Arch. Pharm. Res. **2**(1), 49~64(1979)

Studies on Hydrophobic Drug - Soluble Carrier Coprecitates (II)

Physicochemical Characteristics of Furosemide-PVP Coprecipitates

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(Received 23 February 1979)

Abstract□In an attempt to elucidate further physicochemical properties of furosemide-PVP coprecipitates, extensive investigations such as TLC, UV, IR, NMR, X-ray diffraction, TGA and DTA studies were carried out for the furosemide test systems. X-ray diffraction studies revealed that the pure furosemide and the furosemide contained within a physical mixture were crystalline in nature. However, there was no crystallinity evident in the 1:5 furosemide-PVP 40,000 coprecipitate system, even after standing for two years. The various ratio furosemide-PVP 40,000 coprecipitate systems revealed that the coprecipitate containing a greater amount of PVP 40,000 than that of furosemide showed a crystalline state of furosemide and that the minimum amounts of PVP to make amorphous form of furosemide was 1:1 ratio of furosemide to PVP. From the furosemide-PVP coprecipitate systems with PVP of different molecular weights of 10,000, 40,000, and 360,000, all the 1:1 ratio coprecipitates did not exhibit any crystallinity of furosemide, whereas all the 2:1 ratio coprecipitates showed a presence of crystalline furosemide. All the coprecipitated preparations with PEG 4,000 and with PEG 6,000 showed the diffraction peaks indicating the presence of crystalline furosemide.

The comparison of infrared spectra of the physical mixture and the coprecipitate showed an interaction such as association between the functional groups of furosemide and PVP in the molecular level, whereas the studies by TLC, UV and NMR showed its dissociation in methanol solution.

The weight losses in TGA curves showed all the same patterns. However, a little different transition form in DTA thermograms was shown between the physical mixture and the coprecipitate, indicating the different thermal property.

Keyphrases□Furosemide—its coprecipitates with PVP and PEG—physicochemical properties of the coprecipitates—IR, NMR, UV, X-ray diffraction, TGA, DTA and TLC analysis—association between furosemide and PVP.

With the development of awareness of the importance of dissolution rate in influencing biological availability, considerable attention is being paid to enhancing the property.

One of the techniques that can potentially enhance the dissolution rate and the extent of absorption of hydrophobic drugs is the formation of hydrophobic drug - soluble carrier system.

This physicochemical modification offers an advantage of possibly enabling one to administer the drug orally in the form which is most available for GI absorption.

There have been many suggestions on why these increases in dissolution rates occur including glass solutions[1,2], solid solution[3], decreased particle size[3], eutectic mixtures[3,4], colloidal dispersions[5~7], complexes[8~15], and coprecipitates[8,16~19].

In an attempt to elucidate further physicochemical modification of furosemide-PVP coprecipitate, the extensive investigations such as TLC, UV, IR, NMR, X-ray diffraction, TGA, and DTA studies were carried out for the furose- mide test systems, respectively.

EXPERIMENTAL

Materials

The furosemide (Teva Middle East Pharm. & Chemical Works), polyvinylpyrrolidone (average mol. wt., 10,000, 40,000, and 360,000), polyethylene glycol (average mol. wt., about 4,000 and 6,000) were pharmaceutical grade. All other chemicals used were reagent grade and used as received.

Apparatus

UV Spectrophotometer (Shimadzu UV 210-A), X-ray diffractometer (Shimadzu GX-2B), infrared spectrophotometer (Perkin-Elmer 467), NMR spectrometer (Varian HA-100 D), differential thermal analyzer (Traco model, DTA-202), thermogravimeter (Cahn RG electrobalance).

Preparation of Furosemide Test Systems

The 1:1 (w/w), 1:2, and various ratio furosemide-PVP coprecipitates were prepared by the solvent method[20~23] using the PVP of different mol. wt., 10,000, 40,000, and 360,000, respectively, and the same ratio physical mixtures were also prepared. The 1:9 ratio furosemide-PEG coprecipitates were prepared by the melting method[22] using PEG of mol. wt., 4,000 and 6,000.

Determination of Melting Point

The melting points for pure furosemide, PVP, furosemide-PVP 40,000 coprecipitate and the same ratio physical mixture were determined by Thomas Hoover Capillary melting point determination apparatus. The pure furosemide was melted between 203–206° with decomposition. However, the pure PVP was not melted until heated up to 300°C. The detectable differences in the melting phenomena were not found between the coprecipitate and the physical mixture until heated up to 300°C.

TLC

TLC was carried on a silica gel G plate under the solvent system of acetone:$CHCl_3$: EtOH:benzene: NH_4OH T.S. (3:3:5:2:1 v/v) and identified by iodine vapor.

UV

UV spectra in 200–350 nm were obtained with Shimadzu 210-A, double beam, recording spectrophotometer.

X-Ray Difffraction

X-ray diffraction was carried out using Norelco X-ray diffractometer. The target was Cu-tube (Ni-filter), 35Kv, 15MA, and the detector was proportional counter, 1.7Kv for detector voltage.

IR

Infrared spectra for furosemide test systems were observed by potassium bromide disk method, with Perkin-Elmer 467, a double beam, infrared spectrophotometer.

NMR

NMR spectra were obtained with Varian HA-100 D NMR spectrometer using deuterated methyl alcohol as solvent and TMS as internal standard.

DTA

Thermograms were obtained using Traco model, DTA-202 thermal analyzer fitted with Ni-Z dish under nitrogen atmosphere. The reference material was 5 mg of alpha-alumina, the heating rate, 15°C/ min., and the upper temperature limit, 1000°.

