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RESEARCH PAPERS

Solid-State Stability of Theophylline Anhydrous in Theophylline Anhydrous-Polyvinylpyrrolidone Physical Mixtures

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ABSTRACT

There are contradictory evidences in the literature concerning the role of excipients with a high affinity for water in the formulation when the formulation is exposed to moisture. A few reports indicate the stabilization of a drug in the presence of hygroscopic excipients. Other reports indicate the rapid moisture-induced changes of the drug in the presence of an excipient with high affinity for water. The objective of this study was to understand the effect of PVP and the relative humidity of storage on the solid-state stability of anhydrous theophylline. In this study, physical mixtures of theophylline anhydrous and polyvinylpyrrolidone were prepared in varying proportions. These mixtures were then stored in a range of humidities at room temperature. X-ray powder diffraction, moisture uptake, HPLC, and FTIR spectroscopy were used to monitor the physical and chemical changes occurring in the mixtures. A hypothesis is presented on the role of amorphous polymeric excipients in the formulation. The hypothesis agrees with the recent knowledge on the mobility of water associated with amorphous polymeric materials. The mechanism of protection by the PVP against the hydration of theophylline could be described as desiccant action. The efficiency of this desiccant action of PVP will then be dependent on the amount of water molecules in the system and the kinetics of reaching the equilibrium moisture content.

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INTRODUCTION

The interaction of water with pharmaceuticals has been widely studied. The interaction of a drug-excipient physical mixture with water is of special interest, since in most solid dosage formulations drugs and excipients occur as a physical mixture (1–3). When drugs and excipients are exposed to atmospheric humidities, they take up water. The residual water present in the sample as a result of the water uptake can lead to changes in the chemical and physical stability of the drug and the excipient. The residual water present in the sample would be considerably more if the sample contained excipients with a high affinity for water. Amorphous polymeric excipients exhibit a high affinity for water (4,5). The effect of these excipients on the physical and chemical stability of the drug is the focus of this study.

LITERATURE SURVEY

There are two schools of thought concerning the role of excipients with a high affinity for water on the physical and chemical stability of the drug. Heidemann et al. have found that hygroscopic excipients enhanced the stability of a drug in a formulation by preferentially binding the water molecules and making water molecules not available for interaction with the drug (6). However, Ando et al. found that the presence of hygroscopic materials caused the crystallization of lactose in tablet formulations when exposed to high humidities (7). Under similar conditions, lactose present in a formulation without the hygroscopic material did not crystallize. The purpose of this study is to understand how an excipient affords or does not afford protection to the drug present in a physical mixture against moisture-induced changes. Polyvinylpyrrolidone (PVP) is an amorphous polymeric excipient with a high affinity for water and is widely used as a binder in tablet formulations. The interaction of PVP with water has been extensively studied in recent times by Zografi et al. (8,9). They had suggested a continuum model for the water–amorphous polymer interaction in terms of chemical and physical energetic states. This is opposed to the traditional broad classification of water associated with a solid into bound and unbound water. Zografi et al. have also studied the interaction of water with crystalline solids above and below their critical relative humidity (10–14).

OBJECTIVE

The model system chosen in this study was a physical mixture of theophylline anhydrous and polyvinylpyrrolidone (PVP K-30). The objective of this study was to understand the effect of PVP and the relative humidity of storage on the solid-state stability of anhydrous theophylline. Theophylline anhydrous on hydration converts stoichiometrically to theophylline monohydrate. Theophylline anhydrous and theophylline monohydrate are both crystalline and have unique x-ray powder diffraction patterns. The hydration of theophylline anhydrous to theophylline monohydrate was followed, using water uptake isotherms, x-ray powder diffraction, and FTIR studies. The chemical stability of theophylline in theophylline-PVP physical mixtures was studied using a HPLC method.

MATERIALS

Theophylline anhydrous U.S.P. (Lot #W39777A03) was obtained from Amend Drug & Chemical Co., Inc., Irvington, NJ 07111, and polyvinylpyrrolidone (Kollidon 30) was obtained from BASF, West Germany.

METHODOLOGY

Sample Preparation

Vacuum-dried theophylline anhydrous and PVP were mixed in various proportions to produce a range of theophylline-PVP physical mixtures. These physical mixtures were then exposed to a range of relative humidities in humidity chambers. Saturated salt solutions were used to maintain the required relative humidity in humidity chambers at room temperature. The formulations and humidity conditions are presented in Tables 1 and 2.

