

SOLUBILITY OF SELECTED DERIVATIVES OF 1,4-BENZODIAZEPINE-2-ONE IN THE PRESENCE OF PVP

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Abstract: Pharmaceutical availability of diazepam, oxazepam and nitrazepam from solid dispersions of PVP have been studied in comparison to those of the corresponding physical mixtures and pure benzodiazepines. The derivatives of 1,4-benzodiazepin-2-one are poorly water soluble drugs. The properties of diazepam-, oxazepam- and nitrazepam-PVP solid dispersions have been determined by the methods of differential scanning calorimetry (DSC) and X-ray diffraction. The effect of PVP on the solubility of selected derivatives of 1,4-benzodiazepin-2-one has been studied. The solubility of diazepam, oxazepam and nitrazepam from its solid dispersion has been found to increase in presence of PVP.

Keywords: solid dispersion, benzodiazepine, PVP, solubility

Pharmaceutical availability is described by the amount of the therapeutic substance released from a given drug formulation measured *in vitro* and the rate of its release. The process of release of the therapeutic substance leads to its appearance in the form of molecular dispersion, i.e. in the dissolved form, in which the drug can be absorbed from the site of administration to the surrounding tissues and the blood circulation system, therefore the character of the process is essential for the therapeutic effect. For the technological and biopharmaceutical reasons the increase in the solubility of therapeutic drugs hardly soluble in water is of great importance (1, 2).

Regarding the diversity of their pharmacological activities, the derivatives of 1,4-benzodiazepin-2-one have been in the group of drugs most often recommended for medical treatment. Unfortunately, these derivatives are hardly or practically no water soluble, so their formulations are almost limited to solid phase. Recently, much effort has been made to improve the solubility of these derivatives (3-10). One of the possible approaches to the problem is to prepare solid phase dispersions of the hardly water soluble drug and a hydrophilic support. Depending on the method of preparation, physico-chemical properties of the therapeutic substances and the support, the dispersions can take the form of eutectic mixtures, solid solutions, amorphous precipitations

of the therapeutic substance on the crystalline support, glassy solutions, or compounds or complexes between the therapeutic substance and the support. The type and character of the support also are of great importance. The aim of the study reported was to obtain the solid phase dispersions of the selected derivatives of 1,4-benzodiazepin-2-one: diazepam, nitrazepam and oxazepam with polyvinylpyrrolidone (PVP) by the method of evaporation and to assess the effect of the support on the water solubility of the derivatives studied.

Material

Polyvinylpyrrolidone K 30 (PVP) Fluka; diazepam, series G11001, nitrazepam series: G11001 oxazepam: G11001 Glaxo Smith Kline; methanol analytical grade, Merck; ethanol 95% vol., Polmos S.A.; hydrochloric acid analytical grade, POCH.

Measuring equipment

X-ray diffractometer TUR 62, differentiation scanning calorimeter DSC –50, Shimadzu, Specord IR 75, Zeiss, Jena, spectrophotometer UV-VIS Cary 118°C, Varian, microanalytical balance, Sartorius, rotating evaporator Rotavapor, shaker type 327, Premed Warszawa.

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Methods

Obtaining of solid dispersions

PVP and the substance studied (diazepam, nitrazepam and oxazepam) were dissolved in a small amount of ethanol 95%, the solutions were combined and the solvent was evaporated at 70°C. The product was stored in a desiccator for about 24 h, then the mass was homogenized and refined by sieving through the mesh size 0.45 mm and 0.2 mm.

Obtaining of physical mixtures

Appropriate amounts of a given derivative of 1,4-benzodiazepin-2-one and polyvinylpyrrolidone were mixed and homogenized by sieving the mixture through the mesh size 0.45 mm and 0.2 mm. The physical mixtures and solid dispersions were prepared to contain 10%, 20%, 30%, and 40% of the drug.

Methods for identification of solid dispersions

DSC Analysis

DSC analysis was performed for the therapeutic substances: diazepam, nitrazepam, oxazepam, for solid dispersions of these substances in polyvinylpyrrolidone, for the physical mixtures of the drugs with PVP and for pure PVP. The sample to be studied together with the standard (Al_2O_3) was placed in the heating chamber. The analysis was made in the temperature range 20 – 480°C, increased at the rate of 10°C/min in a nitrogen atmosphere.