TGA

Thermogravimetric analyses were carried out using Cahn little gen TGA unit with Cahn RG electrobalance. Air atmosphere was used for all analyses with heating rate of 8°C/min.

RESULTS AND DISCUSSION

TLC

If the coprecipitation brings a change in chemical structure, there may be present the other spots following the formation of a new compound besides furosemide and polymer. TLC was carried out for the furosemide test systems under two solvent systems. The representative TLC plates developed under a solvent system of acetone:chloroform:ethanol: benzene:dil. ammonia T.S. (3:3:5:2:1 v/v) are shown in Figs. 1 and 2. Excellent separation of furosemide from PVP and PEG was obtained under two solvent systems. No difference was found, in these results, between the coprecipitate and the physical mixture except furosemide tate and the physical mixture except furosemide and polymer. On the basis of these

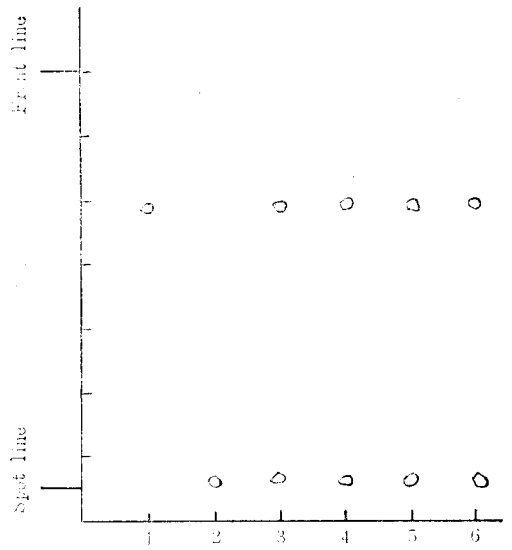

Fig. 1: Thin layer chromatogram of furosemide-PVP test preparations.

Key: 1=pure furosemide; 2=pure PVP 40,000;
3=1:2 furosemide-PVP 40,000 physical mixture;
4=1:2 furosemide-PVP 40,000 coprecipitate;
5=1:2 furosemide-PVP 10,000 coprecipitate;
6=1:2 furosemide-PVP 360,000 coprecipitate.

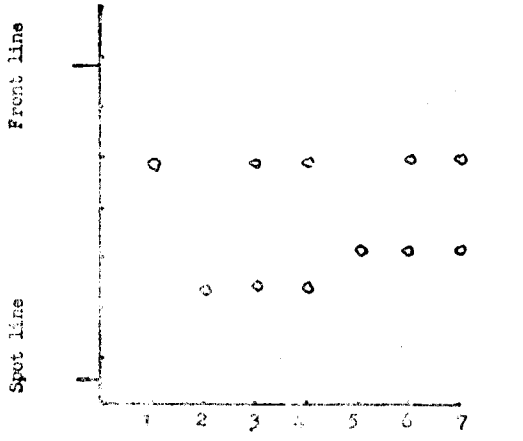

Fig. 2: Thin layer chromatogram of furosemide-PEG test preparations.

Key: 1=pure furosemide; 2=pure PEG 4,000;
3=1:2 furosemide-PEG 4,000 physical mixture;
4=1:2 furosemide-PEG 4,000 coprecipitate;
5=pure PEG 6,000;
6=1:2 furosemide-PEG 6,000 physical mixture;
7=1:2 furosemide-PEG 6,000 coprecipitate.

observations, coprecipitation here never brings the formation of a new chemical compound unlike coprecipitating compound, but means a simultaneous precipitation at these preparing conditions.

Even though the coprecipitation never brings the formation of new chemical com pound, one can postulate that there might be specific characteristics in the coprecipitate systems, and TLC analysis on the undissolved substances remaining after solubility experiment was carried out.

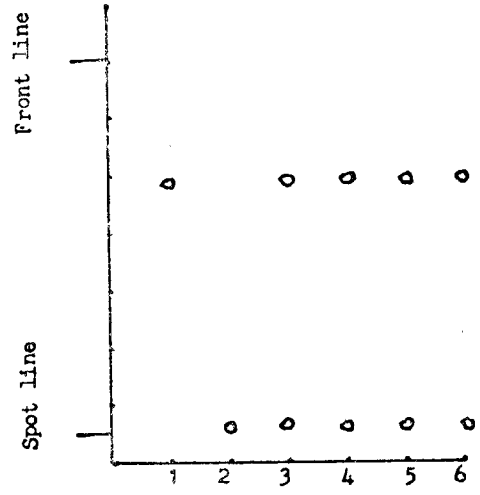

Fig. 3: Thin layer chromatogram of furosemide test preparations.

Key: 1=pure furosemide;
2=pure PVP 40,000;
3=1:1 furosemide-PVP 40,000 physical mixture;
4=1:1 furosemide-PVP 40,000 coprecipitate;
5=The undissolved substances of 1:1 furosemide-PVP 40,000 physical mixture after solubility experiment;
6=The undissolved substances of 1:1 furosemide-PVP 40,000 coprecipitate after solubility experiment;
7=The undissolved substances of 1:2 furosemide-PVP 40,000 physical mixture after solubility experiment;
8=The undissolved substances of 1:2 furosemide-PVP 40,000 coprecipitate after solubility experiment.