Prior to mixing, both the theophylline anhydrous and the PVP were individually dried overnight in an evacuated desiccator with anhydrous calcium sulfate as desiccant. Mixtures of vacuum-dried theophylline anhydrous and PVP were prepared in ratios mentioned in Table 1. Approximately 0.3 grams of each mixture were weighed in aluminum weighing pans and stored in the humidity chambers under the humidity conditions mentioned in Table 2. The sample in each pan was spread to approximately 4 mm thickness. The samples were stored for 45 days at room temperature. At the end of

Table 1

The Composition of Formulations

Formulation #	Composition
1	100% Theophylline anhydrous
2	93.1% Theophylline anhydrous and 6.9% PVP
3	86.3% Theophylline anhydrous and 13.7% PVP
4	67.8% Theophylline anhydrous and 32.2% PVP
5	41.2% Theophylline anhydrous and 58.8% PVP
6	18.9% Theophylline anhydrous and 81.1% PVP
7	100% Polyvinylpyrrolidone

Table 2

Relative Humidities (RH) Used in the Study

Humidity Levels	Medium Used for Maintaining RH
0%	Anhydrous calcium sulfate desiccant
54%	Sodium dichromate (saturated solution)
80%	Potassium bromide (saturated solution)
92.5%	Potassium nitrate (saturated solution)
100%	Water

45 days, the theophylline-PVP physical mixtures were investigated for the chemical and physical changes in theophylline. From this point on, the word *sample* refers to a theophylline-PVP physical mixture that had been stored under a particular relative humidity condition.

Water Uptake Studies

The theophylline-PVP physical mixtures stored under various humidity conditions were weighed at the end of the 45-day storage period. The water uptake was determined by noting the increase in the weight of the physical mixture. The percentage increase in weight of the physical mixture was plotted against the percentage relative humidity for all the formulations.

X-ray Powder Diffraction Studies

Prior to carrying out x-ray powder diffraction, seven parts by weight of the sample were mixed with three parts by weight of silicon as an internal standard. X-ray powder diffraction of the samples was carried out on a Siemens Model D500 diffractometer operated at 20 mA and 40 kV conditions. The radiation source was Cu Ka (1.54 Å wavelength) and the filter was a single-channel spectrum analyzer. The samples were scanned in scan mode from 4 to 40 2θ values, with a step size of 0.04 2θ and a step time of 0.4 seconds. A sample size of 0.2 grams was always used and spread to the same thickness on the sample holder to obtain quantitative results. The samples were spread on a low background quartz Siemens sample holder with the aid of double-stick 3M tape.

Fourier Transform Infrared (FTIR) Studies

The samples obtained from the water uptake experiment were dried overnight in a desiccator to remove the free water. Approximately 1 mg of dried sample was mixed with 100 mg of potassium bromide and pelleted using a hand-operated press on the FTIR sample holder itself. A Nicolet 20SXC FTIR spectrometer was used for acquiring the FTIR spectra of samples. Scans were made from 4000 to 600 cm^{-1} wave number range; 256 scans were accumulated for each sample. The resulted spectra were transformed to the percentage transmittance using OMNIC 1.1 software.

HPLC Studies (High-Pressure Liquid Chromatography)

The chemical stability of theophylline anhydrous in the sample was determined by an HPLC method. The samples obtained from the water uptake experiment were dried in a desiccator overnight. The dried samples were used for the HPLC analysis. To prevent the PVP from interfering in the determination of theophylline and its degradation products, a separation procedure was devised. The separation procedure was based on the differences in the molecular weight of theophylline (180) and the average molecular weight of PVP (45,000). The first step was to dissolve an accurately weighed, dried sample in 100 ml of water. About 2 milliliters of the dissolved solution were ultrafiltered using Centricon-3 centrifugal concentrators. Since Centricon-3 centrifugal concentrators have a molecular weight cutoff of 3000, they were able to separate theophylline from PVP. The filtrate was analyzed by an isocratic HPLC method. The reversed-phase HPLC system consisted of a solvent delivery pump (Model Rabbit HP, Rainin Instruments, Woburn, MA) and a variable UV detector (Knauer,

Berlin) set at 280 nm. A nonpolar stationary phase (μBondapak C18, 10-μm particle size, 3.9 mm × 300 mm; Waters) column was used. The mobile phase was sodium acetate/ acetic acid buffer with 7% acetonitrile and had a pH of 3.85. The flow rate was 1.0 ml/min. The injection volume was 20 μl.

RESULTS AND DISCUSSION

Water Uptake Studies

The results of the moisture uptake experiments are presented in Figure 1. The percentage water uptake was plotted against the percentage relative humidity. The individual curves in the figure refer to various theophylline-PVP samples. The sample containing pure theophylline started taking up water only from 80% relative humidity. Above 80% relative humidity, the water uptake reached and stayed at a 10% increase in weight. The 10% water uptake corresponded to a complete stoichiometric conversion of theophylline anhydrous to theophylline monohydrate. This stepwise pattern is a characteristic of the anhydrate-hydrate system. The sample containing 100% PVP exhibited a smooth exponentially rising water uptake curve characteristic of amorphous polymer systems. Curves of theophylline-PVP mixtures exhibited a combination of stepwise and smooth curve characteristics. The smooth pattern became predominant as the PVP content in the sample increased. From Figure 1, it is evident that PVP picked up much higher levels of water than theophylline at any relative humidity. For example, at 54% relative humidity pure theophylline took no water. However, under the same conditions, pure PVP took as much as 20% water. The curves of special interest are those of the samples containing 6.9% PVP and 13.7% PVP. From Figure 1, it can be seen that there is an overlap between the water uptake curves of these samples with the water uptake curve of pure theophylline. These curves are presented in more detail in Figure 2. The 6.9% PVP sample and 13.7% PVP sample took less water than the pure theophylline sample at 80% RH. This observation is unexpected, since the overall water uptake of these samples should have been higher than that of pure theophylline. This suggests that the water uptake by either theophylline anhydrous or PVP or both is retarded. In a similar manner, the 6.9% PVP sample and 13.7% PVP sample at 85% RH did not show appreciably higher water uptake compared to pure theophylline.

