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THE PREPARATION AND STABILITY OF FAST RELEASE FUROSEMIDE - PVP SOLID DISPERSION

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ABSTRACT

Furosemide-PVP solid dispersion systems were prepared by co-evaporation and freeze-drying methods. The X-ray diffraction patterns indicated that furosemide

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in the coprecipitates was in amorphous form. The dissolution rate of furosemide was markedly increased in these solid dispersion systems. The increase in dissolution was a function of the ratio of drug to PVP used. With 1:7 ratio the best result was obtained. The 49000 mol. wt. PVP yielded the most rapid furosemide dissolution. Dissolution studies have shown that coprecipitate of furosemide-PVP (1:7) is the best combination. Factors contributing to the enhancement of furosemide dissolution from the dispersion in PVP were discussed. The increase in release rates was attributed to the increased wettability, coacervate formation and the complexation.

The effect of aging on furosemide-PVP solid dispersions has been investigated. After storage, under the different humidities (55%, 70% and 85% RH) coprecipitates showed no change in either dissolution rate or X-ray diffraction patterns.

INTRODUCTION

It is known that solid dispersions of poorly soluble drugs and water-soluble carriers increase drug dissolution and bioavailability (1-3). As an inert carrier, povidone (polyvinylpyrrolidone) inhibits crystal growth and phase tranformation (4,5). It has also approved for use in oral medications (6).

Furosemide is a poorly soluble diuretic and exhebits erratic dissolution characteristics and bioavailability (7-9). On the other hand very limited information is available for the solid dispersion system of furosemide (10-12). Therefore an attempt to modify the dissolution characteristics of furosemide by preparing solid dispersion system using polyvinylpyrrolidone (PVP) was made and the effects of preparation techniques, molecular weight of PVP and the particle size of coprecipitate on the drug dissolution were also investigated.

Furthermore the effect of aging on the dissolution of solid dispersion systems has not been extensively reported (13,14). In this paper the stability of furosemide-PVP solid dispersion systems was also studied.

EXPERIMENTAL

Materials

Furosemide (Hoechst A.G. Frankfurt, W. Germany), polyvinylpyrrolidone [PVP K-25, K-30, K-90 (BASF, D-ludwigshafen, W. Germany)], methanol (Riedel-de-Haen A.G. Seelzo-Hannover W. Germany).

Methods

Preparation of Solid Dispersions

Solid dispersion systems containing different ratio of furosemide-PVP were prepared as follows.

I- Co-evaporation Method : A weighted quantity of furosemide and PVP were dissolved in a minimum volume of methanol and the solvent was removed by evaporation in a rotary evaporator (Ika-werk, Janke & Kunkel GmbH) and dried. The residue was powdered and particles in 100-mesh size were used.

II- Freeze-drying Method : Both furosemide and PVP were dissolved in a minimum amount of ammonium solution (10%) and the solution was freeze-dried (Lyovac GT2, Leybold-Heraeus). The residue was stored in dessicator then dried and powdered as mentioned above. The residual ammonia in the solid dispersion systems was checked.

Different furosemide to PVP ratios were used in the preparation of solid dispersion systems.

Physical mixtures of furosemide-PVP of weight fractions similar to coprecipitates were prepared by mixing the drug and carrier in a mortar with a spatula.

TLC technique was applied for detecting possible decomposition.

X-Ray Diffraction Studies

X-ray powder diffraction patterns were obtained using an X-ray powder diffractometer [General Electric xRD-7 (three circle)] employing nickel filtered CuK α radiation.

IR-Analyses

Perkin Elmer infrared spectrophotometer was used to obtain IR analyses of samples.

Dissolution Rate Studies

For the dissolution rate determinations, Levy's beaker method was used (15). The dissolution medium was 0.1 N hydrochloric acid at 37 ± 0.5° and rotated at 100 rpm. Weighted amounts of coprecipitate or physical mixture were directly added on the medium and drug content was spectrophotometrically (Varian Techtron Series 634 Spectrophotometer) determined at 272 nm. The results are the mean of 6 determinations. Corrections were made for any absorption due to PVP.

Effect of PVP Molecular Weight on Drug Release

By using PVP K-25, K-30, K-90 (average molecular weight 25000, 49000, 1100000) coprecipitates and physical mixtures of furosemide and PVP were prepared as described previously.

Effect of Coprecipitate Particle Size on Drug Release

Coprecipitates having different particle size were prepared and the dissolution rates of these coprecipitates were determined as mentioned above.

