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ACCELERATED STABILITY OF AN X-RAY AMORPHOUS FRUSEMIDE-POLYVINYLPYRROLIDONE SOLID DISPERSION

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ABSTRACT

An accelerated stability study compared the chemical, solid state and physicochemical stability of an X-ray amorphous frusemide-polyvinylpyrrolidone (PVP) solid dispersion system (the test system) with a standard frusemide sample during storage for 12 months at 6, 20, 30, 37 and 45°C.

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No chemical degradation was found in any sample and the drug phase in the solid dispersion was shown by X-ray analysis to remain in the amorphous or non-crystalline state even after storage for 12 months at up to 45°C and 40%RH. DSC data for the test dispersion demonstrated a change in the PVP-moisture endotherm after storage for 12 months at 37° and 45°C, while a lack of frusemide endotherms confirmed X-ray data which indicated the presence of an amorphous drug phase. IR analyses indicated that the intermolecular frusemide-PVP hydrogen bond interaction in the solid state remained intact during the study leading to the conclusion that the specific drug-polymer interaction retards or inhibits drug recrystallisation by reducing molecular motion in the solid state. The dissolution rate of the test dispersion was found not to decrease during the study reflecting the stability of the X-ray amorphous drug phase.

Whilst the combination of high humidity (75%RH) and high temperature (45°C) was found to be detrimental to the physical state of the amorphous frusemide-PVP dispersion, provided moisture-resistent packaging is used for these pharmaceutical formulations, acceptable shelf lives are predicted.

INTRODUCTION

The stability testing of pharmaceutical formulations at elevated temperatures is undertaken to examine chemical, physical and microbiological properties over short periods of time. These studies provide useful information concerning the suitability of formulations for

use as commercial products so as to provide an adequate shelf-life and consistent, predictable in vitro and in vivo dissolution behaviour.

A major criticism of drug-polymer solid dispersion systems has been poor stability, reflected in progressively decreasing in vitro dissolution rates on storage[1].

Reductions in dissolution rates for aged samples have been reported for drug-polyethylene glycol (PEG) systems, for example, griseofulvin-PEG[2] and indomethacin-PEG[3]. These effects are thought to involve a particle coarsening or an increase in crystallinity of the drug particles within the dispersion, as demonstrated by differential scanning calorimetry (DSC), X-ray powder diffraction (XPD) and microscopic methods. Storage time, temperature, humidity and drug content in the dispersion were found to be important factors in the stability of drug-PEG dispersions[4].

However, few reports have demonstrated reduced dissolution rates for aged drug-polyvinylpyrrolidone (PVP) systems. Several authors have reported no changes in physicochemical properties after storage for periods of 9 months to 2 years at room temperature[5,6,7]. However, high humidity levels have been shown to be detrimental to some drug-PVP solid dispersion systems[8,9,10]. It was demonstrated[10] using DSC and XPD, that PVP markedly reduced the recrystallisation of indomethacin from a XPD-amorphous solid dispersion in comparison to the rapid recrystallisation of the drug from an amorphous form of the drug alone.

Since the maximum in vitro dissolution rate for drug-PVP solid dispersion systems generally involves an amorphous drug phase[11], it is essential to prevent time-dependent recrystallisation of the drug. Drug recrystallisation is likely to occur from metastable amorphous drug

phases on storage, enhanced by increased temperature and/or humidity unless retarded by the use of polymers that inhibit crystallisation, such as PVP. The validity of this approach is examined here for an XPD-amorphous frusemide (furosemide)-PVP solid dispersion system.

MATERIALS AND METHODS

Frusemide BP was obtained from A.P.S. Ltd., Cleckheaton, UK (lot no. 309277) and PVP as Kollidon 25 from BASF, West Germany. All other chemicals were of analytical grade unless stated.

The frusemide-PVP test solid dispersion system (nominally 40% w/w frusemide + 60% w/w PVP) was prepared by the solvent evaporation method from a methanolic solution in a vacuum oven (Gallenkamp OVL570, 2.5×10^3Pa, 50°C). The experiments to be described were carried out on the dried, seived portion (90-250μm).

Frusemide content was assessed by HPLC using a Pye Unicam LC pump, Partisil-ODS 10μm column, acetonitrile-orthophosphoric acid (0.0157M) (35%:65%v/v) mobile phase and 20μL injection loop. Frusemide, shown to be well separated from the main degradation product (2-amino-4-chloro-5-sulphamoyl-anthranilic acid)[12], was analysed by UV spectroscopy at 272nm. Each sample, and an external frusemide standard, were injected alternately at least in triplicate.