Each 0.5g of furosemide and PVP 40,000, and each 1g of the 1:1 furosemide-PVP 40,000 coprecipitate, and the 1:1 furosemide-PVP 40,000 physical mixture, in considerable excess of solubility of furosemide, were placed respectively into 200ml of glass-stoppered flasks together with 100ml portions of distilled water and all flasks were shaken vigorously by means of a mechanical shaker. After Millipore filtration, the undissolved substances were dried on H_2SO_4 desiccator and dissolved in small amounts of methanol, and were used in TLC. The results in TLC (Fig. 3) showed the different phenomenon between the physical mixture and coprecipitate systems. The furosemide-PVP 40,000 coprecipitate of 1:1 ratio as well as 1:2 ratio showed the presence of furosemide and PVP, whereas the physical mixture did not show the presence of PVP. During the solubility experiment, the PVP was completely dissolved in the physical mixture systems, whereas it was not in the coprecipitate system.

Both components in the coprecipitate act as one unit, and therefore it is considered that there might be some binding forces such as association as will be later proved by IR spectra.

UV

UV spectra for the furosemide test systems in 0.5% methanol-water solution as solvent are shown in Fig. 4. The furosemide and PVP 40,000 are shown at a concentration of 5 mcg/ml, and the 1:1 furosemide-PVP 40,000 coprecipitate and the same ratio physical

mixture at those of 10 mcg/ml.

Furosemide[24,25] showed absorption peaks at 274 nm, and 227 nm, and PVP[26], at about 200nm. N-vinylpyrrolidone has a conspicuous absorption maximum at 235 nm which might be present only to a minute extent in the spectrum of the polymer and this is used as a method to follow the conversion of monomer to polymer during polymerization[26]. However, the PVP 40,000 showed the only absorption peak at about 200 nm and did not show any absorption at 235 nm. Hence it is considered that N-vinylpyrrolidone is not present in the polymer PVP 40,000.

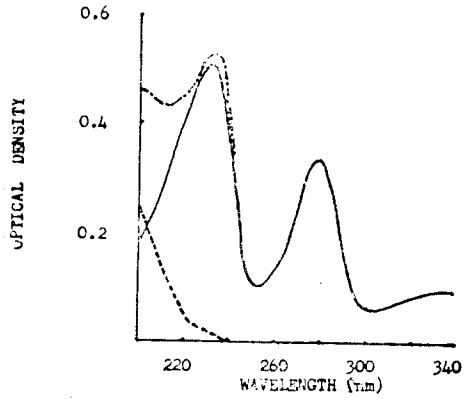

Fig. 4: UV spectra of furosemide test preparations.
Key: —=furosemide (5 mcg/ml); ···=PVP (5 mcg/ml)
-·-=1:1 furosemide-PVP physical mixture (10 mcg/ml);
-··-=1:1 furosemide-PVP coprecipitate (10 mcg/ml).

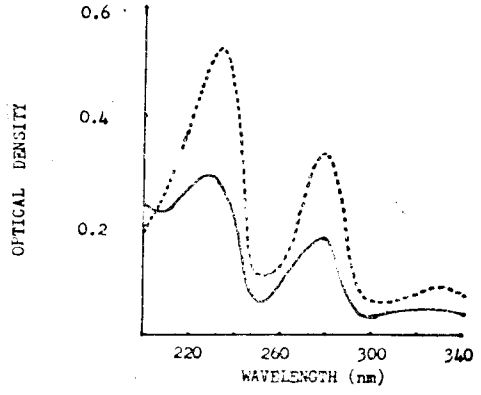

Fig. 5: UV spectra of the undissolved substances remaining after solubility experiment (5 mcg/ml).
Key: —=1:1 furosemide-PVP physical mixture; ···=1:1 furosemide-PVP coprecipitate.

Furosemide and PVP 40,000 showed, as one would expect, distinguishable patterns and the 1:1 furosemide-PVP 40,000 coprecipitate showed an identical spectrum with the same ratio physical mixture.

It is interesting to investigate different phenomena in TLC between the coprecipitate and physical mixture. At this point, UV spectra of the 1:1 physical mixture and the same ratio coprecipitate were compared for the undissolved substances remaining after the solubility experiment used in TLC. The 1:1 furosemide-PVP 40,000 coprecipitate and the same ratio physical mixture remaining after solubility experiment, at concentration of 5 mcg/ml are shown in Fig. 5.

The 1:1 furosemide-PVP 40,000 coprecipitate remaining after the solubility experiment showed an identical spectrum with that of before the solubility experiment, suggesting the presence of furosemide and PVP 40,000. To the contrary, the same ratio physical mixture showed an identical spectrum with that of furosemide at concentration of 5 mcg/ml. This result illustrates that the PVP 40,000 in the physical mixture was completely dissolved in an aqueous medium and the water-insoluble furosemide only remained in the undissolved substances after the solubility

experiment, whereas the PVP 40,000 in the coprecipitate was not dissolved in the aqueous medium in spite of its water-soluble property. On the basis of the same results by TLC, it is most probable that binding forces between the two components may be present in the coprecipitate preparation.

If the 1:1 ratio coprecipitate shows binding forces between the two components, there might be an influence of PVP 40,000 amount used in coprecipitating. The 2:1 furosemide-PVP 40,000 coprecipitate and the undissolved substances remaining after the solubility experiment, as well as the 1:2 ratio, respectively, are shown in Fig. 6.

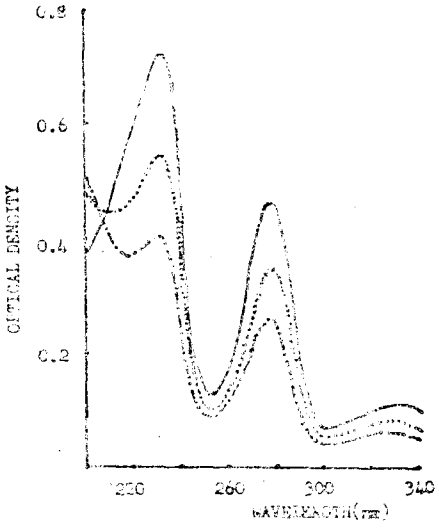

Fig. 6: UV spectra of furosemide test preparations. (10 mcg/ml).