XRD analysis

XRD powder method was applied to study the solid dispersions, physical mixtures and pure substances studied (drugs and polyvinylpyrrolidone). The CuK_α ($\lambda = 1.5418 \text{ \AA}$) radiation monochromatized by a nickel filter, lamp voltage of 30 kV, current intensity 30 mA were used. XRD patterns were recorded over the range $2^\circ < 2\theta < 40^\circ$ and are presented in Figure 1.

Solubility tests

The weighted portions of each drug, its physical mixture and solid dispersion were placed in separate flasks of 50 cm³ capacity, supplemented with 15 cm³ of water and shaken at room temperature for 24 h. The precipitate was centrifuged, dissolved in 0.1 M HCl (diazepam, nitrazepam) or in methanol solution of 0.05 M HCl (oxazepam) and the contents of the compounds analyzed were determined by the spectrophotometric method at the wavelength characteristic of a given compound. The results are presented in Table 1.

RESULTS AND DISCUSSION

The aim of the study was to check the possibility of improving the solubility of selected derivatives of 1,4-benzodiazepin-2-one: diazepam, nitrazepam and oxazepam in water by formation of solid dispersions of the derivatives with polyvinylpyrrolidone (PVP). The selected support was PVP as it has hydrophilic properties and is commonly used as an ancillary substance in pharmacy. The solid dispersions obtained by evaporation contained 10%, 20%, 30% and 40% of the therapeutic substance. The products were identified by the differential scanning calorimetry (DSC) and X-ray diffraction methods. Results of the DSC analysis of solid dispersions were interpreted in reference to the DSC curves obtained for pure substrates and for their physical mixtures of the corresponding concentrations. The DSC curve of PVP shows two endothermic peaks: at about 66°C related to the melting of the substance and at about 435°C assigned to its decomposition. The DSC curves of diazepam and oxazepam show single endothermic peaks at 134°C and 203°C, respectively, corresponding to the melting points of both compounds. The DSC curve of nitrazepam shows two peaks: the endothermic one at about 230°C related to the melting point of the drug and the exothermic one at about 289°C corresponding to the decomposition of the drug. The DSC curves of the physical mixtures of PVP with diazepam in the concentrations 10%, 20%, 30% and 40% show two endothermic peaks (at ~ 66°C and 435°C) related to PVP and an endothermic peak at ~134°C characteristic of diazepam. In the DSC curves of the solid dispersions of diazepam and PVP, there are peaks related to the presence of PVP and the peak at 134°C assigned to diazepam occurs only in the DSC curves of the mixtures containing 30% and 40% of diazepam and it is much less intense than in the DSC curves of the corresponding physical mixtures. The peak assigned to diazepam does not appear in the curves recorded for the solid dispersions containing 10% or 20% of the drug.

The DSC curves of the physical mixtures and solid dispersions of PVP with nitrazepam in the concentrations of 10%, 20%, 30% and 40% show the endothermic peaks corresponding to the melting and decomposition of the support, while the exothermic peak at about 289°C characteristic of nitrazepam appears only on the curves recorded for the physical mixtures or solid dispersions containing 40% of nitrazepam. The DSC curves of the physical mixtures and solid dispersions of PVP with oxazepam in