X-ray powder diffraction spectra (XPD) were obtained on a Philips PW1200/00 generator (20mA, 30KV) with a proportional detector probe and copper-potassium-alpha radiation. A scan speed of 2° 2Ø/min was used for diffraction angles, 2Ø, equal to 4-40°. Powdered samples were

prepared by filling a cavity in a metal sample holder and smoothing with a glass slide.

Differential scanning calorimetry (DSC) thermograms were obtained at least in duplicate using a Dupont 910 DSC and 1090 thermal analyser calibrated with indium metal (99.9% purity, Dupont, melting point 156.6°C) and checked with dicyandiamid (Reichert, Vienna, melting point 210°C). A scan speed of 10°C/min between 40-270°C was used for sample sizes of 6-7mg.

Dispersive IR spectra were obtained on an automated spectrophotometer (Perkin Elmer PE681 with data station). This apparatus averaged repeated scans and by spectral subtraction procedures, removed the PVP spectral vibrations from drug-PVP spectra, allowing differential analysis of the frusemide vibrations. Samples to be examined were compressed into a disc with potassium bromide.

Dissolution data were obtained from a constant surface area disc (details of the method used have been previously published[11]), using a pH 4.95 sodium acetate-acetic acid buffer system (37°C). Frusemide dissolution was monitored by UV spectroscopy at 272nm using an automated diode array spectrophotometer (Hewlett Packard HP8451A). Each sample was analysed at least in duplicate and the coefficient of variance (CV) of the dissolution test was 2.29% CV (n=8). The dissolution rate was defined as the slope of the mass dissolved-time profile, with units of mg/min.

PROTOCOL FOR THE STABILITY STUDY

A 40% w/w frusemide-PVP solid dispersion, classified as XPD-amorphous[13], was chosen as the model test sample from a series

of frusemide-PVP dispersions[11] on the basis of optimal in vitro dissolution enhancement and compared with an untreated frusemide sample (the standard). Powder sieve fractions of 90-250μm were used throughout. An accelerated stability protocol was developed using five temperatures (6, 20, 30, 37, 45 ±1°C) and samples were analysed after storage for 0, 1, 3, 7 and 12 months. Initially the effect of humidity was not included in the study and freshly prepared frusemide-PVP dispersion and untreated frusemide samples were equilibrated at 20°C and 40% RH for 48 hours in open containers prior to the study. Subsequently the containers were sealed and stored in the dark. After 3 months of storage the effect of humidity was assessed at two temperatures (20°, 45°C) with a humidity of 75% RH (saturated sodium chloride solution in a desiccator).

The test dispersion sample was compared with the frusemide standard and pure PVP alone (the polymer being treated in the same manner as the solid dispersion).

In addition to visual observations examination of the samples comprised;

A. Chemical Analysis:	Utilising HPLC quantification of the frusemide content.
B. Solid State Analyses:	To assess the stability of the XPD-amorphous drug phase in the solid dispersion and the integrity of the drug-polymer interaction, samples were examined by XPD, DSC and IR.
C.Physicochemical Analysis:	This comprised measurement of the dissolution rate.

RESULTS AND DISCUSSION

Physical Appearance

No change in the physical appearance of the frusemide standard occurred under any storage condition. The colour of the test solid dispersion, initially off white-pale yellow, progressively deepened with increasing storage time at elevated temperature and high humidity. The dispersion sample at 45°C and 75% RH became a solid yellow mass within 3 months and the PVP alone produced a soft yellow gel-like mass under the same conditions, while powder samples stored under all other conditions remained in the free-flowing state. The changes in colour and consistency of the test dispersion when stored at high temperature and humidity are considered to arise from changes in the material characteristics of the polymer rather than those of the drug, and these effects were examined by DSC.

Chemical Stability

The frusemide content of the standard frusemide and test solid dispersion was determined after storage for 0, 7 and 12 months.

The HPLC assay of the frusemide standard was found not to change during the study (>99% w/w). The frusemide content in the test dispersion, initially 38.4% w/w, was found not to change after storage for 12 months at temperatures up to 45°C and 40% RH (table I). A small reduction (3-6% w/w) in the frusemide content was detected in samples

TABLE I

Average frusemide content (n=3) in the test frusemide-PVP solid dispersion, initially, and after ageing under controlled conditions for 7 and 12 months.