Key: ---=1:2 furosemide-PVP coprecipitate before solubility experiment;
····=1:2 furosemide-PVP coprecipitate after solubility experiment;
——=2:1 furosemide-PVP coprecipitate before solubility experiment;
——=2:1 furosemide-PVP coprecipitate after solubility expermeint.

The 2:1 ratio furosemide-PVP 40,000 coprecipitate remaining after the solubility experiment showed an indentical spectrum with that of before the solubility experiment. This result clearly shows that binding forces between the two components are present and the PVP 40,000 in the coprecipitate is not dissolved in the aqueous medium.

However, in case of the 1:2 ratio, the respective contents of furosemide and PVP 40,000 in its coprecipitate before and after the solubility experiments were different.

The 1:2 ratio coprecipitate after the solubility experiment showed a low content of PVP and a high content of furosemide. The excess and/or free PVP in the 1:2 ratio coprecipitate might be dissolved in an aqueous medium. Thus, the undissolved substances remaining after the solubility experiment of the 1:2 coprecipitate shows the low content of PVP and high content of furosemide, as compared with the same test preparation of that of before the solubility experiment.

It is considered that even if the excess and/or free furosemide is present in the 2:1 furosemide-PVP coprecipitate, the excess and/or free furosemide is not dissolved in an aqueous medium due to the insolubility in water of furosemide. UV spectrum of the 2:1 coprecipitate after the solubility experiment was identical with that of before the solubility experiment.

X-ray Diffraction on the Furosemide-PVP Coprecipitates

Since the dissolution rates of the physical mixture systems were not appreciably ehhanced, while those of the coprecipitated systems

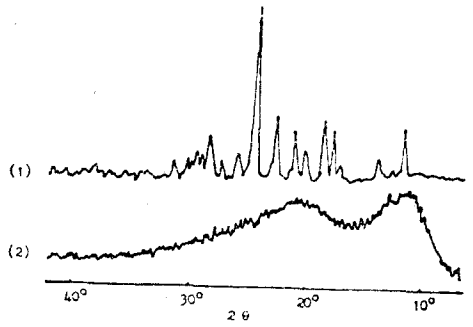

Fig. 7: Comparison of X-ray diffraction spectra.
Key: (1)=pure furosemide;
(2)=pure PVP 40,000.

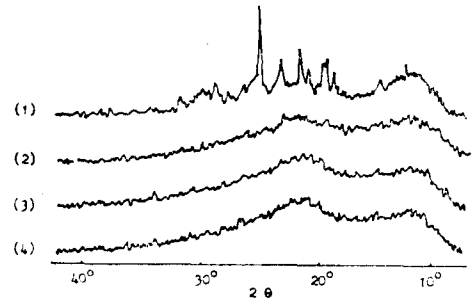

Fig. 8: Comparison of X-ray diffraction spectra.
Key: (1)=1:5 furosemide-PVP 40,000 physical mixture;
(2)=1:5 furosemide-PVP 40,000 coprecipitate (immediately);
(3)=1:5 furosemide-PVP 40,000 coprecipitate (after 1 year);
(4)=1:5 furosemide-PVP 40,000 coprecipitate (after 2 years).

were markedly ehanced, there might be a possibility that different phases are present in the coprecipitate systems. At this point, X-ray diffraction studies were undertaken in an attempt to unravel some of the factors. X-ray diffraction patterns for pure furosemide, pure PVP 40,000, the 1:5 furosemide-PVP 40,000 coprecipitate, and the same ratio physical mixture are shown in Figs. 7 and 8.

The coprecipitate and the physical mixture can be readily differentiated. Fig. 7 depicts that the pure furosemide showed those diffraction peaks indicating the presence of crystallinity by the X-ray diffraction study. Interestingly, the physical mixture also showed crystallinity supposedly due to the presence of crystalline furosemide, and the extent of diffraction peaks was dependent on the combination ratio of furosemide and PVP. Thus, the mere presence of PVP in the physical mixture should not interfere with the characterization of furosemide present. On the other hand, the 1:5 ratio furosemide-PVP coprecipitate and that of after standing for a year or two at room temperature, as in case of pure PVP, did not show any crystallinity (Fig. 8).

This result implies that furosemide may be present in an amorphous form in the 1:5 furosemide-PVP 40,000 coprecipitate system.

If this 1:5 coprecipitate does not show any crystallinity of furosemide, there may be an influence of PVP amount used in coprecipitating, excess or small, and the combination ratio between furosemide and PVP is very interesting.

Figs. 9 and 10 show X-ray diffraction spectra for the furosemide-PVP 40,000 coprecipitates in the weight ratios of the 10:1, 2:1, 1.5:1, 1.1:1, 1:1, 1:1.5, 1:2, and the 1:5. The 1.1:1 furosemide-PVP 40,000 coprecipitate as well as the 1.5:1, 2:1, and 10:1 ratios also showed the crystallinity, suggesting the presence of furosemide in a crystalline state, whereas the 1:1 coprecipitate (Fig. 10) as well as the 1:1.5, 1:2

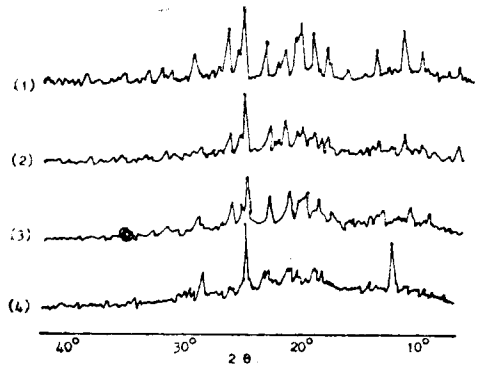

Fig. 9: Comparison of X-ray diffraction spectra.
Key: (1)=10:1 furosemide-PVP 40,000 coprecipitate;
(2)=2:1 furosemide-PVP 40,000 coprecipitate;
(3)=1.5:1 furosemide-PVP 40,000 coprecipitate;
(4)=1.1:1 furosemide-PVP 40,000 coprecipitate.