Solubility and Surface Tension Measurements

The effect of PVP concentration on the solubility of furosemide, in distilled water and 0.1 N hydrochloric acid at 25 ± 0.2° was determined by shaking an excess of powdered drug with solvent in a water-bath. Samples were withdrawn and assayed spectrophotometrically at 272 nm.

Surface tension was measured by using drop weight method.

Stability Studies

Powdered samples were stored in screw-capped bottles at different relative humidities (55%, 70% and 85% RH) at ambient temperature for 5 months and the dissolution rates of coprecipitates were determined. The X-ray diffraction patterns were also investigated during the tests.

RESULTS and DISCUSSION

Properties of Furosemide-PVP Solid Dispersion Systems

The X-ray diffraction patterns of furosemide, PVP, furosemide-PVP solid dispersion systems and physical mixtures are shown in Fig. 1. By coprecipitation with PVP, the sharp diffraction peaks attributed furosemide crystals disappeared. As seen in this figure, the

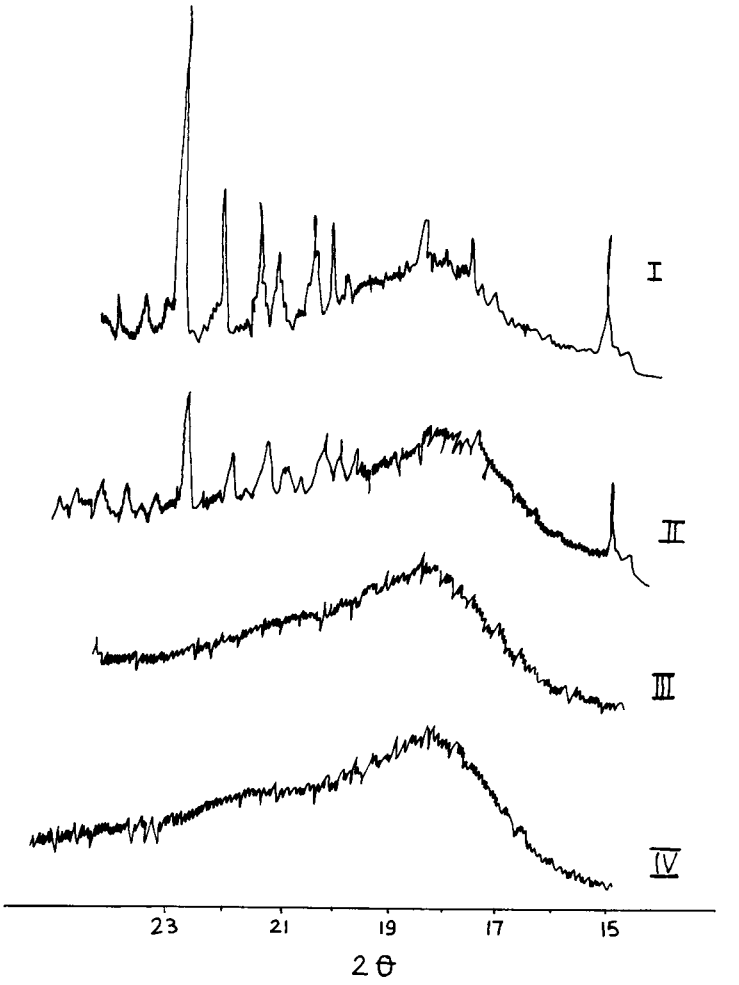

FIGURE 1

X-ray Diffraction Patterns; Furosemide (I), Furosemide-PVP, Physical Mixture (II), Furosemide-PVP Coprecipitate (III), PVP (IV)

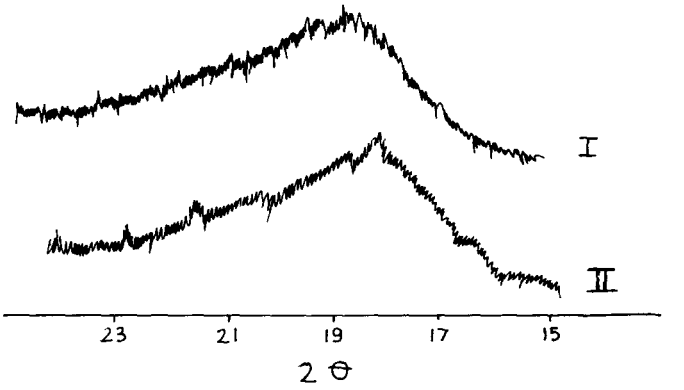

FIGURE 2

X-ray Diffraction Patterns of Furosemide-PVP Coprecipitates Prepared by Different Methods Co-evaporation (I), Freeze-drying (II)