Temp (°C)	RH (%)	Frusemide Content (±S.D.) (% W/W) Storage Time (Months) 0	7	12
6	40		38.7 (0.5)	38.3 (0.2)
20	40		38.8 (0.3)	38.2 (0.1)
30	40	38.4 (0.3)	38.4 (0.4)	38.6 (0.2)
37	40		38.3 (0.8)	38.8 (0.3)
45	40		36.8 (0.8)	38.2 (0.1)
20	75[1]		37.4 (0.2)	36.6 (0.1)
45	75[1]		36.2 (0.7)	-

[1]samples were stored initially at 20°C and 40% RH for 3 months.

exposed to 20° and 45°C and 75% RH, but this may reflect moisture absorbed by the PVP since no sign of degradation was observed in the stability-indicating assay.

Solid State Stability

XPD spectra were obtained for the initial samples and after storage for 8 and 12 months. No changes were seen in the standard frusemide spectra after storage for 12 months at 45°C and 40% RH. The XPD spectra for the test frusemide-PVP solid dispersion (figure 1), initially and after storage for 12 months at 6, 20, 30, 37 and 45°C and 40% RH displayed typical amorphous spectra, with no evidence of frusemide diffraction peaks. The initial XPD spectrum for the test dispersion and the aged spectra, while both displaying an amorphous pattern, appeared to differ slightly in intensity, an effect which is attributed to equipment variation at the two testing stages. The dispersion sample stored at 45°C and 75% RH being a solid mass was unsuitable for analysis. The drug phase in the 40% w/w frusemide-PVP solid dispersion was shown not to recrystallise under the conditions of the test and this is indicative of a stabilisation effect of the PVP component.

DSC thermograms were obtained for the initial samples and after ageing for 7 and 12 months. No changes were observed in the DSC thermograms of the standard frusemide samples after storage for 12 months at up to 45°C and 75% RH.

The DSC thermograms of the initial and aged test dispersion are shown in figures 2 and 3. No endotherms corresponding to those in the

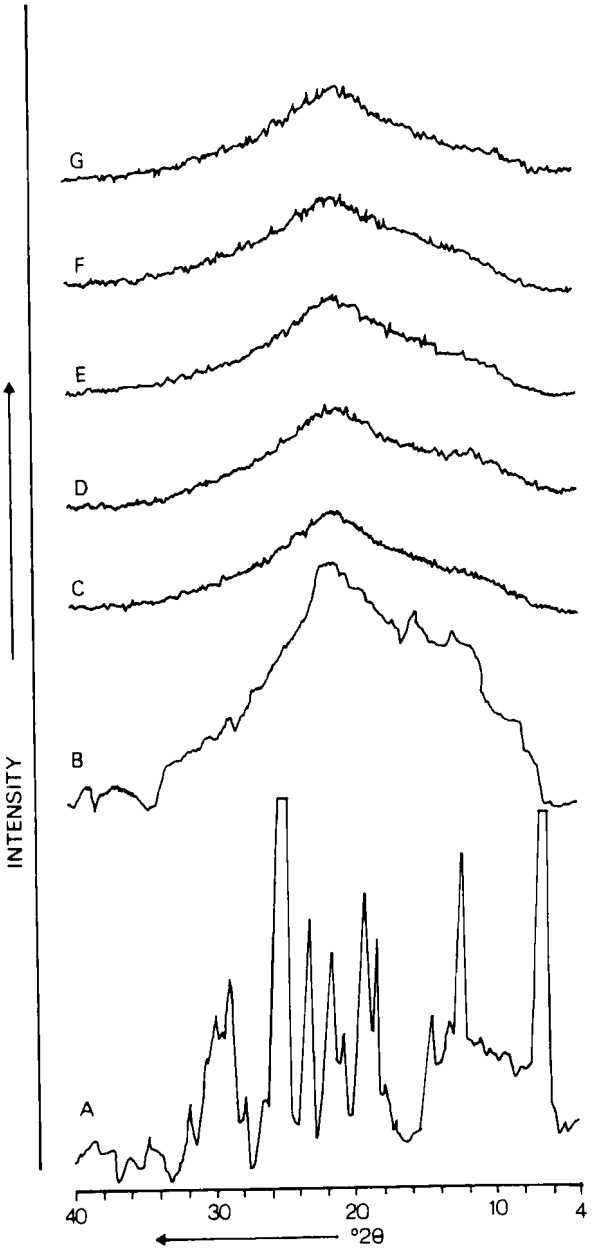

FIGURE 1

XPD spectra for untreated frusemide (A) and the frusemide-PVP test dispersion initially (B), and after storage under the following controlled conditions for 12 months; 6°C/40% RH (C), 20°C/40% RH (D), 30°C/40% RH (E), 37°C/40% RH (F), 45°C/40% RH (G).