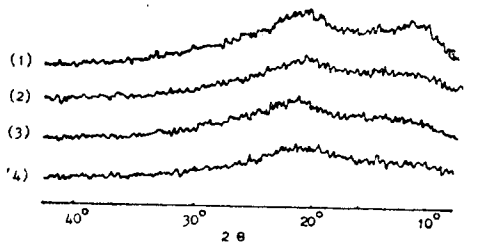

Fig. 10: Comparison of X-ray diffraction spectra.
Key: (1)=1:5 furosemide-PVP 40,000 coprecipitate;
(2)=1:2 furosemide-PVP 40,000 coprecipitate;
(3)=1:1.5 furosemide-PVP 40,000 coprecipitate;
(4)=1:1 furosemide-PVP 40,000 coprecipitate.

and 1:5 ratios, as pure PVP, did not show any crystallinity. However, the comparison of X-ray diffraction studies in the 2:1 ratio furosemide-PVP 40,000 test systems exhibited that the coprecipitate showed crystallinity of furosemide in very weak intensity, whereas the physical mixture showed sharp crystallinity due to the presence of free furosemide (Fig. 11).

In general, PVP forms molecular adducts

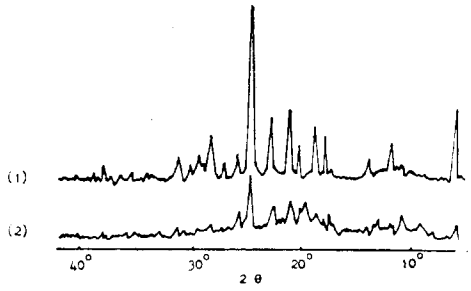

Fig. 11: Comparison of X-ray diffraction spectra.
Key: (1) =2:1 furosemide-PVP 40,000 physical mixture;
(2) =2:1 furosemide-PVP 40,000 coprecipitate.

with many organic substances[27]. Since PVP is a macromolecular polymer, one can postulate that furosemide might be interweaved among the PVP frame structure, that the functional groups of furosemide and the PVP might interact relatively and that the crystallinity of furosemide was not shown by X-ray diffraction.

According to these results, in those cases of coprecipitates such as the 10:1, 2:1, 1.5:1, and 1.1:1 ratios, the functional groups of furosemide and PVP might interact relatively, and the excess amount of furosemide showed the crystallinity by X-ray diffraction. Therefore the minimum amount of PVP may be required to make amorphous form of furosemide in coprecipitation procedure, and these observations might have general applications to the coprecipitation of relatively water-insoluble drugs.

Since the wide range of moleular weights of PVP might be used in coprecipitating, the 1:1 and 1:2 ratio furosemide-PVP coprecipitates with PVP of molecular weight of about 10,000, 40,000 and 360,000 were compared by X-ray

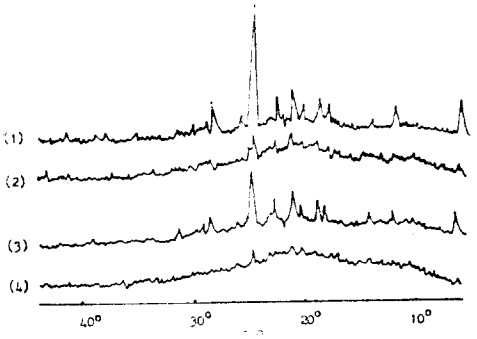

Fig. 12: Comparison of X-ray diffraction spectra.
Key: (1)=2:1 furosemide-PVP 10,000 coprecipitate;
(2)=1:1 furosemide-PVP 10,000 coprecipitate;
(3)=2:1 furosemide-PVP 360,000 coprecipitate;
(4)=1:1 furosemide-PVP 360,000 coprecipitate.

diffraction studies (Fig. 12).

From the furosemide coprecipitates with PVP 10,000, 360,000 and 40,000, all the 2:1 coprecipitates exhibited the crystallinity of furosemide in weak intensity due to the presence of crystalline furosemide, whereas all the 1:1 ratio did not show any crystallinity. According to these results, all the 1:1 furosemide coprecipitates with PVP 10,000, PVP 40,000 and PVP 360,000 did not show any crystallinity of furosemide.

Since PVP is a synthetic polymer consisting essentially of linear 1-vinyl-2-pyrrolidinone groups[28~30], each gram of PVP, in spite of different molecular weights, might have all the same 1-vinyl-2-pyrrolidinone groups, and it is supposed that X-ray diffraction data showed all the same patterns, regardless of the molecular weight of PVP.