X-ray Powder Diffraction Studies

X-ray diffraction spectra of theophylline anhydrous and theophylline monohydrate are presented in Figure 3. In both spectra, the peak observed at the 2θ value of 28 is due to the silicon that was added as an internal

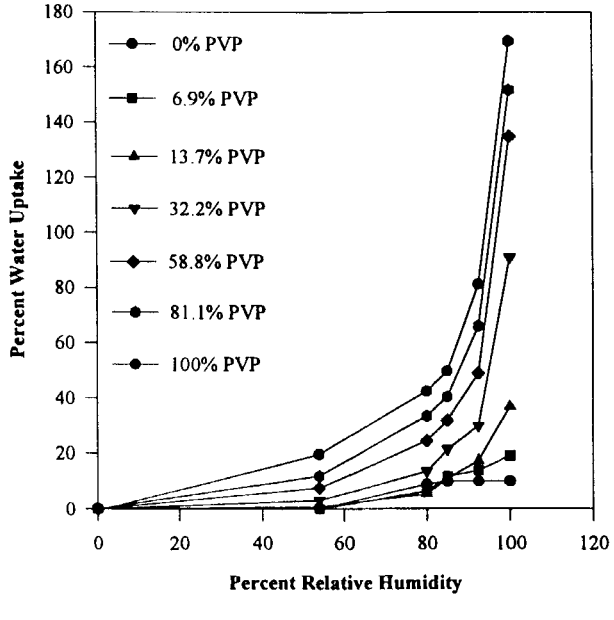

Figure 1. Water uptake isotherms of theophylline-PVP physical mixtures.

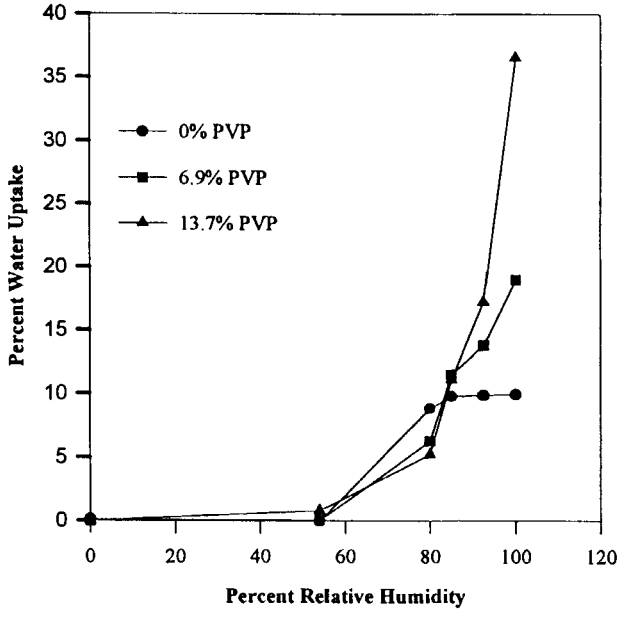

Figure 2. Water uptake isotherms of theophylline-PVP physical mixtures.

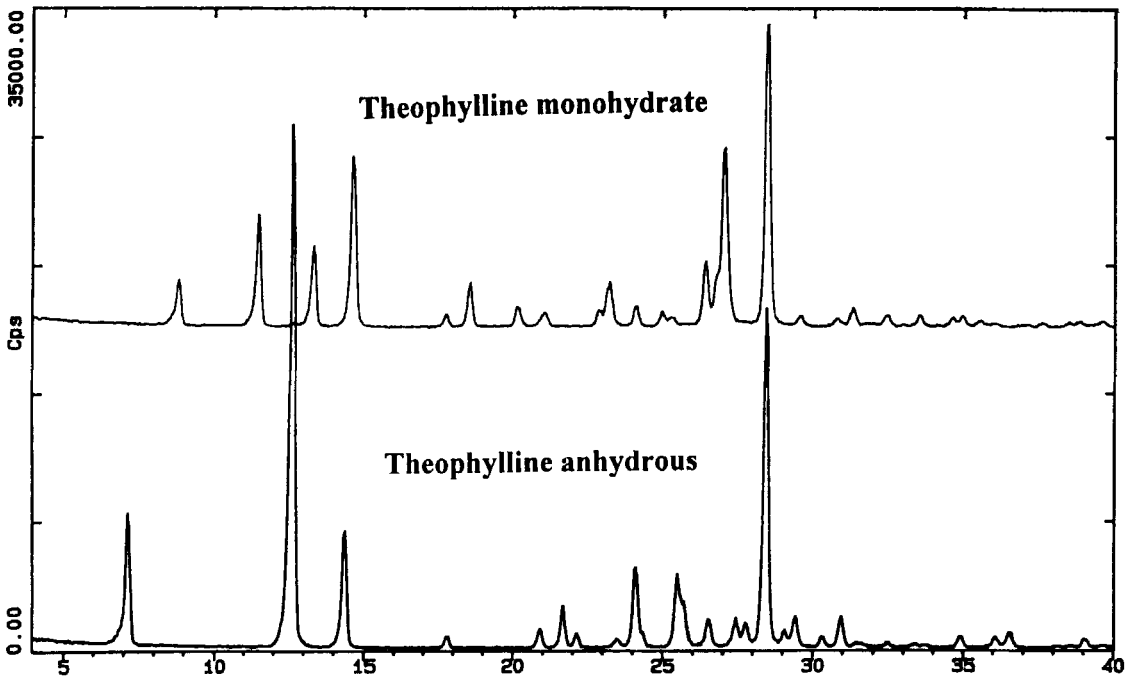

Figure 3. X-ray powder diffractograms of theophylline anhydrous and theophylline monohydrate (x-axis: 2θ values; y-axis: intensity).

