG 6000 and diclofenac sodium were dissolved in a small amount of ethanol 95%, the solutions were combined and solvent was evaporated at 70^{o}C. The product was stored for 24 h in a dessicator, then the mass was refined and homogenized by sieving to the mesh size of 0.20 mm. The solid dispersions contained 10 and 30% of the active substance.

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Physical mixtures of diclofenac sodium studied and the support PEG 6000 containing 10, 20, 30 and 40% of the active component were obtained by sieving through the mesh size of 0.20 mm.

Identification of solid dispersions obtained
X-ray diffraction study

The solid dispersions, physical mixtures and pure therapeutically active compounds were subjected to X-ray diffraction study by the powder method, using the monochromatic Cu Kα (λ = 1.5418 Å) radiation with Ni filter (X-ray diffractometer Bruker D8 Advance). The diffraction patterns were recorded in the angular range $2^o < 2\theta < 40^o$.

DSC study

The obtained solid dispersions, physical mixtures and pure therapeutically active substances were analyzed also by the differential scanning calorimetry (DSC). Portions of 2 mg of the substance studied and the standard (Al_2O_3) were placed in the heated head of the DSC apparatus (Shimadzu DSC-50). The measurements were carried out in the range from 20 to 450°C, at the rate of temperature increase 10°C/min in nitrogen atmosphere.

Scanning electron microscopy studies

The surface morphology was examined by scanning electron microscopy (Hitachi S-3000N). Samples were previously sputter-coated with a gold layer.

Determination of the contents of diclofenac sodium in solid dispersion with PEG 6000 by spectrophotometric method

The UV spectra of diclofenac sodium in a water solution, *in substantia* and in the presence of PEG 6000 were recorded in the range 200-400 nm. No

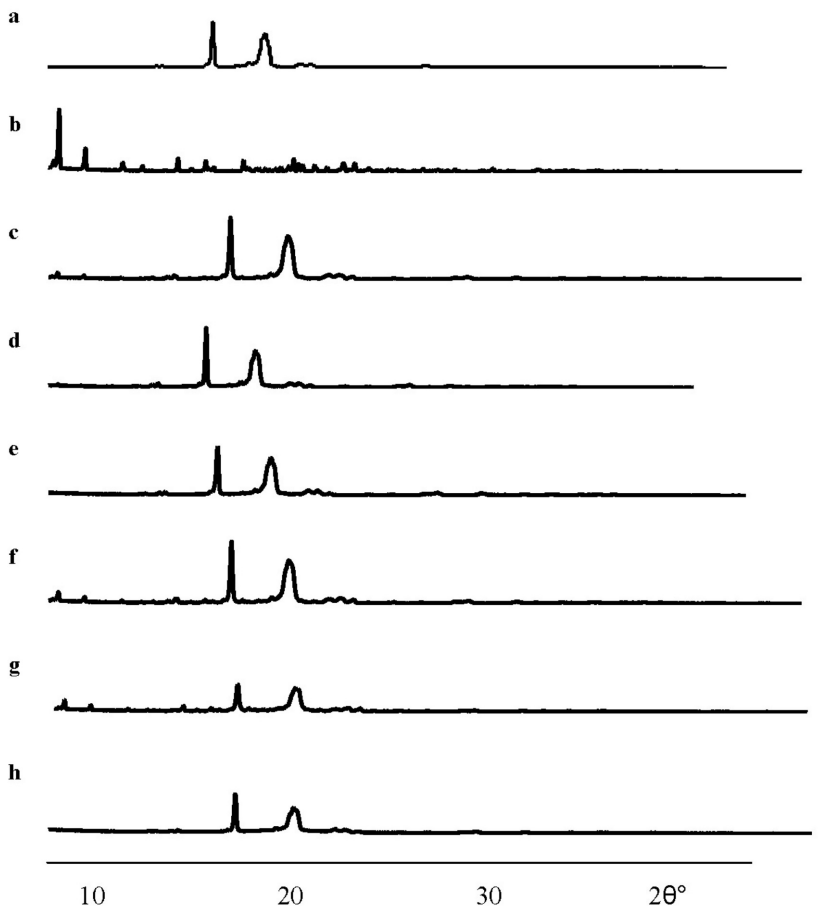

Figure 1. X-ray diffraction patterns. **a**: PEG 6000, **b**: diclofenac sodium, **c**: physical mixture 10%, **d**: 10% solid dispersion I, **e**: 10% solid dispersion II, **f**: physical mixture 30%, **g**: 30% solid dispersion I, **h**: 30% solid dispersion I

