ELSEVIER

Il Farmaco 57 (2002) 723–727

IL FARMACO

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Characterization and solubility study of solid dispersions of flunarizine and polyvinylpyrrolidone

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Received 5 November 2001; accepted 17 March 2002

Abstract

Flunarizine is a selective calcium entry blocker poorly water-soluble. In this report, the interactions of this drug with polyvinylpyrrolidone in solid dispersions, prepared according to the dissolution method using methanol as the solvent, have been investigated. For purposes of comparison physical mixtures were prepared by simple mixture and homogeneization of the two pulverized components. Combinations of flunarizine/polyvinylpyrrolidone of the following percentage proportions were prepared: 10/90, 20/80, 30/70, 40/60, 50/50, 60/40 and 80/20 (mean particle size of 0.175 mm). The physicochemical properties of solid dispersions were investigated with X-ray diffraction, infrared spectroscopy, differential scanning calorimetry and solubility in equilibrium. X-ray patterns and differential scanning calorimetry have shown that polyvinylpyrrolidone inhibits the crystallization of flunarizine when percentages drug/polymer are 10/90, 20/80 and 30/70. The infrared spectra suggest that there was no chemical interaction between flunarizine and polyvinylpyrrolidone. Equilibrium solubility studies showed that drug solubility was enhanced as the polymer content increased. In general, the solubility increase was greater in solid dispersions than in physical mixtures and the solubility in equilibrium for solid dispersions and physical mixtures at the same drug/polymer proportion showed significant differences ($P < 0.05$).

Keywords: Solid dispersions; Flunarizine; Polyvinylpyrrolidone; Differential scanning calorimetry; Equilibrium solubility

1. Introduction

It is well established that dissolution is frequently the rate-limiting step in the gastrointestinal absorption of a drug from a solid dosage form. The relationship between solution rate and absorption is particularly distinct when considering drugs of low solubility. Consequently, numerous attempts have been made to modify the dissolution characteristics of certain drugs in an effort to attain more rapid and more complete absorption.

In 1961, solid dispersions were proposed to increase the dissolution and oral absorption of poorly-water soluble drugs [1]. Subsequently, pharmaceutical applications of solid dispersion systems were extensively reviewed [2,3].

Several investigations [4–8] demonstrated that the formation of solid dispersions of relatively water-insoluble drugs with various pharmacologically inert carriers can increase significantly their in vitro dissolution rates. Many substances have been recommended as carriers for solid dispersions. One of these is polyvinylpyrrolidone, a vehicle often employed due to its low toxicity, high aqueous solubility and physiological tolerance. These and other properties make this a very suitable vehicle for formulations into dosage forms [9–14].

Flunarizine is a selective calcium entry blocker at least as effective as pizotifen in migraine prophylaxis [15,16] and in a longer term study as effective as cinnarizine central origin vertigo [17].

This drug is poorly water-soluble [18] and in this paper we have investigated the solubility of flunarizine and we have prepared solid dispersion systems of flunarizine and polyvinylpyrrolidone to improve its

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0014-827X/02/$ - see front matter
PII: S0014-827X(02)01262-4

solubility. For purposes of comparison, physical mixtures were prepared by simple mixture and homogeneization of the two pulverized components.

2. Materials and methods

2.1. Materials

Flunarizine was kindly supplied by Esteve Química S.A., Barcelona, Spain. Polyvinylpyrrolidone marketed as Kollidon 25 (Basf Española S.A., Seville, Spain) with an average molecular weight of 25 000, was used without further treatment. The solvent was methanol reagent grade (Scharlau Chemie S.A., Barcelona, Spain).

2.2. Sample preparation

Flunarizine/polyvinylpyrrolidone solid dispersions were prepared according to the dissolution method [1]. Methanol was used as the solvent and evaporated in an oven at 50 °C during 48 h. Dessication was completed in a vacuum oven until constant weight was achieved and the resulting solids were pulverized and sieved to obtain the granulometric fraction (0.15–0.2 mm) with a mean particle size of 0.175 mm.

Physical mixtures were prepared by simple intensive mixing of the two components previously sieved (under 0.15–0.20 mm). These physical mixtures were tested by comparison to solid dispersions.

Combination of flunarizine/polyvinylpyrrolidone of the following percentage proportions were prepared: 10/90, 20/80, 30/70, 40/60, 50/50, 60/40 and 80/20. These mixtures were placed in sealed, opaque recipients and stored away from light and humidity.