standard. Theophylline anhydrous has an orthorhombic lattice structure. The unit cell parameters are a = 8.5 Å, b = 24.64 Å, c = 3.83 Å, and $\alpha = \beta = \gamma = 90°$. The characteristic strong lines of theophylline anhydrous appear at 7, 12.4, and 14.3 2θ values. Theophylline monohydrate has a monoclinic lattice structure. The unit cell parameters are a = 13.3 Å, b = 15.4 Å, c = 4.5 Å, $\alpha = \gamma = 90°$, and $\beta = 99.3°$. The characteristic strong lines of theophylline monohydrate appear at 8.9, 11.5, 13.3, and 14.58 2θ values. Since PVP is an amorphous polymer, it does not interfere with the x-ray powder diffraction of theophylline anhydrous and monohydrate.

Figure 4 shows the x-ray powder diffraction spectra of samples stored at 0% and 54% relative humidity. Under each group of humidity, the diffractograms are listed in the order of decreasing concentration of PVP from the top. The diffractogram at the bottom is that of pure theophylline. As the PVP concentration decreased, the signal intensity from theophylline anhydrous increased in these diffractograms. At 0% and 54% relative humidities, theophylline was present in its anhydrous state irrespective of the presence or absence of PVP. It was noted in the water uptake studies that the sample containing 81.1% PVP took as much as 12% moisture. The moisture taken up was possibly localized in PVP and not available for the hydration step.

Figure 5 presents several important observations in samples stored at 80% and 85% relative humidities. The pure theophylline sample showed peaks characteristic of both the anhydrous and monohydrate forms. This suggests that at 80% relative humidity theophylline converted from the anhydrous to the monohydrate form and therefore existed above the critical relative humidity of the hydration step. The 6.9 % PVP sample showed much stronger anhydrous peaks in addition to the hydrate peaks, indicating that a considerable proportion of theophylline existed in this sample in the anhydrous state, although in the same time period the pure theophylline sample itself converted into the monohydrate state to a larger extent. The sample containing 13.7% PVP showed evidence of no monohydrate form at all. This trend suggests that the addition of PVP led to the retardation of monohydrate formation.

This trend was also supported by the water uptake experiment. It was observed in the water uptake experiment that the samples containing 6.9% and 13.7% PVP took much less water than pure theophylline. It appears that at these humidities, PVP competitively took up the water molecules and thus prevented the hydration of

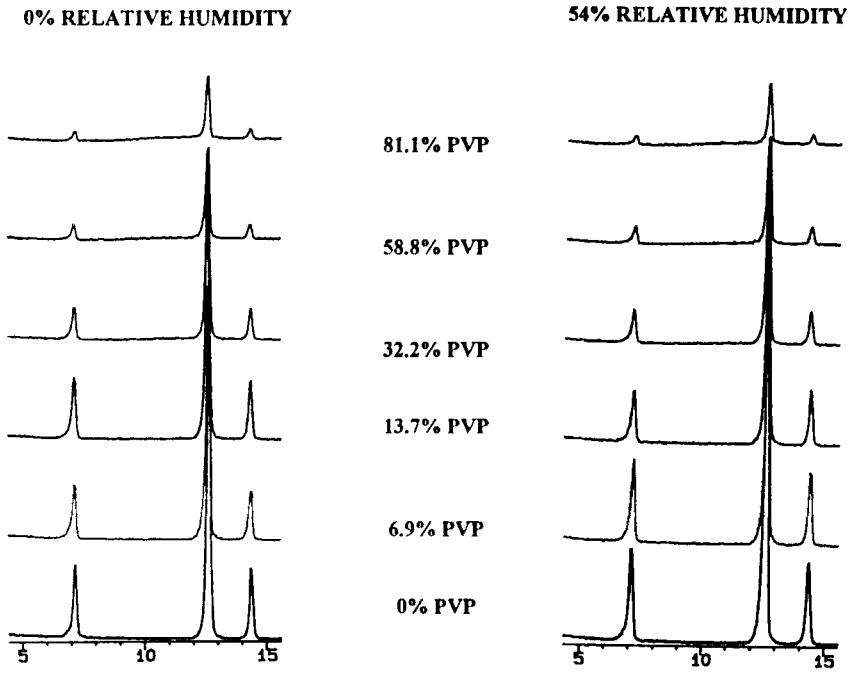

Figure 4. X-ray powder diffractograms of theophylline-PVP physical mixtures (x-axis: 2θ values; y-axis: intensity).