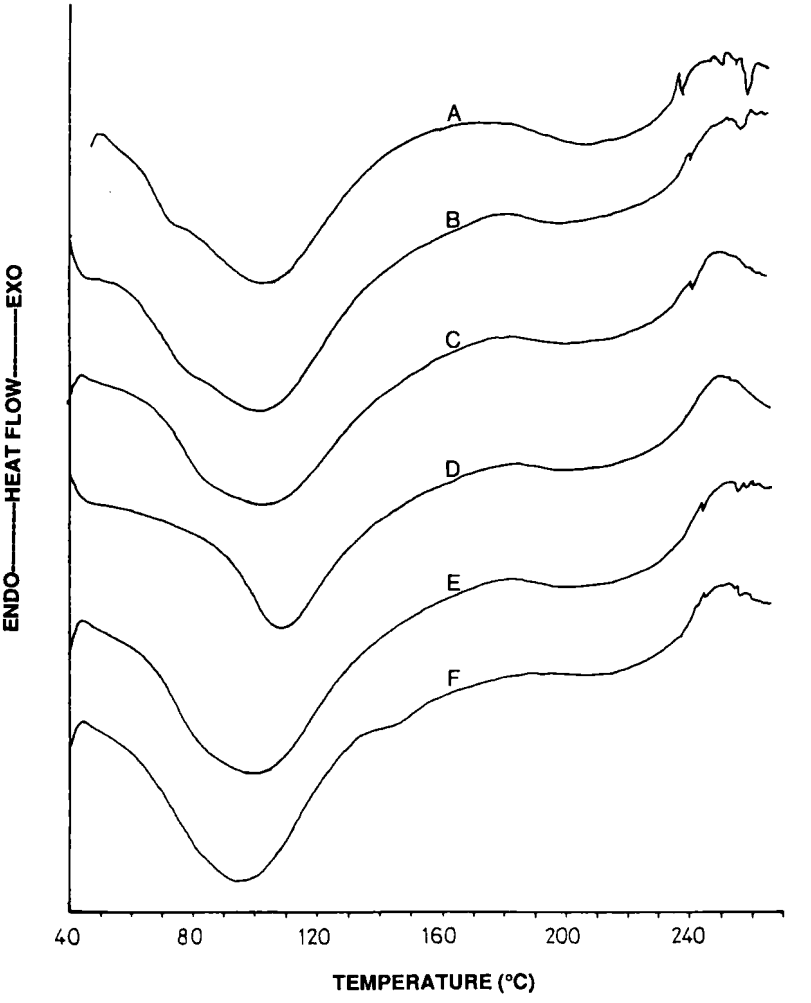

FIGURE 2

DSC thermograms for the test frusemide-PVP dispersion initially (A), and after storage for 7 months under the following controlled conditions; 6°C/40% RH (B), 20°C/40% RH (C), 45°C/40% RH (D), 20°C/75% RH (E), 45°C/75% RH (F).