X-ray Diffraction on the Furosemide - PEG Coprecipitates

X-ray diffraction studies for the pure forms

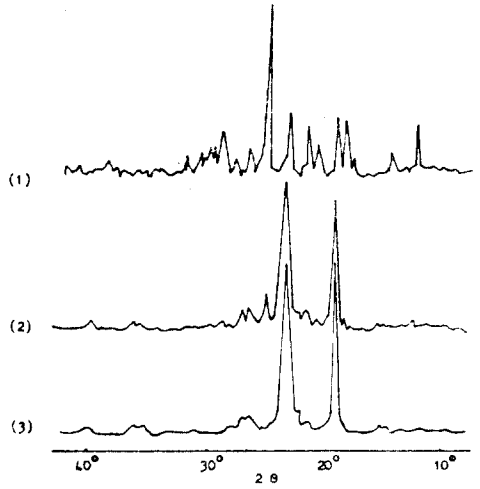

Fig. 13: Comparison of X-ray diffraction spectra.
Key: (1)=pure furosemide; (2)=pure PEG 4,000;
(3)=1:9 furosemide-PEG 4,000 coprecipitate.

of furosemide, PEG 4,000 and PEG 6,000, and the 1:9 furosemide-PEG 4,000 coprecipitate and the 1:9 furosemide-PEG 6,000 coprecipitate were undertaken. X-ray diffraction spectra of furosemide were depicted in Figs. 13 and 14, by 5×10^2 in intensity, and pure PEG 4,000 and pure PEG 6,000 was by 2×10^3, whereas the coprecipitate with PEG 4,000 and that with PEG 6,000 were depicted by 1×10^3 in intensity, owing to the too high peak heights in the X-ray diffraction process.

The pure furosemide exhibits diffraction peaks at 2θ degree of 6.2 , 12.3 , 18.3 , 21.6 , 25.1 , and 28.9 , etc., at which pure PEG 6,000 does not show any diffraction peaks. Interestingly, the furosemide coprecipitate[31] with PEG 4,000 (Fig. 13), and that with PEG 6,000 (Fig. 14) showed the diffraction peaks at the same 2θ degree, showing the diffraction

peaks of furosemide, owing to low concentration of furosemide in the ratio of 1:9 in coprecipitate systems. All the coprecipitated preparations with PEG 4,000 and 6,000 showed diffraction peaks indicating the presence of crystalline furosemide, and the presence of PEG should, therefore, hardly interfere with the characterization of furosemide present in the PEG coprecipitate system.

IR Spectra

In an attempt to elucidate further physicochemical property, infrared absorption spectra were made for the furosemide test systems. The infrared spectra for the 1:1 furosemide-PVP coprecipitate and the same ratio physical mixture are shown in Fig. 15 with pure furosemide and PVP as a reference.

From the infrared spectrum of pure furosemide, an absorption band is observed at 3340 cm^{-1} and 3260 cm^{-1} in the region of 3500–3200 cm^{-1}, and a sharp band is observed at 1655 cm^{-1} and 1560 cm^{-1} in the region of 1700–1500 cm^{-1} (Fig. 15).

The 3340 cm^{-1} band is assigned to the NH stretching vibration of Ar-$NHCH_2$ and the 3260 cm^{-1} band to the NH stretching vibration of SO_2NH_2 and the 1655 cm^{-1} band which appears at such high frequency region is assigned to the bending vibration of amino group, the 1560 cm^{-1} band is to the asymmetric stretching vibration of carboxy group and the 1318 cm^{-1} band is to the asymmetric stretching vibration of sulfonyl group in furosemide structure, according to the assignment described in JP IX.

PVP shows an absorption band at 1680 cm^{-1} due to carboxyl group, and at 2940 cm^{-1} due to the CH-stretching vibration. However, the absorption band at 3500 cm^{-1} is probably due to the adsorbed water which was identified by Karl-Fischer water determination and DTA and TGA results, according to the assignment

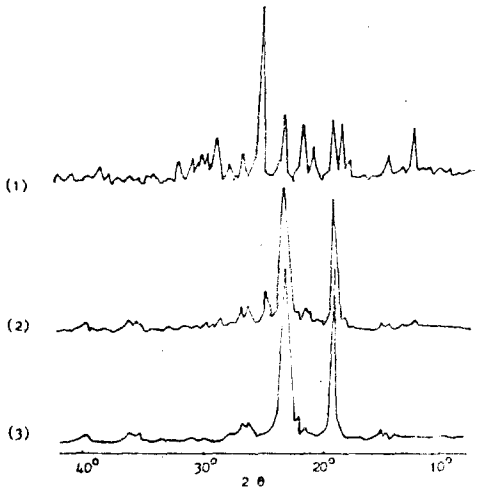

Fig. 14: Comparison of X-ray diffraction spectra.
Key: (1)=pure furosemide; (2)=pure PEG 6,000;
(3)=1:9 furosemide-PEG 6,000 coprecipitate.

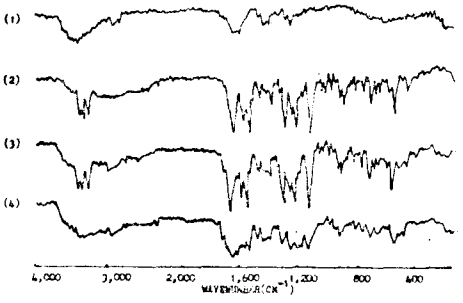

Fig. 15: Comparison of Infra-red spectra.
Key: (1)=pure PVP 40,000; (2)=pure furosemide;
(3)=1:1 (w/w) furosemide-PVP 40,000 physical mixture;
(4)=1:1 (w/w) furosemide-PVP 40,000 coprecipitate.

by Oster[26]. N-vinylpyrrolidone shows a strong absorption at 1630 cm^{-1} due to the vinyl group which exhibits an absorption peak at 235 nm in UV spectrum. However, PVP showed no absorption band at 1630 cm^{-1} in IR spectrum and no peak at 235 nm in UV spectrum. Therefore, it is considered that N-vinylpyrrolidone, a monomer, is not present in a polymer, PVP.