absence of furosemide diffraction peaks indicates that an amorphous form existed in the coprecipitates. As indicated in earlier report, PVP did not show any cristallinity (16). The similar X-ray diffraction patterns were obtained with furosemide-PVP solid dispersion systems prepared by freeze-drying method (Fig.2). However, characteristic furosemide diffraction peaks remained constant in physical mixtures. With PVP, furosemide formed well-defined coprecipitates.

Figure 3 shows the diffraction patterns of furosemide-PVP coprecipitates composed of different drug to PVP ratios such as 3:1, 1:1, 1:3, 1:7 and 1:10. No

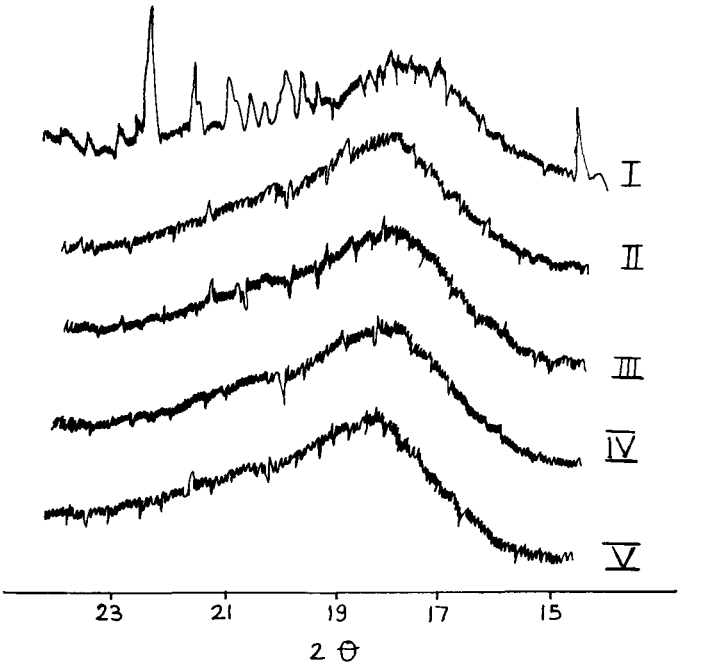

FIGURE 3

Comparison of X-ray Diffraction Patterns of Furosemide-PVP Coprecipitates; Drug-PVP (3:1) (I), Drug-PVP (1:1) (II), Drug-PVP (1:3) (III), Drug-PVP (1:7) (IV), Drug-PVP (1:10) (V)

difference was observed in the diffraction patterns of these coprecipitates.

The IR spectrum of furosemide shows a sharp band at 3400 cm^{-1} and 3350 cm^{-1} while the IR-spectrum of furosemide-PVP coprecipitate shows a broad band at these regions. The other sharp bands disappeared in the system. The IR spectrum provided evidence that there was complex

formation between furosemide and PVP, probably via hydrogen bonding. This finding is in accordance with Shin's report (11) that an interaction is present between the functional groups of furosemide with PVP.

Furthermore no decomposition was detected by thin-layer chromatography.

Dissolution Studies

Dissolution parameters of pure drug, furosemide-PVP coprecipitates and physical mixtures were given in Table I. With furosemide-PVP solid dispersion systems, approximately sixtyfold increase in drug release was obtained. The dissolution process followed first order kinetic. Dissolution rate constants are $k=0.0037\ min^{-1}$ and $k=0.2197\ min^{-1}$ for pure drug and furosemide-PVP coprecipitate. For physical mixture, k value is 0.0099 min^{-1}. Furosemide in the physical mixture dissolved more rapidly than furosemide alone.

Comparison of the two different techniques, co-evaporation and freeze-drying, no significant difference was found in drug release. The results are summarized in Table I. With coprecipitates prepared by freeze-drying method, a higher dissolution rate was obtained at low weight fractions of PVP. However solid dispersion systems prepared by co-evaporation and freeze-drying methods, both exhibited fast drug release than furosemide and physical mixture (Fig. 4).