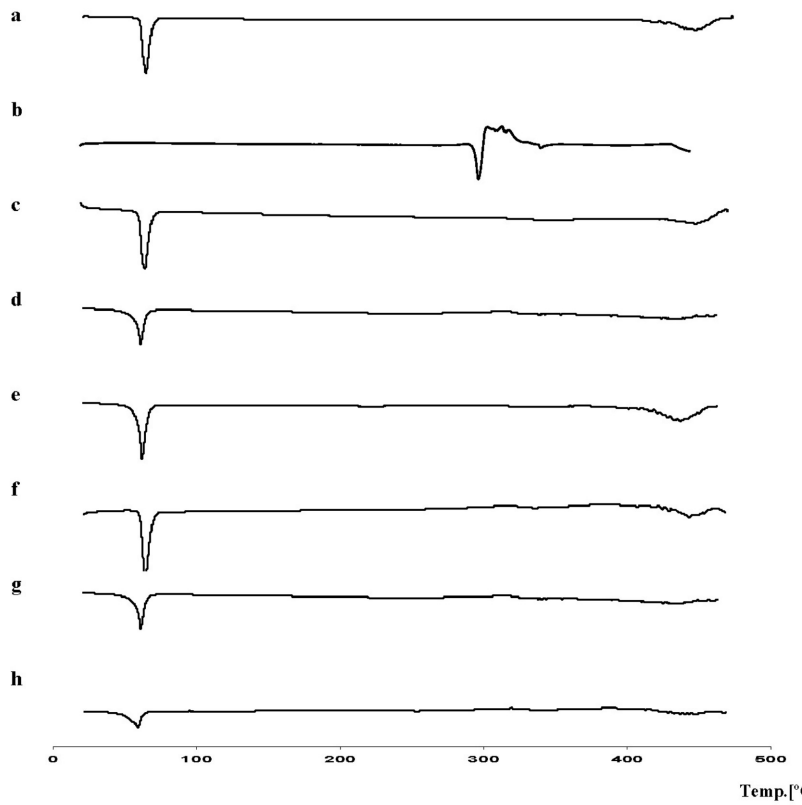

Figure 2. Results of differential scanning calorimetry. **a**: PEG 6000, **b**: diclofenac sodium, **c**: physical mixture 10%, **d**: 10% solid dispersion I, **e**: 10% solid dispersion II, **f**: physical mixture 30%, **g**: 30% solid dispersion I, **h**: 30% solid dispersion II

absorbance was observed for PEG 6000 in the water solution at the analytical wavelengths characteristic of the active compound studied (diclofenac sodium - 276 nm). Therefore, the method is specific and the presence of the support does not affect the results of determinations. The concentration of the diclofenac sodium in a water solution was determined by use of a Jasco-530 UV/VIS spectrophotometer.

The accuracy and precision of the spectrophotometric method of determination of the compounds studied were also established. The overall percent recovery of diclofenac sodium in the presence of PEG 6000 were 101.8% with relative standard deviations of 0.58%.

Dissolution rate studies

Dissolution profiles were obtained using a USP 25 paddle method (Erweka DZT apparatus), evaluating 100 mg of diclofenac sodium (*in substantia)* as reference or equivalent amounts of each sample.

The dissolution medium was 500 mL bidistilled water at 37 ± 1°C at 50 rpm; withdrawals were obtained at presetted times and the drug concentration was measured spectrophotometrically at λ = 276 nm .