And the infrared spectrum of the physical mixture showed the absorption bands illustrating the presence of furosemide and PVP. However, in the spectrum of the coprecipitate, the sharp band observed in the region of 3500–3200 cm^{-1} became broad and weak. From the comparison of the spectra of the physical mixture and the coprecipitate, the stretching bands assigned to the non-bonded aromatic imino group and sulfonylamide group in furosemide molecule became weak and broad in the furosemide-PVP coprecipitate system, whereas the physical mixture showed the stretching vibrations.

Therefore, it is presumed that the coprecipitate shows an interaction such as association between the functional groups of furosemide and PVP in the molecular level. The association between furosemide and PVP is expected to be most probable between the imino group and sulfonylamide group of furosemide and carbonyl group of PVP.

According to the TLC and UV results of the undissolved substances remaining after the solubility experiment, the coprecipitate showed the presence of PVP, whereas the physical mixture did not show. If we presume that the binding forces such as association between furosemide and PVP are not present in the coprecipitate system, the furosemide and PVP will act respectively, and PVP will dissolve in aqueous medium, whereas the furosemide did not dissolve completely. The undissolved substances remaining after the solubility experiment of the coprecipitate and the physical mixture will show different patterns in IR spectra comparing with those of the samples before the solubility experiment.

Therefore, in order to elucidate this different phenomenon, suggesting some binding forces between the two components, IR spectral analysis was carried out on the undissolved substances remaining after the solubility test used in TLC. From the IR spectra of undissolved substances after the solubility test (Fig. 16), the 1:1 furosemide-PVP 40,000 coprecipitate showed the same pattern as that before the solubility test, whereas the physical mixture did not show the presence of PVP, but that of furosemide.

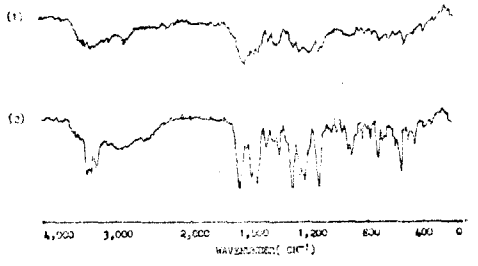

Fig. 16: Comparison of Infra-red spectra on the undissolved part after solubility test.
Key (1)=1:1 (w/w) furosemide-PVP 40,000 coprecipitate;
(2)=1:1 (w/w) furosemide-PVP 40,000 physical mixture.

It is evident that the coprecipitate is the associate of furosemide and PVP and acts as one unit.

NMR Spectra

The NMR spectra for the 1:1 furosemide-PVP 40,000 coprecipitate and the same ratio physical mixture are shown in Fig. 17. The NMR signals for the protons with different environments in the furosemide molecule appear in the 8.5, 7.4, 6.9, 6.3, and 4.3 ppm regions, respectively, and the sharp signals in 4.8 ppm region shows the presence of CD_3OH as impurity of deuterated methanol and small amounts of H_2O in PVP ,and that in 3.3 ppm region, the CD_2HOD.

From the NMR spectra of the physical mixture and the coprecipitate, the above five peaks in furosemide are found in the same regions and the broad peaks appearing in 1.8–2.5 ppm regions are expected to be due to the protons in the PVP molecule.

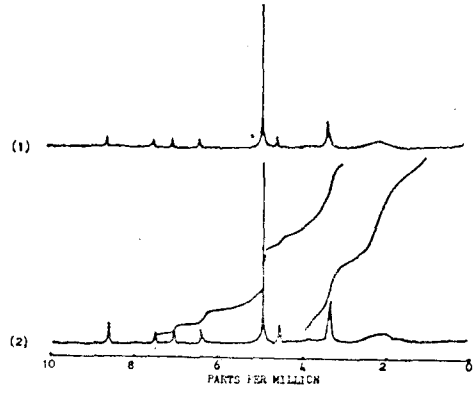

Fig. 17: Comparison of NMR spectra.
Key: (1)=1:1 furosemide-PVP 40,000 physical mixture;
(2)=1:1 furosemide-PVP 40,000 coprecipitate.

No difference was found in NMR spectra between the physical mixture and the coprecipitate. Since the furosemide test preparations were dissolved in methanol the association between the functional groups of furosemide and PVP might easily dissociate in methanol.

DTA and TGA

The DTA and the TGA thermograms for furosemide test systems are shown in Figs. 18~21. The TGA thermograms (Fig. 18) of furosemide showed a weight loss of about 3.3 % at 205° which was within the reported melting point range, of 203–206° with decomposition, and the weight loss until 300 was about 22%, and the DTA curves of furosemide exhibited a single, sharp exothermic peak at temperature of 220° , and an endothermic peak at about 280°C. The weight loss of about 3.3% at 205° in TGA thermograms seems most probably to be due to the ammonia decomposition in the furosemide molecule. Visual observations in a melting point apparatus suggested that a dark brown caramelized melting mass was observed at approximately 206° and both peaks in DTA curves should be due to degradation of furosemide (Fig. 18).

The weight loss of about 5% until 100° in TGA curves of PVP (Fig. 19) and the water content of 5% determined by Karl-Fisher method was in agreement, indicating that the water be adsorbed into the PVP polymer frame structure. TGA thermogram of PVP showed very slow weight loss in the range of 100–250°. At temperature range of 400–450°, it is supposed that PVP was decomposed, and this decomposition was also supported by

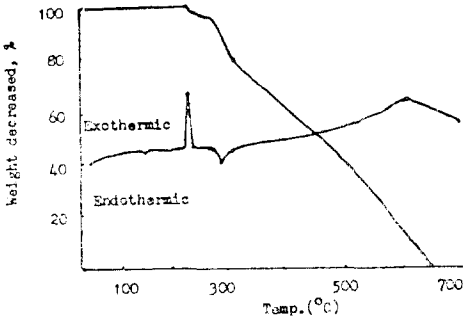

Fig. 18: DTA and TGA thermograms of furosemide.