TABLE I

First-order Dissolution Rate Constant (k)
Half-life (t_{50}), A_{30} and A_{45} Values of
Furosemide-PVP Coprecipitates

Drug to PVP ratio		k (min^{-})	t_{50} (min)	$A_{30\%}$	$A_{45\%}$
Coprecipitate	Furosemide	0.0037	187.29	6.75	14.03
	1:1	0.0134	51.54	29.05	41.44
	1:3	0.0257	26.96	52.47	65.39
	1:5	0.0546	12.68	71.54	75.07
	1:7	0.2197	3.15	90.36	91.44
	1:10	0.2021	3.42	87.16	88.28
	1:20	0.2965	2.33	96.32	97.40
Freeze-dried	1:1	0.0248	27.94	50.22	64.86
	1:3	0.0191	36.28	30.18	50.00
	1:7	0.1731	4.00	82.88	84.00
	1:10	0.1863	3.71	87.43	87.50
Physical Mixture	1:1	0.0099	70.00	34.75	40.01
	1:3	0.0099	70.00	29.39	32.20
	1:5	0.0099	70.00	39.18	44.96
	1:7	0.0099	70.00	39.18	42.17
	1:10	0.0099	70.00	36.48	45.04
	1:20	0.0138	50.00	43.39	47.97
Coprecipitate (80-mesh)[x]		0.2699	2.56	91.96	93.61
Coprecipitate (120-mesh)		0.2327	2.97	96.09	99.32

[x]Particle size of coprecipitate

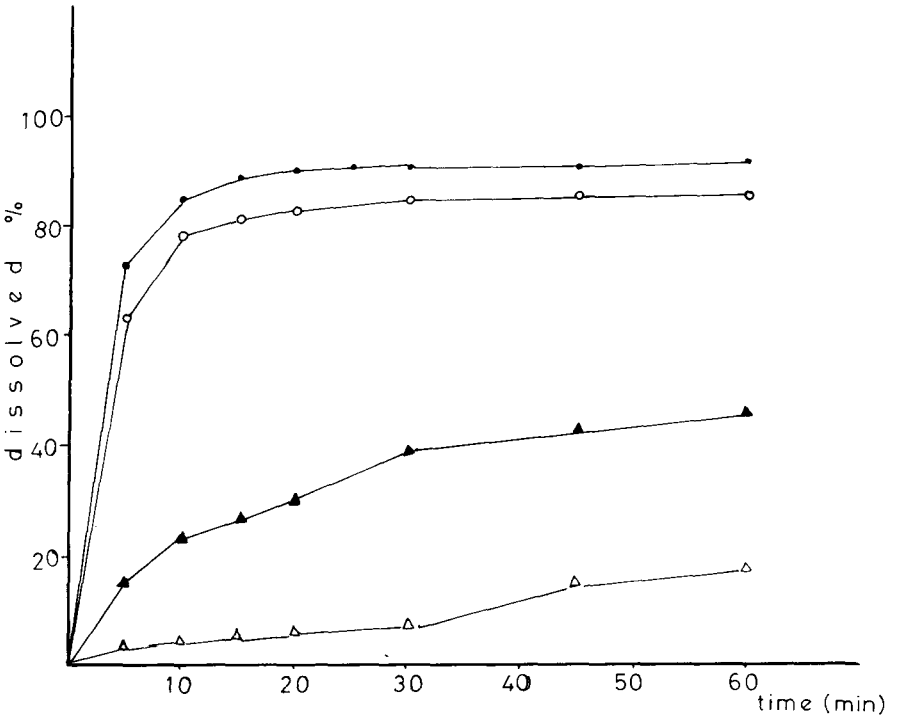

FIGURE 4

Dissolution Profiles of Furosemide (▲), Furosemide-PVP, Physical Mixture (▲), Coprecipitate Prepared by Method (I) (●) and Method (II) (o)

The effect of furosemide-PVP ratio on the release rate of drug was next studied. Dissolution characteristics of furosemide-PVP solid dispersion systems having different weight fractions of PVP such as 1:1, 1:3, 1:5, 1:7, and 1:20 are shown in Fig. 5 and Table I. The best release was obtained with (1:7) ratio.

