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RESEARCH PAPER

Quantitative Analysis of Povidone (PVP) in Drug–PVP Matrix Using Multicomponent Analysis

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ABSTRACT

A method for the quantification of povidone (PVP), in solid dispersions and physical mixtures of the polymer and a very slightly soluble drug substance, has been developed by multicomponent analysis using the concepts of chemometrics. Because the UV-absorbance spectra of PVP is completely overlapped by the UV-absorbance spectra of the drug substance, a direct spectrophotometric method of PVP is impossible. However, UV-spectrophotometric data were analyzed by the Quant + Perkin Elmer software for quantitative multicomponent analysis using chemometrics, and by the optimal method developed using a solvent of pH 7.4, a fast, reliable, and precise detection of PVP was obtained when the content of PVP in the powder sample exceeded 20% (m/m). Two methods were developed by the calibration procedure, using buffers of pH 7.4, respectively pH 8.5. By applying a solvent of pH 8.5, more sample could be taken into use because of the enhanced solubility of the drug substance, and hence it was believed that as more PVP was taken into use, a better prediction of PVP would be obtained. However, as more drug substance was taken into use, the UV-absorbance spectrum of PVP was even more overlapped, and an inferior prediction was obtained.

INTRODUCTION

Povidone (PVP) is a widely used excipient in the field of pharmaceutics as a binder and coating agent in solid dosage formulations and as a suspending, stabilizing, and viscosity-increasing agent in liquid and semisolid formulations (1,2). Moreover, PVP has been proposed for the dissolution enhancement of very slightly soluble drug substances by the solid dispersion technique and by its ability to interact with certain drug molecules (1,3,4).

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Quantitative analysis of PVP can be made by chromatographic methods, for example, by paper chromatography (5), by a chromatographic–colorimetric method of vital red complexes (6), by pyrolysis–gas chromatography (7), and by size-exclusion chromatography (8). Moreover, the determination of PVP has been done by IR spectrophotometry (9) and by spectrophotometrical analysis of iodine–PVP complexes (10) and vital red–PVP complexes (11) being formed in aqueous acidic solutions. These analytical methods are, however, complicated and time consuming, and the analysis may be influenced by molecular interactions between drug and PVP. There is still a need for a simple and reliable method for the determination of PVP in drug formulations.

The present investigation was undertaken to develop an analytical method for the determination of PVP in coprecipitates and physical mixtures of PVP and a very slightly soluble drug substance (12). The UV-absorption spectra for PVP and the drug substance show a gross overlap that makes it impossible to perform a direct spectrophotometric determination of PVP when the drug is present. It was investigated, however, whether analysis of UV-spectrophotometric data by quantitative multicomponent analysis using the concepts of chemometrics (13) was applicable for the simultaneous estimation of the content of PVP and drug in coprecipitates and physical mixtures. This chemometric method was previously successful in the analysis of binary systems of acetylsalicylic acid and salicylic acid (14).

MATERIALS AND METHODS

Materials

2-Hydroxy-5-[[4[(3-methyl-2-pyridinylamino)sulfonyl]-phenyl]-ethynyl]benzoic acid (IUPAC), in the following called (A), is a weak acid, being more soluble in basic medium than acidic medium. PVP (BASF, Ludwigshafen, Germany) was used in a K30 quality with a molecular weight of approximately 40,000 g/mol. Physical mixtures and coprecipitates of (A) and PVP were prepared as described elsewhere (12). Buffer solutions were prepared using ultrapure water, and all reagents for buffer solutions were of Merck analytical grade quality and used as obtained.

Methods

UV-absorbance spectra (Perkin Elmer Lambda 14P spectrophotometer with UV-winlab version 2.0 software) of 20 binary mixtures of (A) and PVP were used for calibration, whereas 9 binary mixtures of the two components were used to validate the accuracy and precision of the method derived from the calibration procedure. The concentrations of the two components were chosen to cover the range of expected content of (A) and PVP in the samples to be analyzed, while taking into consideration the sample size and the solubility of (A). (A) and PVP were used in a concentration range of 30–100 μg/ml, respectively 1–50 μg/ml, when a solvent of pH 7.4 was used. By using sodium borate buffer, pH 8.5, the solubility of (A) was improved, enhancing the quantity of sample being taken into use, and the obtained concentration ranges for the standard solutions were 70–2600 μg/ml for (A) and 17–105 μg/ml for PVP.