RESULTS AND DISCUSSION

Taking into regard the importance of water solubility of therapeutic substances, in this study an attempt was made to improve water solubility of sodium diclofenac by formation of solid dispersions with PEG 6000. This substance has been chosen as a support because it is hydrophilic, has a low melting point, shows no pharmacological effect and is nontoxic. PEG 6000 is a commonly used auxiliary substance in pharmacy. Improving the solubility of diclofenac sodium was obtained from a solid dispersion with various carriers and different methods. For example, solid dispersion of diclofenac sodium in the presence of urea and sodium citrate was studied by evaporation method [9]; diclofenac sodium in the presence of Eudragit RS 100 and Eudragit RL 100 by solvent method [10]; with ethylcellulose by freeze-drying

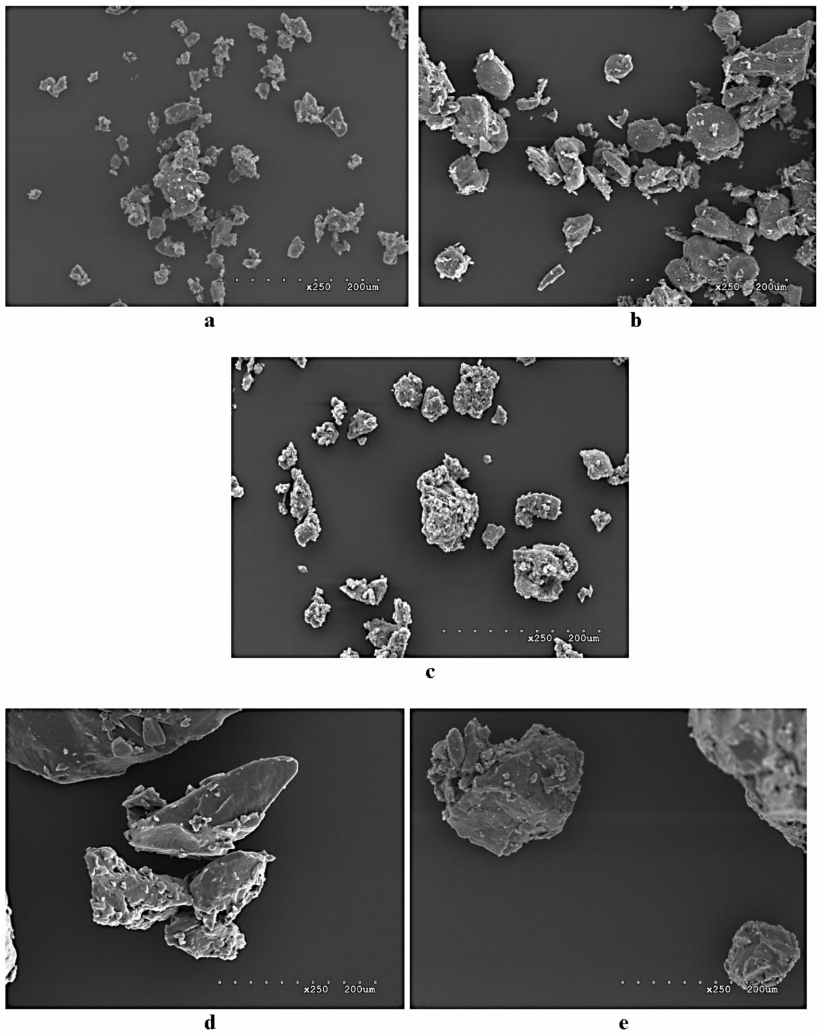

Figure 3. SEM microphotographs of: **a**: PEG 6000, **b**: diclofenac sodium, **c**: physical mixture 30%, **d**: 30% solid dispersion I, **e**: 30% solid dispersion II

method [11] and finally with PVP and mannitol by solvent method 12]. It was stated, that in the presence of PEG 6000 and Gelucire 50/13 the increase of solubility of acidic form of diclofenac and diclofenac/N-(2-hydroxyethyl)pyrrolidine was observed after creating solid dispersion by melting method [13].