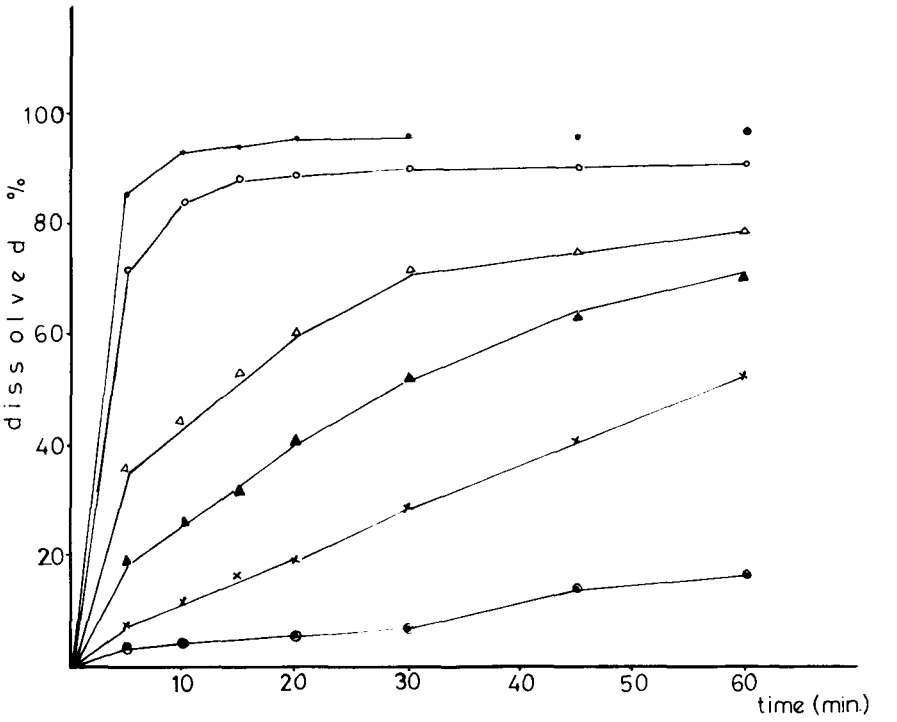

FIGURE 5

The Effect of Furosemide-PVP Ratio on Drug Release, Furosemide (⊙), Furosemide-PVP Coprecipitate (1:1) (x), (1:3) (▲), (1:5) (Δ), (1:7) (o), (1:20) (●)

Figure 6 shows plot of t_{50} values versus % furosemide in dispersions. There is no difference of t_{50} values until 12%, but above this ratio a general increase in t_{50} values is found. As indicated in Table I, an increase was observed until the ratio 1:7 and then increases in the weight fraction of PVP did not affect

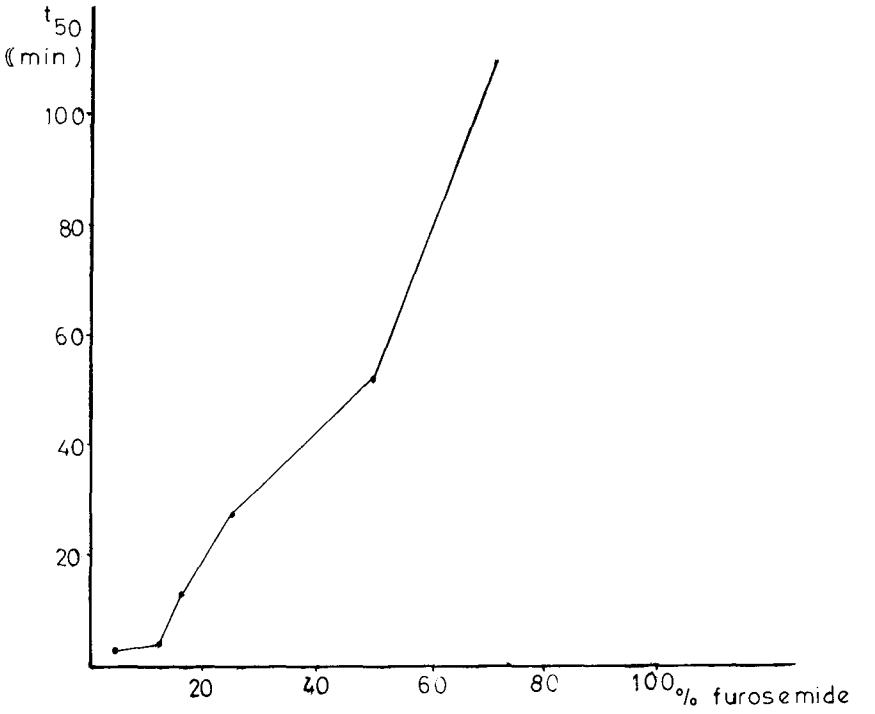

FIGURE 6

Plot of Dissolution Half-lives (t_{50}) of Coprecipitates Versus % Furosemide in PVP Dispersions

furosemide release. It is considered that a critical mixture ratio is present for dissolution of furosemide from furosemide-PVP solid dispersion systems and this ratio is approximately (1:7). When the weight ratio of PVP increased above this value, no enhancement was observed in drug release. The increase in dissolution rate is seen to be dependent of PVP ratio.