The mixtures to be analyzed were dissolved in sodium phosphate buffer pH 7.4 (15) or sodium borate buffer pH 8.5 (15). The accurately weighed sample was dissolved in 50.00 ml buffer by ultrasonication at 40°C for 90 min, and the solutions were left until the next day when UV-absorbance spectra were obtained. Quartz cuvettes of a pathlength of 0.10 or 0.02 cm were used, and the applied solvent was used as reference to eliminate interference from the solvent in the obtained spectra. UV-absorbance spectra were recorded in the range of 190–800 nm and transferred via the file manager to Quant+ Perkin Elmer software for quantitative multicomponent analysis using chemometric methods, version 3 (1994) and version 4 (1997). Here the principle component regression algorithm was used, and calibration using standards, validation using known test solutions, and prediction using the unknown samples were performed.

Several methods were developed in the calibration procedure, removing data being property outliers, optimizing the wavelength ranges of importance, and optimizing the number of principal components. Altogether by these actions, the ability of the method to predict the content of (A) and PVP in unknown samples was enhanced. The methods developed in the calibration procedure were initially tested by full cross-validation, and to compare the ability of methods set up to predict the content of (A) and PVP in unkown samples, the calculated F value for each component in each method was compared. The F value is a measure of how well the experimental data fits the model set up in the method. The better fit, and the better expected predictability, is achieved for higher values of F. Moreover, the methods were tested by plotting estimated values for the standards versus the specified values, giving in ideal cases a slope of 1.0000 (14).

In validation each prediction was performed in duplicate, whereas the content of (A) and PVP was performed in triplicate when the unknowns were analyzed.

The detection limit (DL) and quantitation limit (QL)

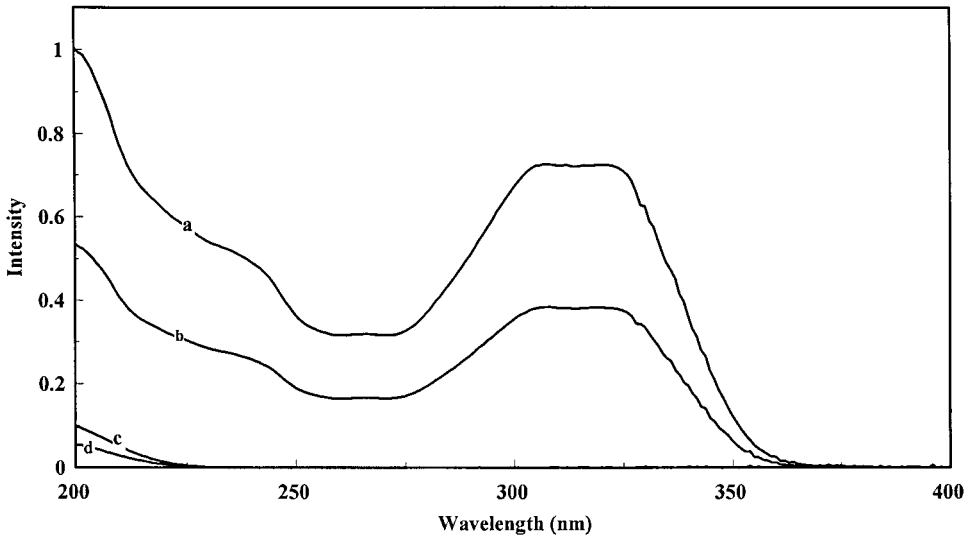

Figure 1. UV-absorbance spectra obtained for pure (A): (a) 83.6 μg/ml, (b) 44.6 μg/ml and pure PVP, (c) 20.3 μg/ml, (d) 11.4 μg/ml in sodium phosphate buffer pH 7.4.

was determined by visual evaluation (16) and by application of Eqs. (1) and (2) on prediction results obtained for six individual spectra recorded on the pure solvent. μ_{blank} is the mean value and σ_{blank} is the SD of six individual predictions.

$$DL = \mu_{blank} + 3.3 \times \sigma_{blank} \quad (1)$$

$$QL = \mu_{blank} + 10 \times \sigma_{blank} \quad (2)$$

RESULTS AND DISCUSSION

The UV-absorbance spectra obtained in sodium phosphate buffer pH 7.4 of pure (A) and pure PVP are shown in Fig. 1. The spectrum of PVP is completely overlapped by the UV-absorbance spectrum obtained for pure (A), having also a broad peak with absorbance maxima at 306–324 nm. Table 1 summarizes the F values and the slopes obtained by plotting estimated values versus specified values for PVP (Fig. 2), respectively (A), in solvent of either pH 7.4 or pH 8.5. It is obvious that prediction of PVP is superior using the solvent of pH 7.4 compared with the solvent of pH 8.5. Higher F values and slopes

Table 1

Data for the Optimized Methods Developed Using Either Sodium Phosphate Buffer pH 7.4 or Sodium Borate Buffer pH 8.5