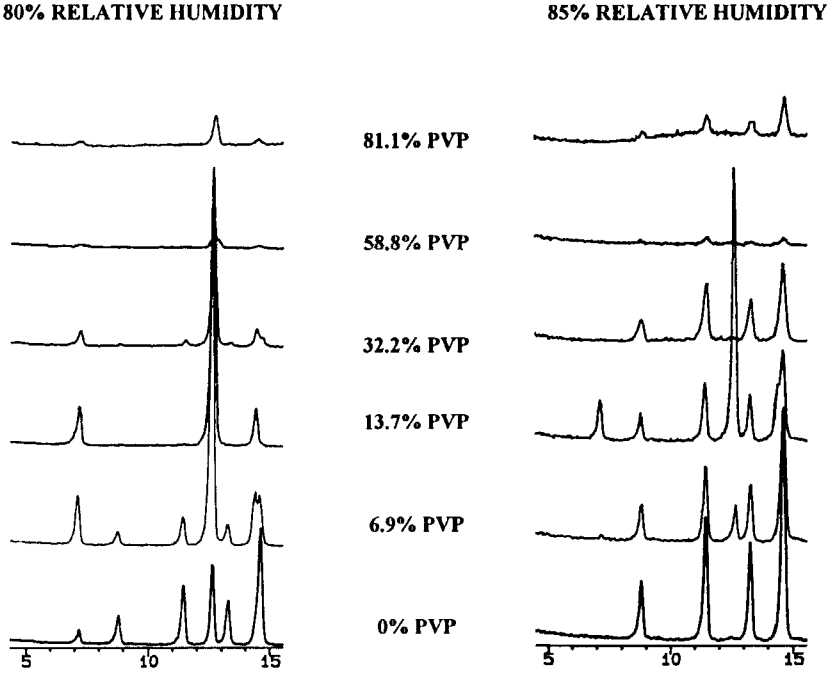

Figure 5. X-ray powder diffractograms of theophylline-PVP physical mixtures (x-axis: 2θ values; y-axis: intensity).

theophylline anhydrous to the monohydrate form. However, the samples containing 32.2% PVP indicated the presence of a mostly anhydrous form with trace levels of theophylline monohydrate. If the competitive mechanism were the only mechanism, there ought to be no trace of monohydrate in the 32.2% PVP sample. In samples containing 58.8% and 81.1% PVP only the anhydrous peaks were seen.

The observations made at 85% relative humidity also showed a similar trend. The pure theophylline sample had totally converted into monohydrate. The sample with 6.9% PVP was also primarily in the monohydrate form, although small anhydrate peaks were seen. The anhydrate peaks in the 13.7% sample were stronger than those seen in the 6.9% PVP sample. The extent of hydrate formation at 85% relative humidity was considerably more than that observed in 80% relative humidity. This led to the conclusion that the rate of hydration increases with the increase in relative humidity. This observation is also supported by the work of Zografi et al. (8–14). The samples containing 32.2% PVP, 58.8%PVP and 81.1% PVP indicated the presence of only the hydrate form. This suggests that PVP favors hydration by some mechanism while retarding hydration by competitive uptake. The hydration-favoring mechanism becomes significant when the proportion of PVP is above 32%.

Figure 6 shows the x-ray powder diffractograms of samples stored at 92.5% and 100% relative humidity. Theophylline was present as the monohydrate form in all the samples irrespective of the proportion of PVP in them. The protective phenomenon of PVP against hydration observed at 80% and 85% relative humidity totally disappeared in 92.5% and 100% relative humidity.

Fourier Transform Infrared (FTIR) Studies

Figure 7 illustrates the FTIR spectrum of theophylline anhydrous, theophylline monohydrate, and PVP. The following assignments were made for theophylline anhydrous. The bands at 1666 and 1715 cm^{-1} were assigned for the carbonyl stretch. The band at 1567 cm^{-1} was assigned for the imino (–CH=N–) stretch. Theophylline monohydrate showed a broad band around 3340 cm^{-1}. This band was assigned to the hydroxyl group stretching vibration of water molecules that are hydrogen bonded to theophylline molecules and other