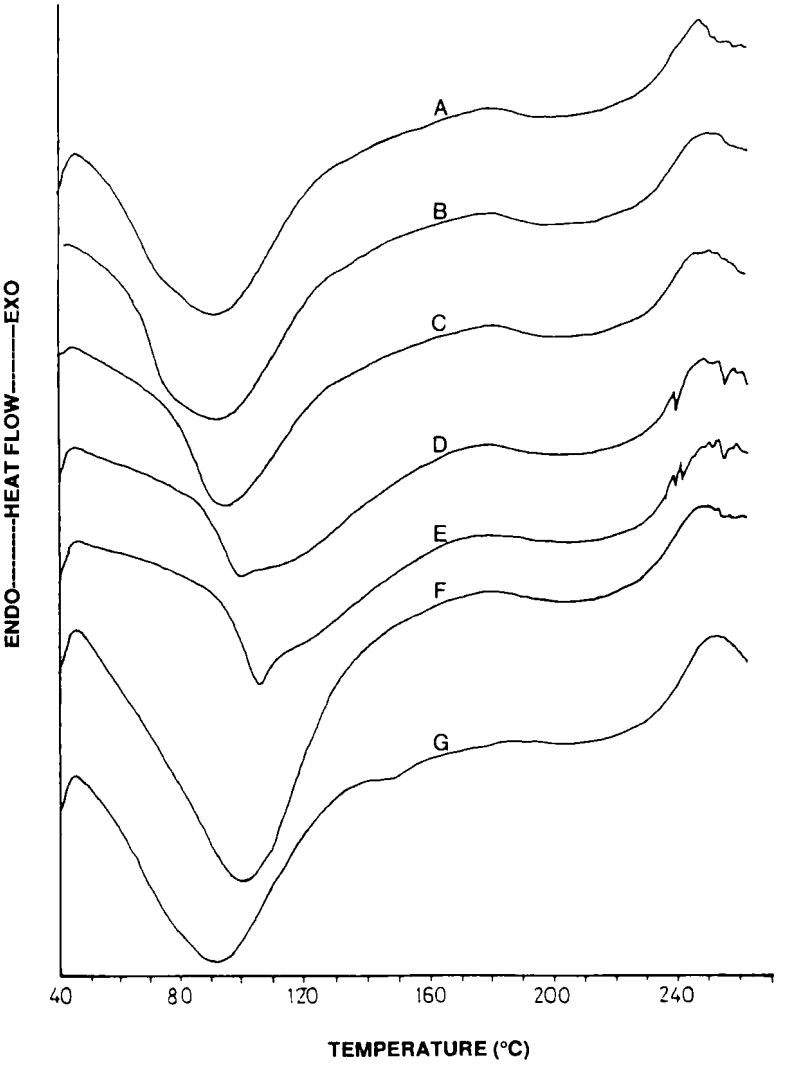

FIGURE 3

DSC thermograms for the test frusemide-PVP dispersion after storage for 12 months under the following controlled conditions; 6°C/40% RH (A), 20°C/40% RH (B), 30°C/40% RH (C), 37°C/40% RH (D), 45°C/40% RH (E), 20°C/75% RH (F), 45°C/75% RH (G).

frusemide standard thermogram were seen in any sample and this supports the conclusion from the XPD data that the aged dispersions are amorphous or non-crystalline in nature. However, changes in the aged samples were apparent for the broad endothermic peak centered at 100-110°C in the initial DSC scan of the test dispersion, which represents moisture loss from the PVP component. This endotherm was seen to decrease in magnitude and become sharper while the peak temperature increased with increasing storage temperature at the lower humidity level (40% RH). This effect may indicate that the surface moisture associated with PVP is lost initially, and the more tightly bound water molecules remaining produce a sharper endothermic peak at a higher temperature. The magnitude of these effects was shown to be time-dependent, being observed after 7 months storage but more pronounced after 12 months.

An infrared study of the interaction between frusemide and PVP in the solid state has been reported[14]. Spectral subtraction procedures were utilised that revealed wavelength shifts for frusemide N-H stretching vibrations in the XPD-amorphous dispersion samples (40% w/w drug). These shifts were attributed to a solid-state hydrogen bond interaction between the frusemide sulphonamide group and PVP. It is hypothesised that this interaction will retard or inhibit recrystallisation of frusemide from the metastable XPD-amorphous phase. To test this hypothesis IR spectral subtractions for the XPD-amorphous dispersion and standard frusemide samples were obtained at the 7 and 12-month testing stages.

No changes in the IR spectra of the aged standard frusemide samples were found and the spectra resembled that of crystalline frusemide (figure 4). Spectral subtraction procedures were used to