2.3. Methods

The physicochemical properties of the solid dispersions and physical mixtures were investigated with infrared spectroscopy, X-ray diffraction, differential scanning calorimetry and solubility in equilibrium.

Infrared spectra were recorded on a Perkin–Elmer 298 infrared, from samples prepared in KBr discs. The scanning range was 4000–600 cm^{-1} at a scan period of 14 min.

X-ray diffraction patterns of powdered samples were obtained with a Philips PW 1712 apparatus using Cu Kα radiation ($\lambda = 0.154$ nm). Samples were scanned from 2° 2θ to 60° 2θ for qualitative studies. The scan rate selected was 2°/min [19].

Differential scanning calorimetry was performed on samples using a Mettler differential scanning calorimetry instrument (model FP 80). Samples of about 5 mg were weighed ($\pm$0.5 mg) and encapsulated in flat-bottomed aluminum pans. The thermograms were recorded at a heating rate of 5 °C/min from 50 to 240 °C/min.

For equilibrium solubility studies, an excess of pure flunarizine alone, in solid dispersions and in physical mixtures was placed in three 10-ml glass tube containing each 3 ml of distilled water. The tubes were sealed and agitated at 120 rpm in a thermostated shaking water bath (Julabo SW 21) set at 25 $\pm$ 0.1 °C. After 4 days, the samples were filtered through a 0.45 μm Millipore filter (Ireland) and 1 ml of each solution was diluted in duplicate to 100 ml with distilled water. Each diluted sample was analyzed spectrophotometrically in triplicate (Perkin–Elmer Lambda-2 spectrometer) to determine the amount of dissolved drug (wavelength 252.2 nm). A calibration was previously performed and it was confirmed that polyvinylpyrrolidone produced no absorption signal at this wavelength across a wide range of concentrations. Also, it was checked the UV absorption of flunarizine in the presence of polyvinylpyrrolidone and there was no interference between both substances. The results presented are mean values of 18 determinations.

Data for solubility studies were statistically analyzed with the Statgraphic software program (Statgraphic plus v. 4.1, Los Angeles, CA, 1999).

3. Results and discussion

The infrared spectra of flunarizine and polyvinylpyrrolidone alone and of solid dispersions and physical mixtures are shown in Fig. 1. The bands of flunarizine and polyvinylpyrrolidone were clearly visible in their spectra and are also discernible in the spectra for the solid dispersions and physical mixtures, becoming more intense as the percentage of drug in the mixture increased. The signals were generally stronger in physical mixtures than in solid dispersions.

These results suggest that there was no chemical interaction between flunarizine and polyvinylpyrrolidone.

X-ray patterns (Fig. 2) showed no sharp peaks attributable to flunarizine in the solid dispersions of 10/90, 20/80 and 30/70 (w/w) drug/polymer indicating that flunarizine crystals were transformed to an amorphous or a microcrystalline form during the cosolvent process. The solid dispersions with 40/60, 50/50, 60/40 and 80/20 (w/w) drug/polymer presented several diffraction peaks, which denoted that the drug was present in crystalline form.

On the other hand, peaks attributable to flunarizine began to insinuate in physical mixtures from a 10/90 (w/w) drug/polymer and as the proportion of flunarizine increased, the peaks for the drug became more intense. Since the peaks produced by solid dispersions and physical mixtures of the same composition were com-

parable, we concluded that the drug was insoluble in the solid carrier, i.e. in formulations containing more than 40% flunarizine, no solid solution was formed between the drug and polymer.

Fig. 3 shows characteristic thermograms for pure flunarizine and polyvinylpyrrolidone and binary mixtures. A first run on our samples showed a pronounced endotherm with peaks between 110 and 130 °C. Previous related work on polyvinylpyrrolidone [20] revealed similar peaks between 110 and 120 °C which were attributed to removal of water. This suggestion, which was substantiated by findings that enthalpies of vaporization are close to the value for water, is adopted to explain the present observations. Polyvinylpyrrolidone can be dried by prolonged contact with drying agents such as anhydrous copper sulfate or by heating in vacuum, but samples prepared in this way tend to give initial differential scanning calorimetry scans, which are too noisy to allow unequivocal identification of a glass transition. A better procedure is to dry samples by preliminary runs in the differential scanning calorimetry apparatus. Consequently, the moisture content of our samples was removed by a first run at a heating rate of 10 °C/min in a temperature range from 50 to 130 °C.