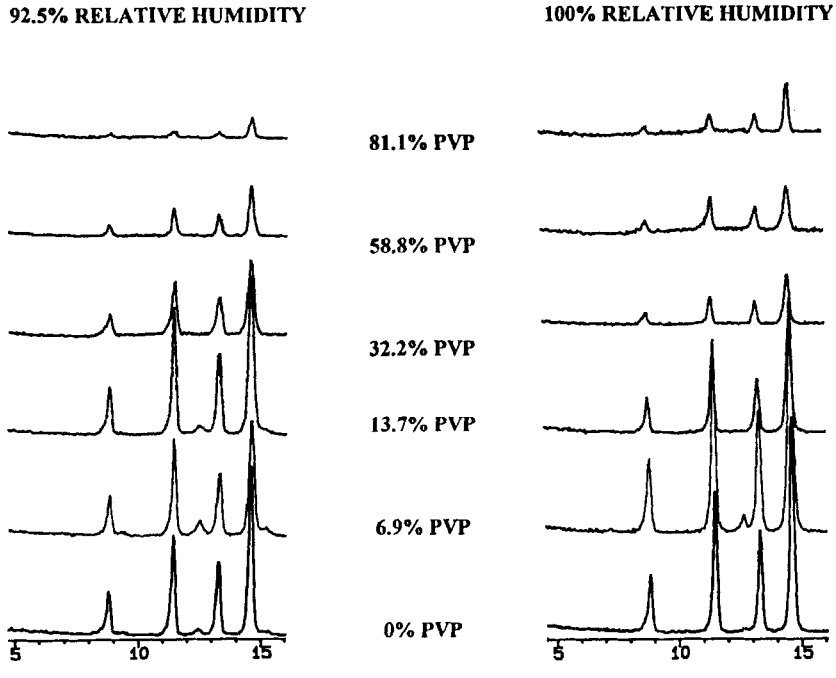

Figure 6. X-ray powder diffractograms of theophylline-PVP physical mixtures (x-axis: 2θ values; y-axis: intensity).

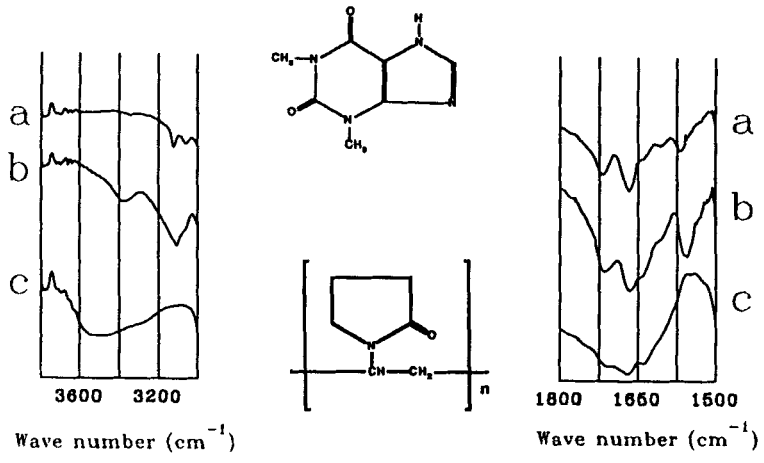

Figure 7. FTIR spectra of (a) theophylline anhydrous, (b) theophylline monohydrate, and (c) polyvinylpyrrolidone.

water molecules. Theophylline monohydrate also showed an absorption band at 1650 cm^{-1} that was attributed to the bending vibration of water molecules. In theophylline monohydrate, the imino band appears at 1555 cm^{-1} compared to at 1567 cm^{-1} for theophylline anhydrous.

The FTIR spectrum of PVP shows the following characteristics: an aliphatic (-C-H) stretch below 3000 cm^{-1} and a carbonyl absorption band around 1650 cm^{-1}. Figures 8 and 9 show the FTIR spectra of theophylline-PVP mixtures stored at various humidities. In each composition group, the characteristics of hydrate form appeared at 80% relative humidity, suggesting that irrespective of the percentage of PVP present in the sample, the hydrate form is present at 80% relative humidity. This is contrary to what was observed in the x-ray powder diffractogram of the 13.7% sample stored at 80% relative humidity. It was noted in this spectrum that the sample was totally anhydrous.

The other observations from FTIR spectra are as follows. The spectra were similar to those of PVP in samples containing 58.8% PVP and 81.1% PVP. The absence of any significant shift in the absorption bands of either theophylline anhydrous or theophylline monohydrate in different formulations indicated the absence of chemical interaction between theophylline and PVP. Higuchi and Kuramoto have also shown that PVP does not form a chemical complex with theophylline (15).

Chemical Stability

The retention time of theophylline in the HPLC experiment was 8.5 minutes. The sensitivity of the HPLC procedure adopted here was indicated by the fact that this method could separate the isomers theophylline and theobromine. None of the samples indicated any degradation of theophylline. Thus, theophylline was chemically stable during the experiment.

The Role of PVP and Relative Humidity on the Hydration of Theophylline Anhydrous

According to Zografi et al. (8–10), the hydrate formation starts appearing at the critical relative humidity and the hydration rate increases with the increase in relative humidity. This effect was clearly observed in our study. At the end of 45 days, at 80% relative humidity, pure theophylline had converted into a mixture of anhydrous and hydrate forms. During the same time period, the samples stored at 85%, 92.5%, and 100% relative humidities were all completely converted into monohydrate. A similar phenomenon of the increasing hydration rate with the increase in humidity also appears in 6.9% and 13.7% PVP samples. From our data, the critical relative humidity of theophylline is below 80% relative humidity.