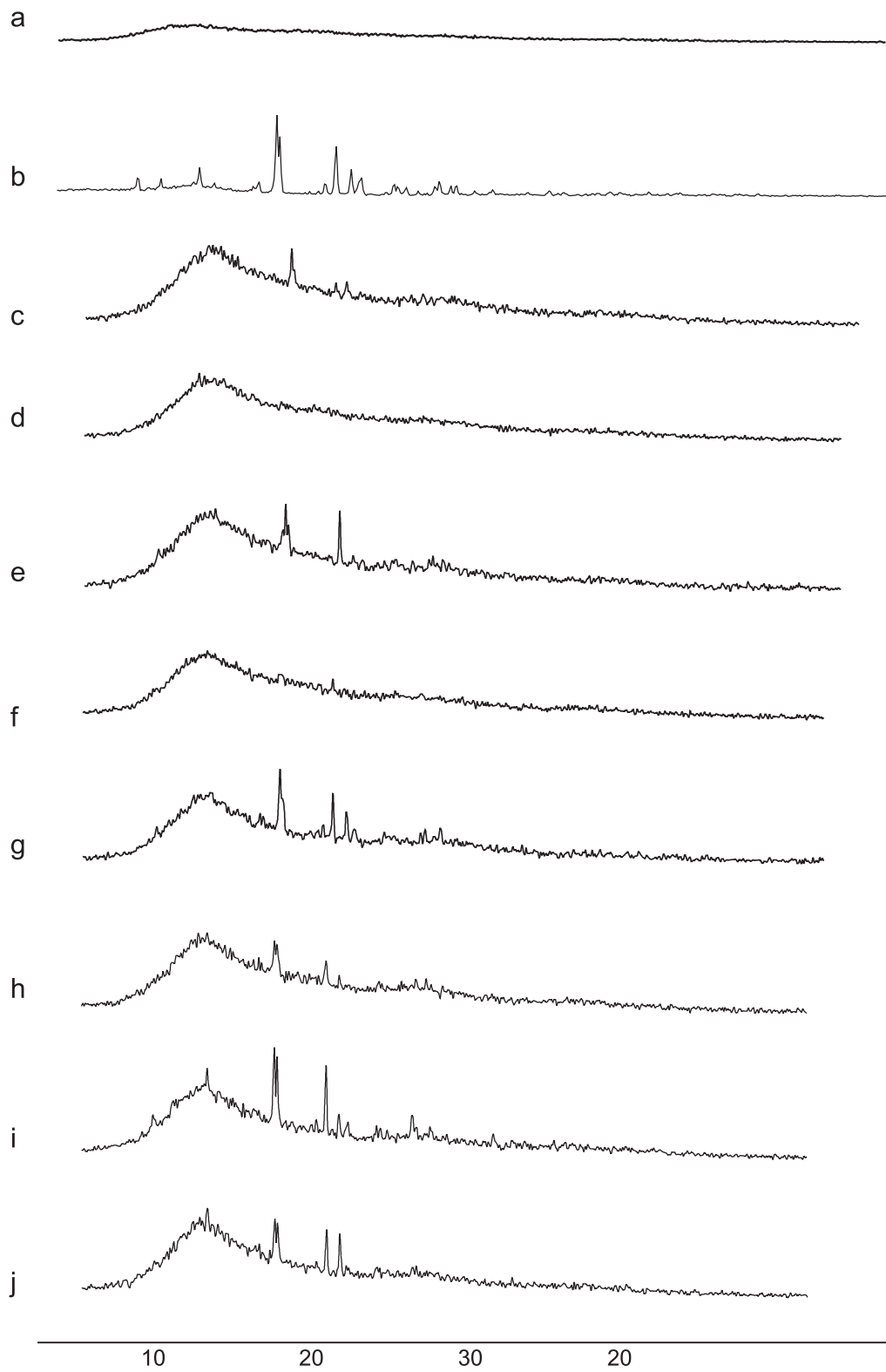


Figure 1. X-ray diffraction patterns: a – PVP, b – diazepam, c – physical mixture 10%, d – solid dispersion 10%, e – physical mixture 20%, f – solid dispersion 20%, g – physical mixture 30%, h – solid dispersion 30%, i – physical mixture 40%, j – solid dispersion 40%

Table 1. Solubility of selected derivatives of 1,4-benzodiazepin-2-one in water at room temperature.

Solubility [mg/100 cm ³]								
Diazepam								
<i>In substantia</i>	Physical mixture				Solid dispersion			
	10%	20%	30%	40%	10%	20%	30%	40%
3.97	13.74	14.65	14.91	15.36	27.07	28.36	28.92	29.19
Nitrazepam								
<i>In substantia</i>	Physical mixture				Solid dispersion			
	10%	20%	30%	40%	10%	20%	30%	40%
2.54	5.12	6.21	6.74	6.91	10.22	11.28	11.51	12.17
Oxazepam								
<i>In substantia</i>	Physical mixture				Solid dispersion			
	10%	20%	30%	40%	10%	20%	30%	40%
3.65	14.24	14.68	15.30	15.76	28.13	28.71	29.21	29.28

the concentrations 20%, 30% and 40% show three endothermic peaks; two of them at about 66°C and 435°C are assigned to the support and the one at about 203°C is characteristic of oxazepam. The DCS curve recorded for the physical mixture and solid dispersion of PVP with 10% of oxazepam display only the endothermic peaks related to the presence of PVP. With increasing concentration of oxazepam in the physical mixture and in the solid dispersion the endothermic peak at about 203°C corresponding the melting point of the drug becomes increasingly more pronounced and is greater on the curves of the physical mixtures. The above observations suggest that in the process of solid dispersion production the therapeutic substance studied is to some extent dissolved in PVP giving a solid solution.