A characteristic fusion endotherm appeared for the drug, with a peak melting point at 208.1 °C.

Because of the amorphous structure of the polymer, no peak melting point was seen in the thermograms.

The differential scanning calorimetry scans showed a glassy transition (82.7–68.9 °C) in the solid dispersions of 10/90–50/50 (w/w) drug/polymer and a characteristic fusion endotherm, equivalent to flunarizine, appeared in the solid dispersions from a 40/60 (w/w) drug/polymer, indicating partial crystallinity. Heat of fusion of the flunarizine and solid dispersions allowed quantitative estimates of their crystallinity [21].

The solid dispersions of 10/90, 20/80 and 30/70 were amorphous, whereas the solid dispersions from 40/60 to 80/20 gave values of 10.4, 31.6, 33.3 and 54.6 J/g giving a crystallinity indices of 14.13, 42.93, 45.24 and 74.18%, respectively. The increase in crystallinity indicates that the compatibility level of the two components is exceeded [22].

The T_g of solid dispersions decreased when increased flunarizine percentage indicative of a more rigid crystalline structure that may have restricted molecular mobility and of a partial miscibility of the two components about 30% flunarizine.

All thermograms for the physical mixtures above 20% flunarizine showed the fusion endotherm of the drug, with no glassy transition. The differential scanning calorimetry curve for the physical mixtures 10/90 showed a glassy transition ($T_g = 72.2$ °C) and no endothermic peak was noted due to the low flunarizine content.

Water solubility found for pure flunarizine during the assay time was 0.0165 ± 0.00047 g/l.

The solubility of the drug from solid dispersions and physical mixtures with different flunarizine percents is showed in Fig. 4. It can be noted from this figure that drug solubility was enhanced as the polymer content in the samples increased. This phenomenon can be ascribed in the physical mixtures to a higher wettability of flunarizine in presence of polyvinylpyrrolidone. In the

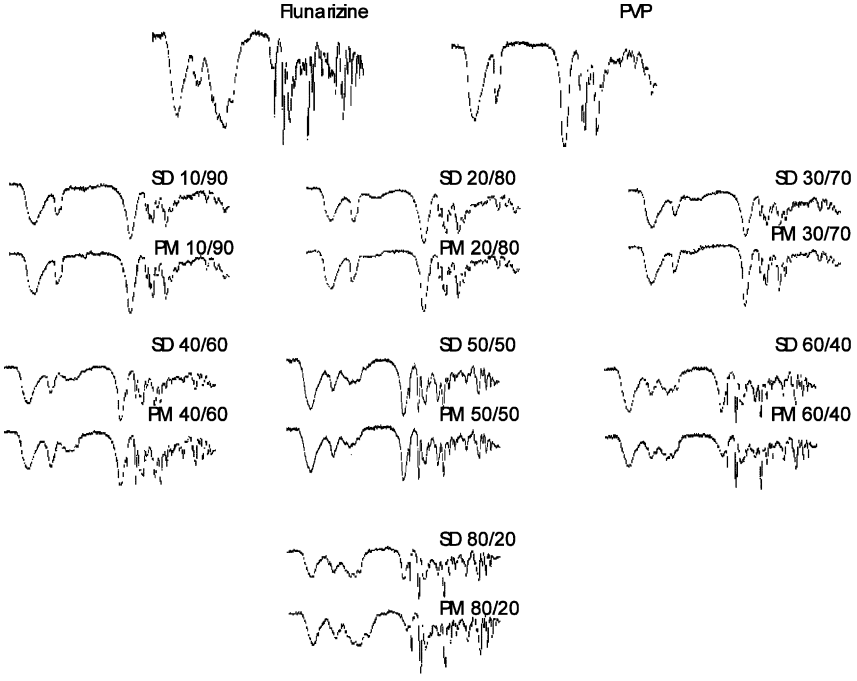

Fig. 1. Infrared spectrograms of flunarizine and polyvinylpyrrolidone (PVP) as pure chemicals, solid dispersions (SD) and physical mixtures (PM).