According to Zografi et al. (3,4), the mobility of water molecules associated with the PVP is high at all relative humidities. Below its critical relative humidity, PVP stays in the "glassy" state. Despite the high mobility of water molecules, they are not freely available for interaction below the critical relative humidity. Above the critical relative humidity, the polymer exists in the "rubbery" state. In this condition, both PVP and water molecules attain high mobility. As a result, the water molecules are freely available for interaction with the drug. The critical relative humidity of PVP at 25°C

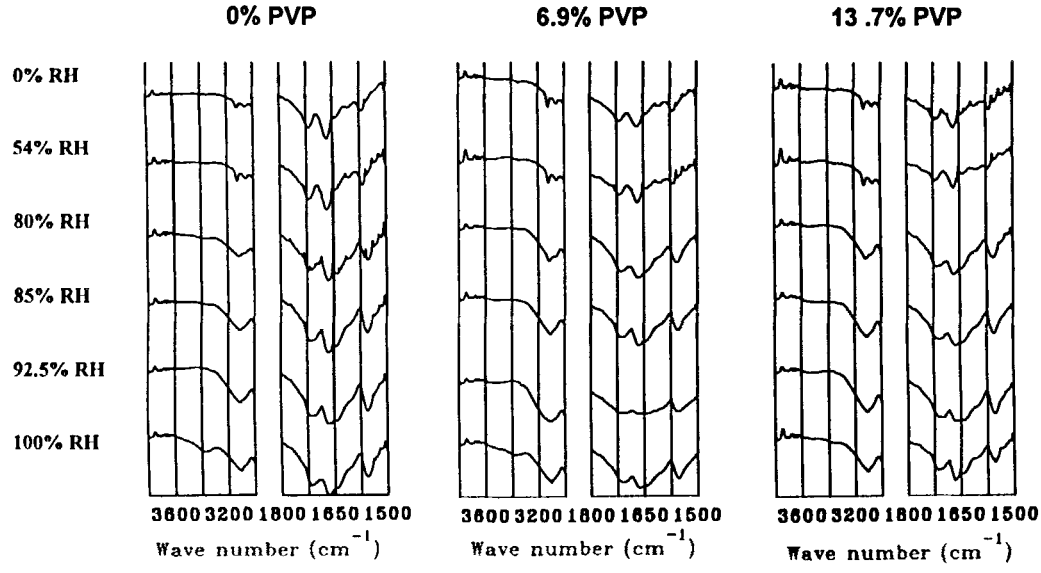

Figure 8. FTIR spectra of theophylline-PVP physical mixtures.

is close to 80% relative humidity from the literature (11).

Figure 10 presents the proposed mechanism of theophylline-PVP-water molecule interaction. Theophylline anhydrous could form monohydrate by two mechanisms. Water molecules in the atmosphere directly interact with the theophylline anhydrous to form theophylline monohydrate. The other mechanism occurs when the water molecules associated with the PVP are made available to theophylline to form theophylline monohydrate. These are illustrated as mechanisms 1 and 3 in Figure 10.

At 54% relative humidity, theophylline was below its critical relative humidity, and showed no tendency to form monohydrate by itself. Since PVP existed in its glassy state, water molecules were not available for

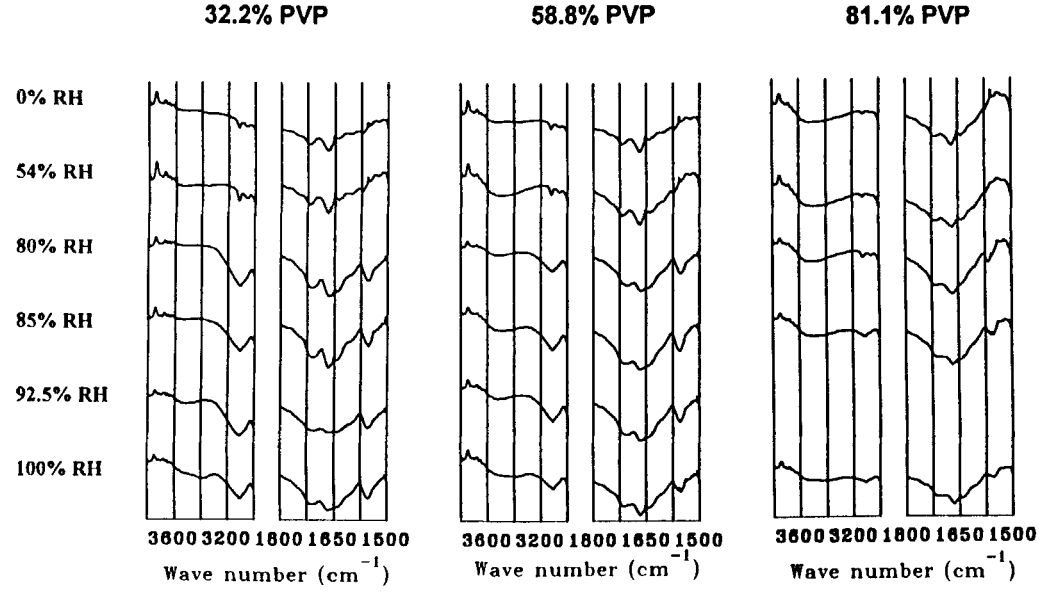

Figure 9. FTIR spectra of theophylline-PVP physical mixtures.

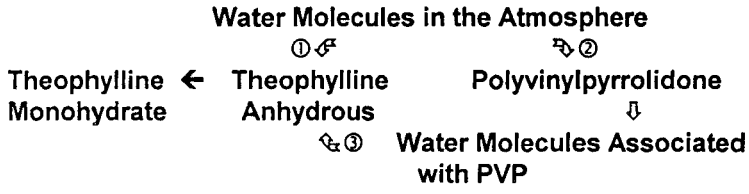

Figure 10. Proposed mechanism for the interaction of water molecules with theophylline anhydrous in the presence of PVP.

theophylline to form monohydrate, even though PVP present in the sample took considerable water at 54% relative humidity.