Property	Concentration (μg/ml)	F Value	Slope Estimated versus Specified
	Sodium phosphate buffer pH 7.4		
(A)	30–100	3214	0.9973
PVP	1–50	720.9	0.9843
	Sodium borate buffer pH 8.5		
(A)	70–2600	351.1	0.9908
PVP	17–105	13.9	0.4822

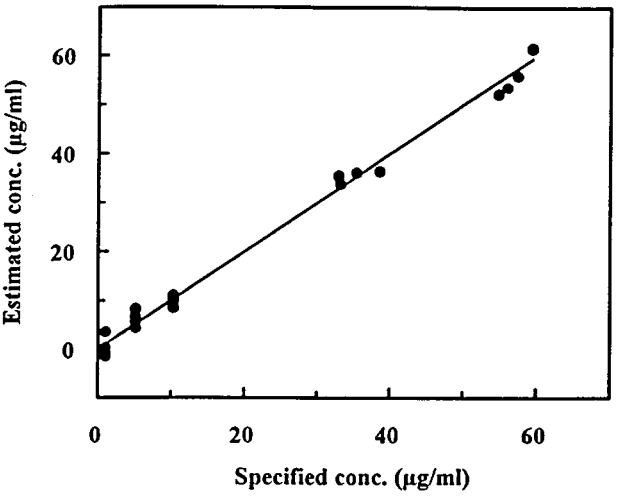

Figure 2. Estimated value versus specified value for concentrations of PVP obtained during calibration procedure using a solvent of pH 7.4. A slope of 1.0000 is represented by the straight line.

Table 2

Results from Validation Procedure Performed by Prediction of Nine Test Solutions of Known Content of PVP and (A)

Test Solution (μg/ml)	Specified Conc. of (A) (μg/ml)	Predicted Conc. of (A) (μg/ml)	Specified Conc. of PVP (μg/ml)	Predicted Conc. of PVP (μg/ml)
1	50.6	49.8	7.2	4.9
		50.2		8.2
2	36.6	38.0	20.6	21.7
		37.8		24.0
3	42.2	44.7	40.0	39.1
		45.2		43.4
4	72.6	70.9	7.2	3.8
		71.8		6.5
5	77.4	75.1	21.4	22.8
		75.8		22.6
6	57.6	56.6	43.2	40.7
		57.0		43.9
7	88.2	86.4	7.2	3.7
		86.8		6.8
8	89.2	86.6	26.6	22.4
		86.7		26.6
9	88.4	87.1	40.8	36.1
		87.8		40.4

Predictions were performed in duplicate. The results are shown as concentration (μg/ml) in the applied test solutions.

closer to 1.0000 were obtained using a solvent of pH 7.4; therefore, this method was further validated.

Detection and quantitation limit of the analysis was, using Eqs. (1) and (2), 8.8 μg/ml, respectively 8.9 μg/ml, for PVP. This is above the concentration range of interest, whereas detection and quantitation limit (2.9, respectively 3.0 μg/ml) for (A) was well below the concentration range of interest. Results from the validation procedure using nine solutions of known content of (A) and PVP are listed in Table 2. It is seen, as was also verified in the determination of detection limit using Eq. (1), that when the content of PVP in the dry samples was 10% (m/m) giving a concentration of PVP in the test solution of approximately 7–10 μg/ml, large deviations between predicted and actual concentrations of PVP were obtained. This was especially seen for high concentrations of (A). For (A), a good predictability, with deviations of less than 5%, was obtained. By performing linear regression on plots of estimated versus specified values obtained for the test solutions used in the validation procedure, slopes of 0.9333 and 1.0120 were obtained for (A) and PVP, respectively.

The predicted values of content of (A) and PVP in the unknown dry powder samples of physical mixtures and coprecipitates are listed in Table 3, together with the expected values, taking into account the method of preparation (12). It is obvious that when the content of PVP is below approximately 20% (m/m), the determination of PVP is inadquate and defective because negative values of PVP concentrations were obtained. However, when the content of PVP was larger than 20% (m/m), the determination of PVP gave results in the same order of magnitude as was expected. For (A), generally lower values of SD were obtained as compared with the determination of PVP, and the order of magnitude of content of (A) was in agreement with the values expected when the method of preparation was taken into account.