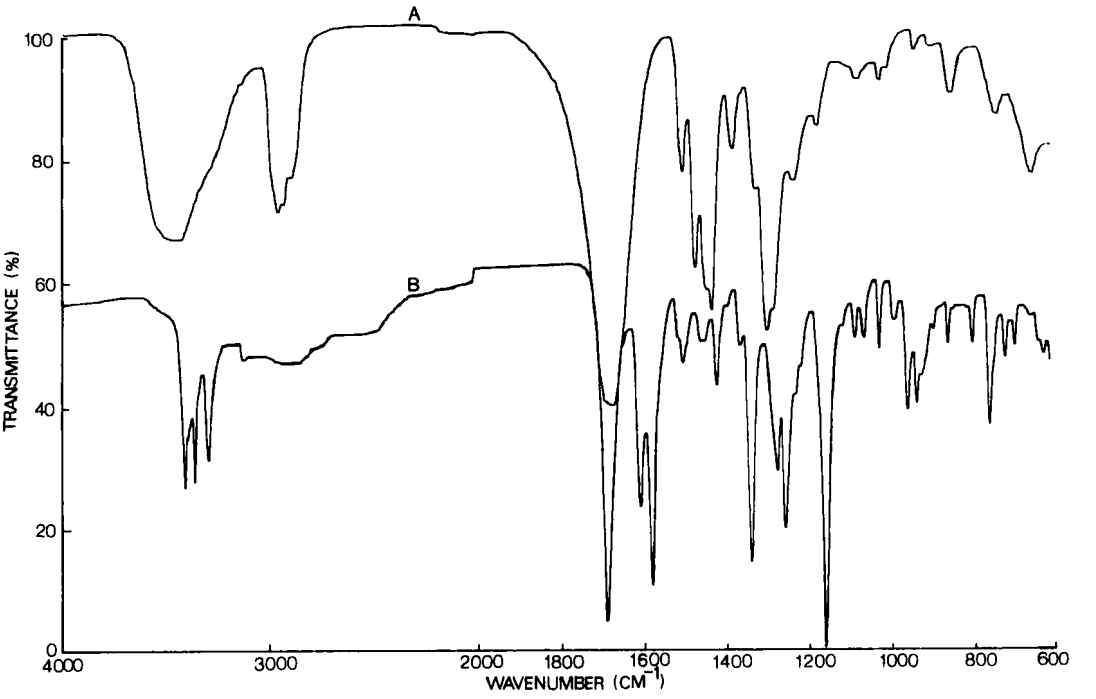

FIGURE 4

Dispersive IR spectra using potassium bromide discs for PVP (A) and untreated frusemide (B).

remove the PVP vibrations (figure 4) from the test solid dispersion spectra and representitive subtracted spectra are shown in figure 5. No changes in the position of the frusemide vibrations, in comparsion to the initial spectrum, were observed in any of the aged samples studied. The data indicate that there were no detectible changes in the frusemide-PVP hydrogen bond interaction in the test solid dispersions stored for 12 months at temperatures up to 45°C and 40% RH. This conclusion, and the absence of frusemide XPD peaks in the aged dispersion, support the proposed model that the specific drug-polymer