At 80% relative humidity, both theophylline anhydrous and PVP were above their critical relative humidity. Therefore, pure theophylline converted into a mixture of anhydrous and monohydrate. When PVP was added to the extent of 6.9%, the hydrate formation was considerably retarded by the competitive uptake of water molecules. The mechanism 3 of hydrate formation by water molecules associated with PVP was not a dominant force in this instance. The possible reasons were that the PVP-theophylline physical contact points were less in this sample and PVP existed only slightly above the critical relative humidity at 80% relative humidity. As a result, a large number of water molecules were not available for interaction. In the sample containing 13.7% PVP, hydration of theophylline by the first mechanism was totally blocked due to the larger proportion of PVP. Hence, there was no evidence of hydrate present in the x-ray powder diffractogram. The mechanism 3 of hydrate formation also occurred but only to a negligible extent. The evidence that the hydrate form was present in this sample is given by the FTIR spectra.

In the 32.2% PVP sample, theophylline existed primarily in its anhydrous state, with small hydrate peaks. This suggests that although by a competitive mechanism the hydrate formation by the first mechanism was totally inhibited, the third mechanism started becoming significant. This effect was probably due to the increased ratio of PVP to theophylline in the sample and correspondingly more physical contact points between theophylline and PVP.

In samples containing 58.8% and 81.1% PVP, evidently the second mechanism must be predominating. However, the x-ray powder diffractogram appeared to be more like that of the anhydrous form. This was possibly due to the following reasons. The relative intensity of theophylline anhydrous was higher than that of theophylline monohydrate. Since the concentration of the theophylline in these samples was low, the hydrate peak was probably buried in the baseline. The evidence that theophylline monohydrate was present in these samples was also provided by the FTIR spectroscopy. Perhaps the most convincing evidence comes from the 85% relative humidity data that support the events taking place at 80% relative humidity.

At 85% relative humidity, the hydration rate of theophylline was higher and the mobility of water molecules associated with PVP was also higher than that observed in 80% relative humidity. The combined effect led to the greater extent of hydration and lesser extent of protection afforded by PVP against hydration.

At 92.5% and 100% relative humidities, PVP was saturated with water quickly due to high relative humidities. Thus, the protective mechanism of PVP against theophylline hydration disappeared. The hydration rate of theophylline was also much higher, since theophylline was far above its critical relative humidity. The water associated with PVP was also freely available for interaction. The combined effects of these phenomena led to complete hydration of theophylline in all the samples stored at 92.5% and 100% relative humidities at the end of 45 days.

CONCLUSIONS

The theophylline hydrate formation is a rate phenomenon dependent on the RH. Above the critical relative humidity, the rate of hydration increases with the increase in relative humidity. The presence of PVP affects the hydrate formation in two different ways: (1) it retards the hydrate formation by competing with theophylline for water molecules and (2) it promotes the hydrate formation by delivering water molecules associated with it to the theophylline molecule located close in proximity. The second mechanism becomes significant only when the percentage of PVP is above 32.2% w/w and/or when the RH is high. The mechanism of protection by the PVP against the hydration of theophylline could be described as desiccant action. The efficiency of this desiccant action of PVP will then be dependent

on the amount of water molecules in the system and the kinetics of reaching the equilibrium moisture content.

REFERENCES

1. C. Ahlneck and P. Lundgren, Acta. Pharm. Suec., 22(6), 305 (1985).
2. C. Ahlneck and G. Alderborn, Acta. Pharm. Suec., 25, 41 (1988).
3. C. Ahlneck and G. Zografi, Int. J. Pharm., 62, 87 (1990).
4. H. M. Sadek and J. L. Olsen, Pharm. Technol., 5, 40 (1981).
5. P. York and A. O. Okhamafe, J. Pharm. Pharmacol., 37, 385 (1985).
6. D. R. Heidemann and P. J. Jarosz, Pharm. Res., 8(3), 292 (1991).
7. H. Ando, S. Watanabe, T. Ohwaki, and Y. Miyake, J. Pharm. Sci., 74(2), 128 (1985).
8. G. Zografi and C. A. Oksanen, Pharm. Res., 10(6), 791 (1993).
9. G. Zografi and B. C. Hancock, Pharm. Res., 10(9), 1262 (1993).
10. G. Zografi, L. Van Campen, and G. L. Amidon, J. Pharm. Sci., 72(12), 1381 (1983).
11. G. Zografi, L. Van Campen, and G. L. Amidon, J. Pharm. Sci., 72(12), 1388 (1983).
12. G. Zografi, L. Van Campen, and G. L. Amidon, J. Pharm. Sci., 72(12), 1394 (1983).
13. G. Zografi and M. J. Kontny, J. Pharm. Sci., 74(2), 124 (1985).
14. G. Zografi, M. J. Kontny, and G. P. Grandolfi, Pharm. Res., 4(2), 104 (1987).
15. T. Higuchi and R. Kuramoto, J. Pharm. Sci., 43(7), 393 (1954).