The solid dispersions were obtained by evaporation and melting. They contained 10% or 30% of the active substance. The products were characterised by the X-ray diffraction in powder. The XRD patterns of the physical mixtures of sodium diclofenac and PEG 6000 as well as those of solid dispersions containing 10 or 30% of the active substance show the diffraction peaks characteristic of PEG 6000 at about 22 and 27 Å. The diffraction peaks at about 9 and 11 Å, are interpreted as corresponding to the presence of active substance and appear in the XRD patterns of the physical mixtures containing 10 or 30% of the active substance and in the XRD pattern of the solid dispersion containing 30% of the active substance. The intensity of these peaks in the XRD pattern of the 30% solid dispersion is lower than in the diffractograms of physical mixtures. The other XRD patterns do not show the peaks related to the presence of sodium diclofenac (Fig. 1). The above results suggest that in the process of obtaining solid dispersions by evaporation, a solid solution of sodium diclofenac in PEG 6000 was formed or the active substance has lost its crystalline character. When solid dispersions are

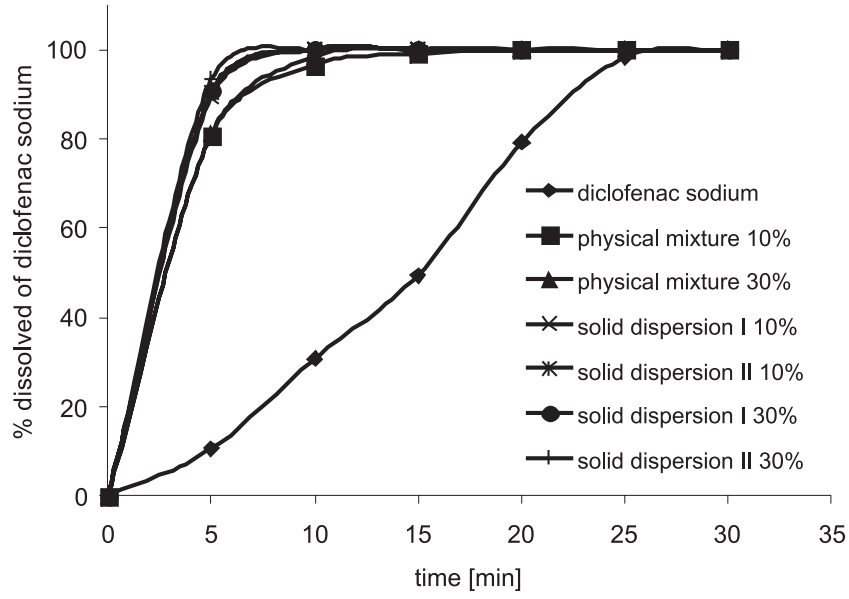

Figure 4. Solubility of diclofenac sodium in water at 37°C

obtained by the method of melting, the active substance dissolves in the support, the dissolution is total in the 10% sample and partial in the 30% sample. The above conclusions are confirmed by DSC results. The DCS curves of 10 and 30% physical mixtures of sodium diclofenac show a single endothermic peak at about 62°C, related to the presence of PEG 6000. The same peak at about 62°C related to PEG 6000 is also seen in the DSC curves recorded for solid dispersions of diclofenac obtained by melting or evaporation, (Fig. 2).

The morphology of sodium diclofenac, PEG 6000, their 30% physical mixture and the 30% solid dispersions obtained by melting and evaporation, was examined under a scanning electron microscope with a magnification of 250 times. The crystals of sodium diclofenac are larger in size than those of PEG 6000 (Fig. 3). The SEM images of the physical mixture and solid dispersions show the crystals of sodium diclofenac and PEG 6000. The SEM images of solid dispersions reveal that sodium diclofenac and PEG 6000 are closely adherent. In general, the solid dispersions contain larger crystals. Sodium diclofenac *in substantia* was found to dissolve after about 30 min, in a 10% physical mixture with PEG 6000 it was fully dissolved after about 10 min, while in 10% solid dispersions (obtained by both methods) it was fully dissolved after 5 min. In the sample containing 30% of sodium diclofenac in a physical mixture with PEG 6000, the time of full dissolution of the active substance increased to over 15 min, while in the samples of 30% solid dispersions (obtained by both methods) the time of full dissolution of sodium diclofenac was the same as in the 10% samples, so about 5 min (Fig. 4). Water solubility of sodium diclofenac in a physical mixture with PEG 6000 is improved with respect to that of sodium diclofenac in substantia. However, the water solubility of sodium diclofenac in the solid dispersion with PEG 6000 is the same as that in physical mixture, so formation of solid dispersion has no further improving effect.

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