The faster dissolution rates of coprecipitates may be attributed to the formation of a high energy amorphous phase of drug as previously reported (16). Here the inhibiting effect of PVP on drug crystallization is important too. In furosemide-PVP coprecipitates, PVP in the medium strongly inhibited the recrystallization of furosemide and no peak was observed in dissolution curves since the dissolution curve represents the difference of the rate of dissolution and the rate of recrystallization (Fig.5). In furosemide-PVP solid dispersion systems, however, different mechanisms may be effective in drug release besides solid state changes. As seen in X-ray diffraction data (Fig. 3), furosemide is present in amorphous form in the solid dispersion systems having low fraction of PVP (1:1), but the release rate of furosemide is not high enough. For 1:1 and 1:7 ratios of furosemide-PVP coprecipitates, k values are 0.0133 and 0.2197 min^{-1} respectively. These findings are considered that a different mechanism may be effective in furosemide release. In furosemide-PVP solid dispersion systems, drug release may be controlled by dissolution of carrier as Corrigan noted (3). Moreover, the ability of low-concentration of PVP to depress solubility of drugs has been previously reported by Gibaldi and Weintraub (17). As Sekikawa et al (18) proposed coacervate formation may play an important role in the dissolution of coprecipitate.

TABLE II

Comparison of Surface Tension-Lowering Effect of PVP with Different Molecular Fractions

Molecular fraction of PVP (%)	Surface Tension dynes/cm
0	71.70
0.50	71.92
0.75	68.45
0.83	68.25
0.85	67.75
0.87	67.24
0.88	67.21

On the other hand carriers may reduce the surface tension of aqueous medium. Sekikawa et al (18) proposed that PVP in the medium may lower the surface tension and facilitate the wetting, thus, the dissolution of drug. In our previous study (19) it was found that wetting was an effective mechanism in furosemide dissolution. In this study, as shown in Table II the surface tension of the medium changed as the weight ratio of PVP increased.

No difference was found between the release rate of coprecipitates having different particle sizes (Table I).

TABLE III

Effect of Molecular Weight of PVP on

Dissolution Rate of Furosemide-PVP Coprecipitates

Drug to PVP ratio		k (min^{-})	t_{50} (min)	$A_{30\%}$	$A_{45\%}$
K-25*	1:7	0.2235	3.10	85.81	86.26
	1:20	0.2086	3.32	91.44	94.14
K-30	1:7	0.2197	3.15	90.36	91.44
	1:20	0.2965	2.33	96.32	97.40
K-90	1:7	0.1006	6.88	95.94	98.27
	1:20	0.0638	10.86	90.84	94.36

*Molecular weights are 25000, 49000 and 1100000 respectively

On the contrary to Hajratwala and Ho (20) the rate of evaporation of solvent had no effect on the dissolution of furosemide-PVP coprecipitates.

Effect of PVP Molecular Weight on Furosemide Release

Table III indicates the release rate of drug from furosemide-PVP coprecipitates prepared by PVP having different molecular weight. It is also found that the chain length significantly changes the dissolution rate of furosemide the 49000 molecular weight polymer is

being the most rapid of the three systems. The similar results were obtained with physical mixtures. The effect decreased in the following molecular weight; K-30 > K-25 > K-90. Our findings are in accordance with Sihn's report (11).

The greater enhancing effect of the lower molecular weight PVP polymer was noted by Simonelli et al and Corrigan et al (16,21).

For this reason 49000 mol wt. polymer (PVP K-30) was used our studies.

Solubility

Fig. 7 shows the solubility of furosemide in aqueous and 0.1 N hydrochloric acid solutions containing PVP in different concentrations. The solubility of furosemide increased as the concentration of PVP increased. Since the dissolution rate is proportional to solubility, the presence of furosemide with PVP in the solid dispersion system increases the dissolution rate of furosemide.