The XRD analysis was performed by the powder method. The results obtained for solid dispersions were interpreted with reference to those obtained for physical mixtures and pure substrates. Only the XRD patterns of the physical mixtures and solid dispersions of PVP with diazepam in the concentration of 40% show the diffraction peaks indicating the presence of diazepam crystals in the range 5-11 Å. Their intensity in the XRD patterns of the solid dispersion is lower than in that of physical mixture. The XRD patterns of the physical mixtures containing 20%, 30% and 40% of nitrazepam and solid dispersions containing 30% and 40% of nitrazepam show the peak characteristic of nitrazepam at 4 Å. This peak is not noted in the XRD patterns of the physical mixture with 10% of nitrazepam and solid dispersions with 10% and 20%

of this drug. The intensity of the peaks characteristic of nitrazepam in the patterns of the physical mixtures and solid dispersions is different. The peak assigned to oxazepam at about 7 Å appears in XRD patterns of the physical mixtures with 20%, 30% and 40% of the drug and in those of solid dispersions with 30% and 40% of the drug. XRD results have not confirmed the presence of oxazepam in the physical mixture of PVP and 10% of oxazepam and in solid dispersions of PVP and 10% and 20% of the drug, and the intensity of this peak is greater in the patterns of the physical mixtures. The XRD pattern of PVP does not show any peaks as it is amorphous substance (Figure 1). As follows from the above observations, the process of production of solid dispersions by evaporation leads to formation of solid solution of the therapeutic drug in PVP, the drug is partly dissolved in the support or loses its crystalline character.

The next stage of the study was to work out a spectrophotometric method in the UV range that could be used for determination of the content of the 1,4-benzodiazepin-2-one derivatives studied in physical mixtures and solid dispersions with PVP. The UV spectrum of PVP in a 0.1 M HCl solution and in a methanol solution with 0.1 M HCl in the range 200-400 nm does not show absorbance at the analytical wavelengths typical of the therapeutic drugs studied, so the presence of the support has no influence on the results of determinations and the method is specific. The method is also sensitive as the molar absorption coefficient values are in the range $1 \cdot 10^4 - 1 \cdot 10^5$. In the concentration range stud-

ied the method is linear as the regression coefficient is close to 1, $r = 0.9998$. The precision and accuracy of the UV spectrophotometric method proposed were also determined. The water solubility of selected derivatives of 1,4-benzodiazepin-2-one *in substantia* and in the physical mixtures and solid dispersions with PVP was studied at room temperature. After shaking of the samples with water for 24 h, the solution was removed, the content of the substances in the residue was determined and the amount of the dissolved derivative was calculated by subtraction. The solubility of diazepam (3.97 mg/dm^3) in water in physical mixtures with PVP increases by about 3.5 times (on average 14.66 mg/dm^3) and in solid dispersions by 7 and more times (on average 28.38 mg/dm^3), depending on the amount of the active substance in the system (Table 1). The influence of the support on the solubility of nitrazepam is also considerable. The solubility of nitrazepam (2.54 mg/dm^3) in the physical mixture with PVP increases twice for the sample containing 10% of the drug (5.12 mg/dm^3) and four times in the solid dispersion containing 10% of the drug (10.22 mg/dm^3). The solubility is greater for the samples with greater contents of the drug (Table 1). The presence of PVP also has important influence on the solubility of oxazepam; in physical mixtures with PVP the oxazepam solubility (3.65 mg/dm^3) increases four times (on average 15.10 mg/dm^3) and in solid dispersions it increases eight times (on average 28.83 mg/dm^3) (Table 1).

The above presented and discussed results permit drawing the following conclusions.

➤ The solid dispersions of diazepam, nitrazepam and oxazepam can be obtained by the method of evaporation.

➤ In solid dispersions the therapeutic substance is partly dissolved in the support.

➤ Identification of solid dispersion formation can be performed with the DSC and X-ray diffraction methods.

➤ The UV spectrophotometric method proposed for determination of the content of the therapeutic substances studied is selective, linear, accurate and precise.

➤ The water solubility of diazepam, nitrazepam and oxazepam in the physical mixtures with PVP is greater than that *in substantia*.

➤ Formation of solid dispersions of the therapeutic substances studied with PVP by the method of evaporation results in a further increase in their water solubility.

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