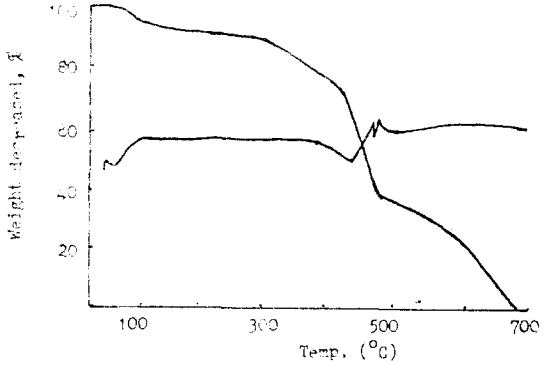

Fig. 19: DTA and TGA thermograms of PVP 40,000.

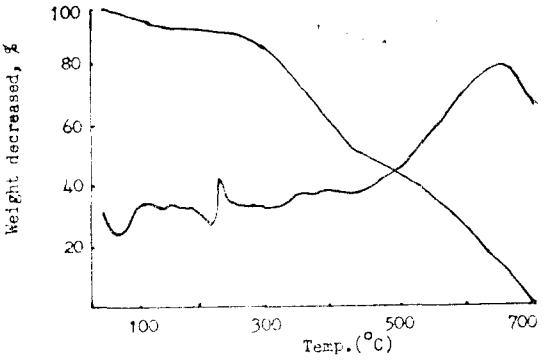

Fig. 20: DTA and TGA thermograms of 1:1 furosemide-PVP 40,000 physical mixture.

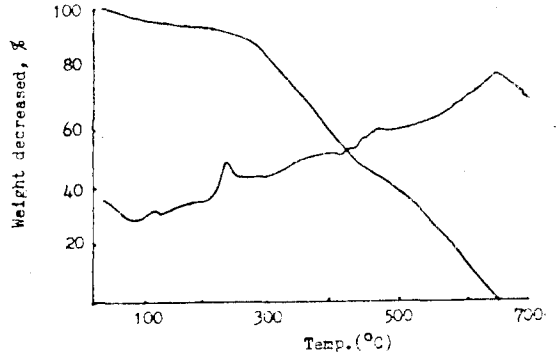

Fig. 21: DTA and TGA thermograms of 1:1 furosemide-PVP 40,000 coprecipitate.

DTA results. In the literature[32], several conflicting values of a galss transition temperature of poly-(N-vinylpyrrolidone) were found ranging from 54 to 175°. These may be attributed to the influence of sorbed moisture due to the hygroscopic nature of PVP.

TGA curves of the physical mixture and coprecipitate (Figs. 20 and 21) showed all the same patterns. Both coprecipitate and physical mixture showed the weight loss of about 5% until 100° meaning dehydration and high weight loss of about 40% between 250–400° showing the degradation. A comparison of DTA thermograms of the physical mixture and coprecipitate showed a slight transition peak, whereas furosemide only showed the sharp exothermic peak that was resulted from the decomposition of furosemide. Their temperature range of transition appeared to be somewhat different from that of furosemide. It is supposed that the thermal property was changed and that the coprecipitate showed a little different transition by comparing with the physical mixture.

CONCLUSIONS

The present investigations on the physicochemical properties of the furosemide-polymer coprecipitates showed the following results: 1) X-ray diffration study revealed that the pure furosemide and the furosemide contained within the physical mixture were crystalline in

nature and that there was no crystallinity in the 1:5 furosemide-PVP 40,000 coprecipitate system even after standing for two years. 2) The various ratio furosemide-PVP 40,000 coprecipitate system revealed that the 1:1 coprecipitate as well as the 1.5:1, the 2:1, and the 10:1 ratio ones showed the crystalline state of furosemide, whereas the 1:1 coprecipitate as well as the 1:1.5, the 1:2, and the 1:5 ratio ones did not show any crystallinity. Thus the minimum amount of PVP was determined to make amorphous form of furosemide in the coprecipitation procedure. 3) From the furosemide-PVP coprecipitate system with PVP of different molecular weights of 10,000 and 40,000 and 360,000, all the 1:1 ratio coprecipitate did not exhibit any crystallinity of furosemide, whereas all the 2:1 ratio showed the presence of crystalline furosemide. 4) All the coprecipitated preparations with PEG 4,000 and with PEG 6,000 showed diffraction peaks indicating the presence of crystalline furosemide and suggesting that the presence of PEG would not interfere with the characterization of furosemide present in the PEG coprecipitate system. 5) No difference was found, by TLC, UV and NMR studies, between the 1:1 furosemide-PVP coprecipitate and the physical mixture. 6) A comparison of infrared spectra of the physical mixture and the coprecipitate showed that an association between the functional groups of furosemide and PVP might occur in the molecular level, which might easily dissociate in methanol. 7) The weight loss in TGA curves showed all the same patterns. However, a different transition form in DTA thermograms was shown between the physical mixture and the coprecipitate indicating the different thermal property.

ACKNOWLEDGMENTS

The author expresses his gratitude to Dr. Chong-Hak Woo, Dr. Shin-Keun Kim, Dr. Min-Hwa Lee, and Dr. Byung-Sul Yu in Seoul National University for stimulating discussions and encouragement.

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