Table II indicates the surface tension of PVP solutions.

Stability Studies

During the storage period, by TLC technique, no drug decomposition was observed and no coloration also occured.

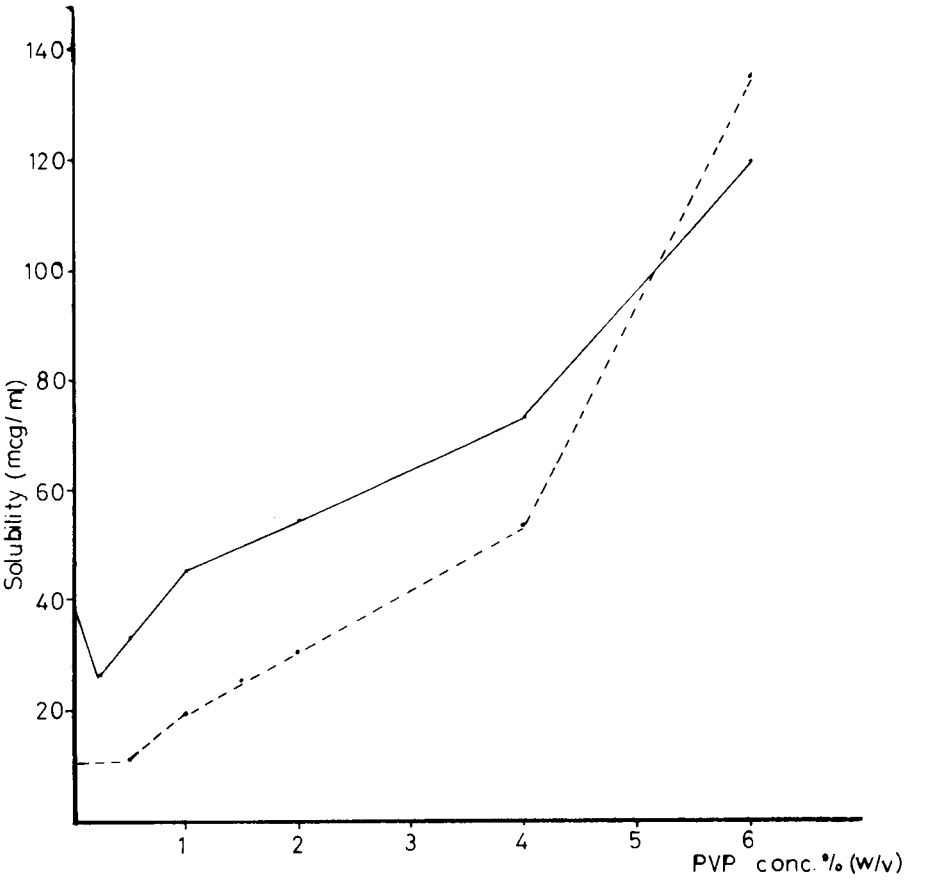

FIGURE 7

Solubility of Furosemide in Aqueous (——) and Acidic (0.1 N HCl) Solutions (---) of PVP at 25°

Tables IV and V show dissolution characteristics of furosemide-PVP solid dispersion systems over 5 months.

At 55% RH, no change in dissolution parameters of coprecipitates was observed during the storage periods.

Release rate of freeze-dried samples stored at the same condition did not alter too (Table IV). The preparation method of coprecipitates has no effect on the stability of these systems.

At 70% RH, dissolution characteristics of furosemide-PVP solid dispersions remained stable over 5 months (Table V). At 85% RH, however, after 12 weeks, a tacky mass formed (Table IV).

The proportion of PVP has no importance on the stability of furosemide-PVP coprecipitates stored at different humidity conditions.

As contrary to previous reports (13,14) it was found that aging did not affect the dissolution rate of furosemide-PVP coprecipitates.

These results are similar to those found by El Gamal et al (22) in phenylbutazone solid dispersions. They have pointed out that PVP did not show a detrimental effect on the dissolution of drug after storage. From this point, PVP was found to be a superior carrier than the others (22).

Figure 8 shows the X-ray diffraction patterns of aged furosemide-PVP coprecipitates. As it is seen, no difference was observed in the X-ray diffraction patterns of coprecipitates. Amorphous form of drug remained unchanged even after 5 months of storage and the diffraction peaks due to furosemide were absent in X-ray diffraction patterns of stored samples.