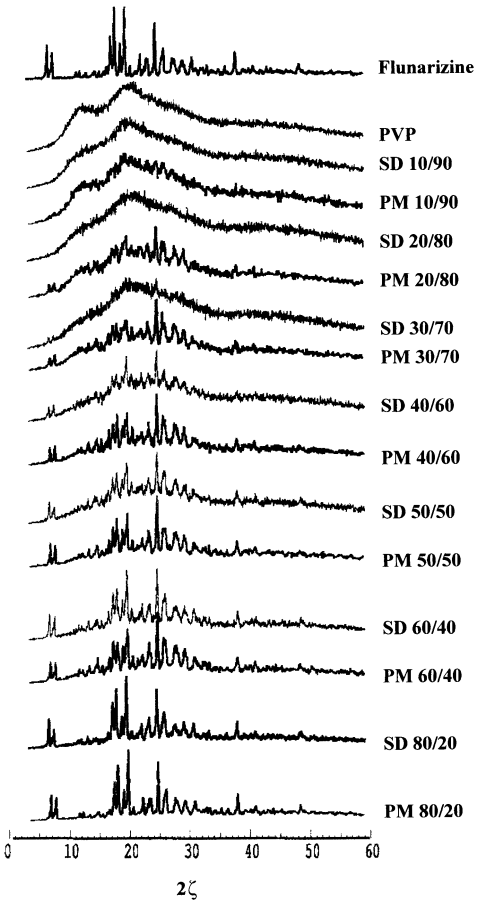

Fig. 2. X-ray diffraction data for flunarizine and polyvinylpyrrolidone (PVP) as pure chemicals, solid dispersions (SD) and physical mixtures (PM).

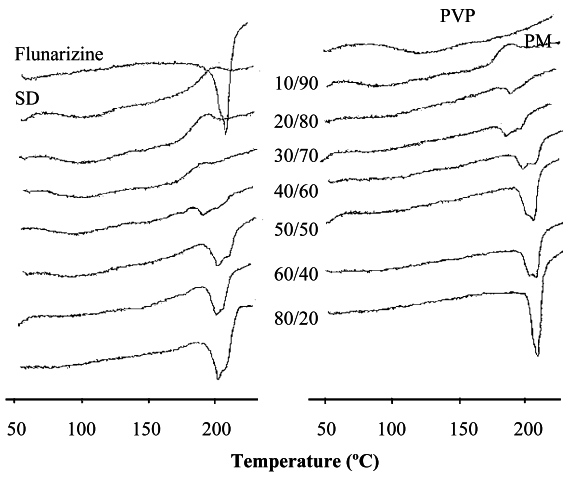

Fig. 3. Differential scanning calorimetric data for flunarizine and polyvinylpyrrolidone (PVP) as pure chemicals, solid dispersions (SD) and physical mixtures (PM).

solid dispersions, it is due to the decrease in crystallinity of the flunarizine and also to a highly dispersed state of the drug resulting in its higher wettability. These results

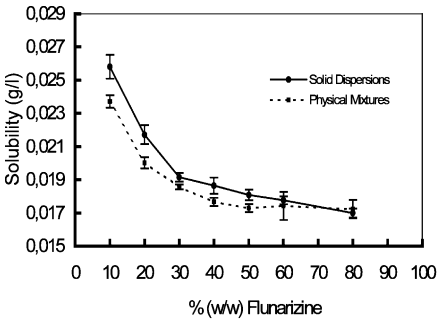

Fig. 4. Equilibrium solubility of solid (SD) and physical mixtures (PM). Each value represents the mean ± SD ($n = 3$).

are in agreement with those of differential scanning calorimetry and X-ray assays.

Linear regression analysis was applied to the solubility data and correlation coefficients ($P < 0.01$) of 0.9830 for solid dispersions and 0.9737 for physical mixtures were attained. These results indicated a linear dependency between solubility and polymer concentration in the samples. Multifactor analysis of variance was applied to the solubility dates too. The interaction factors analyzed were the samples (solid dispersions and physical mixtures) preparation method and the polymer percentage in them. Since $2P$-values were less than 0.05, we probe that these factors have a statistically significant effect on solubility of flunarizine.

Solubility reached with solid dispersions was higher than the one reached with physical mixtures for each proportion of polymer in the samples. It is confirmed that there are statistically significant differences ($P < 0.05$) between both kinds of samples by the comparison of the average values obtained, even the ones with a drug/polymer proportion of 50/50.

One-way analysis of variance and multiple range test LSD (least significant difference) applied to solid dispersions showed that they were all different between them and with respect to the pure drug ($P < 0.05$). The same statistical analysis applied to physical mixtures showed that they differ to the pure drug. Physical mixtures 10/90, 20/80 and 30/70 were different from each other but those with polymer proportion lower than 70% (40/60, 50/50, 60/40, 80/20) showed similar solubility.

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