CONCLUSION

A method, using the concepts of chemometrics in analyzing UV-absorbance spectra, was developed for quantitative analysis of PVP and a very slightly soluble drug

Table 3

Results of Prediction of Content of (A) and PVP in Unknown Powder Samples of Physical Mixtures and Coprecipitates

	PVP % (m/m)			(A) % (m/m)		
Sample No.	Appr. Conc.	Mean	SD	Appr. Conc.	Mean	SD
Physical mixture						
1	0	—	—	100	97.6	0.3
2	1.0	—	—	99.0	95.5	0.7
3	4.8	0.9[a]	—	95.2	91.6	0.9
4	9.1	2.7[b]	—	90.9	91.5	3.9
5	23.1	19.4	3.5	76.9	72.7	1.7
6	25.0	24.4	2.0	75.0	71.2	1.7
7	33.3	29.8	1.3	66.7	61.0	2.6
8	50.0	50.9	0.7	50.0	47.2	0.2
Coprecipitates						
1	0	—	—	77.5	84.5	1.0
2	0.8	—	—	76.9	81.0	1.0
3	3.7	—	—	74.6	89.8	0.4
4	7.2	—	—	71.9	70.7	1.4
5	18.9	11.5	2.1	62.9	61.6	0.5
6	20.6	18.8	2.2	61.6	60.3	0.7
7	27.9	26.6	2.8	55.9	55.4	0.5
8	43.7	38.6	2.2	43.7	43.9	1.0

Results are shown in % (m/m) of the components in the dry powder. The approximal content of (A) and PVP (appr. conc.), when preparation of the physical mixtures and the coprecipitates were taken into account (12), are also presented in this table. $n = 3$.

[a] $n = 1$.

[b] $n = 2$.

substance in a matrix of the two components. Detection and quantitation limits were concerned because the effect of PVP, in some cases, is reached at low concentrations and because the concentration range of interest for PVP was 0–50% (m/m) in the present work. However, because of a relative high detection and quantitation limit only when the content of PVP was above approximately 20% (m/m) in the powder sample to be analyzed, reliable data were obtained. For (A) the quantitative analysis was performed within a deviation of 5% in the whole concentration range of interest. To overcome the quantitation limit of PVP, increased sample sizes were used by performing the analysis in a solvent of pH 8.5, where the solubility of (A) was enhanced. However, the predictability of the method developed using pH 8.5 was inferior when compared with the method developed using a solvent of pH 7.4, probably due to the dominance and overlap of the UV-absorbance spectra of (A) in the region of UV-absorbance features of PVP.

In the field of the solid dispersion technique, where PVP is used as a water-soluble carrier, often in concentrations above 20% (m/m), the use of the concepts of chemometrics in analyzing UV-absorbance spectra, as described here, is believed to be of potential value because the quickness of the analysis, being less than 5 min, and the simultaneous determination of both carrier and drug substance are advantages.

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REFERENCES

1. V. Bühler, *Kollidon®, Polyvinylpyrrolidone for the Pharmaceutical Industry*, Aktiengesellschaft Feinchemie D-67056, Ludwigshafen, 1993.
2. W. D. Walkling, in *Handbook of Pharmaceutical Excipients* (A. Wade and P. J. Weller, eds.), The Pharm. Press, London, 1994, pp. 392–399.

3. J. L. Ford, Pharm. Acta Helv., 61, 69–88 (1986).
4. Y. E. Hamza, O. A. Sammour and, H. A. Abdel-Latif, Pharm. Ind., 56, 286–291 (1994).
5. D. A. Shiraeff, JAOAC, 47, 724–730 (1964).
6. L. J. Frauenfelder, JAOAC, 57, 796–800 (1974).
7. I. Ericsson and L. Ljunggren, J. Anal. Appl. Pyrolysis, 17, 251–260 (1990).
8. K. H. Ziller and H. Rupprecht, Arch. Pharm., 314, 970–972 (1981).
9. K. Ridgway and M. H. Rubinstein, J. Pharm. Pharmacol., 23, 587–589 (1971).
10. G. B. Levy and D. Fergus, Anal. Chem., 25, 1408–1410 (1953).
11. F. P. Chinard, J. Lab. Clin. Med., 39, 666–672 (1952).
12. G. P. Pedersen and H. G. Kristensen, *14th Pharmaceutical Technology Conference*, Vol. III, Barcelona, Spain, North Liverpool, UK, 1995, pp. 15–32.
13. M. J. Adams, *Chemometrics in Analytical Spectroscopy*, The Royal Society of Chemistry, Cambridge, 1995, pp. 155–203.
14. P. C. Schmidt and B. W. Glombitza, Trends Anal. Chem., 14, 45–49 (1995)
15. *European Pharmacopoeia*, 3rd ed., Council of Europe, Strassbourg, France, 1997.
16. *Pharmeuropa, Technical Guide for the Elaboration of Monographs*, 2nd ed., Council of Europe, Strasbourg, France, 1996.