TABLE IV

The Effect of Relative Humidity on Dissolution Characteristics of Furosemide-PVP Coprecipitates Prepared by Different Methods

RH	Method	Drug-PVP ratio	0 week		4 weeks		8 weeks		12 weeks		20 weeks	
			t_{50} [xx]	$A_{30\%}$ [x]	t_{50}	$A_{30\%}$	t_{50}	$A_{30\%}$	t_{50}	$A_{30\%}$	t_{50}	$A_{30\%}$
55% RH	I	1:5	5.13	71.62	5.13	71.62	4.52	78.37	5.97	76.57	5.90	62.61
		1:10	3.05	82.88	2.82	89.41	3.20	80.63	3.57	84.90	3.38	84.85
	II	1:5	8.55	77.47	8.55	74.54	7.37	76.57	8.66	69.14	8.34	71.73
		1:10	4.17	86.03	4.17	86.03	4.50	87.61	3.36	90.65	4.74	81.30
85% RH	I	1:5	5.13	71.62	4.72	79.95	4.72	78.00	-	-	-	-
		1:10	2.34	82.88	2.86	87.83	2.38	81.30	-	-	-	-
	II	1:5	5.13	71.62	4.72	80.00	4.70	79.00	-	-	-	-
		1:10	2.34	82.88	2.80	86.00	2.82	85.00	-	-	-	-

x The amount dissolved in 30 min

xx t_{50} (min)

TABLE V

The Effect of Relative Humidity on Dissolution Characteristics of Furosemide-PVP Coprecipitates (1:7) Prepared by Different Methods

RH	Method	0 week		4 weeks		8 weeks		12 weeks		20 weeks	
		t_{50} [x]	$A_{30\%}$ [xx]	t_{50}	$A_{30\%}$	t_{50}	$A_{30\%}$	t_{50}	$A_{30\%}$	t_{50}	$A_{30\%}$
55%	I	3.0	91.59	3.16	98.87	2.79	98.53	3.36	84.00	2.65	97.86
	II	3.72	87.95	2.92	93.61	3.06	86.48	3.55	86.48	4.22	74.77
70%	I	2.10	96.50	2.10	94.49	2.29	93.01	2.14	94.14	2.14	86.93
	II	2.94	88.96	4.07	88.66	2.25	86.48	4.02	85.88	4.20	85.30

[x] t_{50} (min)

[xx] The amount dissolved in 30 min

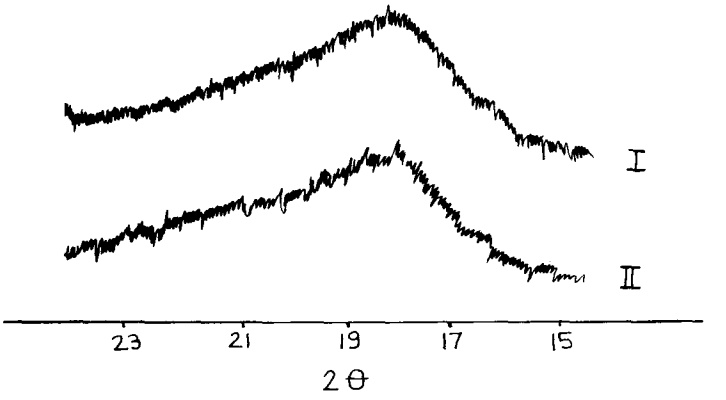

FIGURE 8

X-ray Diffraction Patterns of Freshly Prepared Furosemide-PVP Coprecipitate (I) and Aged Coprecipitate (II)

As a conclusion, it appears that the modification of the dissolution behavior of furosemide by preparing furosemide-PVP coprecipitate results increased drug dissolution. Coprecipitates prepared by co-evaporation or freeze-drying methods had similar properties. Among the different ratios of PVP, there is a critical mixture ratio in furosemide-PVP coprecipitates, at this ratio the best release is obtained. The particle size of coprecipitates and evaporation rate had no effect on drug release. Furthermore the molecular weight of PVP is an important factor.

Based on these results, enhanced dissolution was primarily due to the increased wettability, and to the

solubilization of the drug by carrier. Other factors such as formation of high energy amorphous form and complexation may also contribute to the enhancement of dissolution of furosemide dispersed in PVP.

It was also observed that after a storage period, furosemide-PVP coprecipitates showed no significant change in either dissolution rate or X-ray diffraction patterns.

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