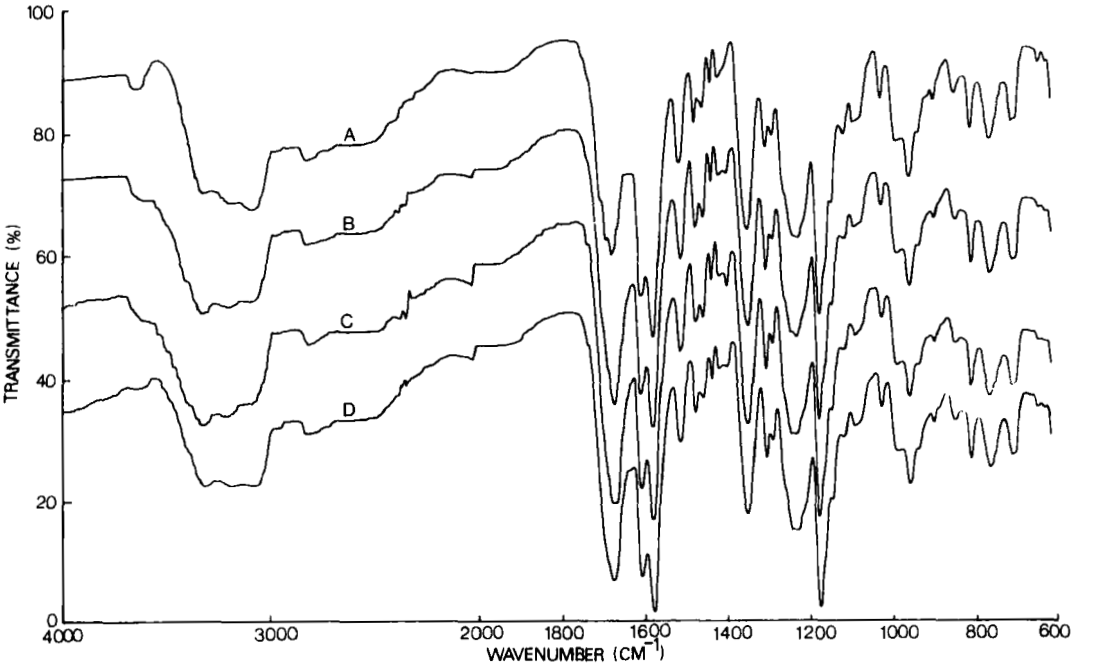

FIGURE 5

IR spectral subtractions (PVP spectral vibrations removed) for the test frusemide-PVP dispersion, initially (A) and after ageing for 7 months under the following controlled conditions; 6°C/40% RH (B), 20°C/75% RH (C), 45°C/40% RH (D).

interaction effectively stabilises an otherwise unstable drug phase. This stabilisation may be achieved by retardation of the migration of frusemide molecules in the solid state inhibiting the formation of crystallisation nuclei.

Physicochemical stability

The principal rationale for using a drug-polymer solid dispersion is to enhance the dissolution rate of the drug. The dissolution rate was

TABLE II

Average frusemide dissolution rate from constant surface area discs (±2.29% CV) in pH 4.95 acetate buffer (37°C) for the test frusemide-PVP solid dispersion initially and after ageing under controlled conditions for 1, 3, 7 and 12 months.

		Frusemide Dissolution Rate (mg/min x1000)				
Temp.	RH	Storage Time (months)				
(°C)	(%)	0	1	3	7	12
6	40	677.8	736.3	702.5	741.4	744.2
20	40		713.9	729.0	694.8	735.5
20	75[1]		-	-	744.9	776.7
30	40		742.9	729.4	739.1	727.7
37	40		732.2	723.1	690.1[2]	743.1
45	40		735.5	746.2	683.8[2]	769.3

[1] samples were stored initially at 20°C and 40% RH for 3 months.

[2] problems were encountered compressing these powders.

measured from constant surface area discs for standard frusemide and test dispersion samples after storage for 0, 1, 3, 7, and 12 months. No significant changes were found in the dissolution rate of the frusemide standard during the study and the dissolution rate ranged from 21.3-24.2 mg/min (x1000).

The dissolution rate data for the test frusemide-PVP XPD-amorphous dispersion are shown in table II. A minor increase in the frusemide dissolution rate (7.4%) from the test solid dispersion was shown at the 1 month testing stage in all samples, but no causative factor could be identified. This increased rate was sustained for the duration of the 12 month study. The data demonstrate that no decrease in the frusemide dissolution rate was evident in the XPD-amorphous frusemide-PVP solid dispersion after storage for 12 months at 45°C and 40% RH. The test solid dispersion retained a dissolution enhancement, relative to crystalline frusemide, of 31-36 (fold) after storage under the test conditions.

The stability data indicate that the XPD-amorphous frusemide phase in the solid dispersion is stable under the conditions of the test and as a consequence the in vitro dissolution rate remains unchanged. These data are consistent with those of other workers who have found amorphous drug-PVP dispersions to be stable for periods ranging from 9 months to 2 years[5,6,7]. The prolonged stability of the XPD-amorphous drug phase may result from the ability of PVP to act as a crystallisation inhibitor and, in the case of the frusemide-PVP system, from the proposed drug-polymer hydrogen bond interaction which may inhibit or retard molecular movement in the solid state.

CONCLUSIONS

1. The accelerated stability study of the test XPD-amorphous frusemide-PVP solid dispersion showed that the drug was chemically stable when stored for 12 months at temperatures up to 45°C and 40% RH.
2. XPD analyses demonstrated that the drug phase in the frusemide-PVP dispersion remained in an XPD-amorphous or non-crystalline state after storage for 12 months at temperatures up to 45°C and 40% RH. DSC thermograms indicated a change in the moisture distribution in the PVP component of the dispersion when stored at 37° or 45°C and 40% RH.
3. No marked changes were found in the dissolution rate from constant surface area discs for frusemide-PVP solid dispersions aged for 12 months at temperatures up to 45°C and 40% RH.
4. The stability data presented indicate that XPD-amorphous drug-PVP solid dispersions can possess suitable stability for use as pharmaceutical formulations.

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