약 제 학 회 지
J. Korean Pharm. Sci.
12 (4) 145~152 (1982)

Enhancement of Dissolution from Pharmaceutical Preparation of Hydrophobic Drugs (I)

—Characteristics of Sulpiride-Polyethylene Glycol Coprecipitates—

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(Received October 7, 1982)

Data from IR spectroscopy and X-ray diffractometry were used for the characterization of sulpiride polyethylene glycol coprecipitates related with polymorphism of sulpiride.

Sulpiride Form Ⅱ transformed to Form Ⅰ during coprecipitating with polyethylene glycol and the transformation rate is increased in proportion to molecular size of polyethylene glycol and the content of polyethylene glycol in coprecipitate

It has been recognized that dissolution is frequently rate-limiting step in the gastrointestinal absorption of a drug from a solid dosage form. The relationship between the dissolution rate and the absorption is particularly distinct when considering drugs of low solubility. Consequently, numerous approaches have been attempted to modify the dissolution characteristics of poorly water soluble drugs, that is decrease of particle size[1], change of crystal form[2], and lyophilization[3]. Especially, rate of solubility of most soluble materials can be increased by lyophilization. Rate of solubility was increased markedly by lyophilization through dispersion of a number of pharmaceutical gums and suspending agents. These included sodium carboxymethylcellulose, veegum, polyethylene glycol, acacia, tragacanth, and sodium alginate.

A more unique way of obtaining microcrystalline dispersions of a drug has been recently suggested by Sekiguchi *et al*[4,5]. They have proposed the formation of a eutectic mixture of a poorly water soluble drug with a physiologically inert easily soluble

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Supported in part by funds provided for pharmaceutical research by Korean Research Institute for Better Living, Ewha Womans University.

carrier.

In this study, sulpiride was coprecipitated with polyethylene glycol as soluble carrier to increase its solubility and the characteristics of sulpiride-polyethylene glycol were investigated related with crystal form interconversion during coprecipitating through the change of coprecipitating ratio and polyethylene glycol molecular size.

Experimental

Materials and Reagents—Sulpiride(Fujisawa Pharm. Co.), polyethylene glycol 20000, polyethylene glycol 6000 (K.P.), polyethylene glycol 4000 (K.P.) and polyethylene glycol 20000 used in this study were pharmaceutical grade. All other chemicals were commercially available reagent grade.

Apparatus—Infrared spectrophotometer (Beckman Acculab 10), X-ray diffractometer (Diano XRD3, 300), and water bath were used.

Preparation of Coprecipitate—The sulpiride-polyethylene glycol coprecipitate systems (1 : 1, 1 : 2, and 1 : 4) were prepared by dissolving both components in methanol and subsequently evaporating off the organic solvent at various molecular size of polyethylene glycol, until the formation of methanol vapor bubbles were no longer observed. Semitransparent, viscous liquids were obtained and were allowed to solidify by cooling. The residues were dried to constant weight in vacuum and screened to 20 ~30 mesh ranges. The sulpiride-polyethylene glycol weight ratios were analytically confirmed.

IR Spectroscopy—A double-beam IR spectrophotometer was used for recording the spectra of the coprecipitates and physical mixtures by the KBr disk method, grinding the mixtures of coprecipitates and KBr and pressing the grinding mixture at 9000 kg/cm^2

X-Ray Diffractometry—X-ray diffractograms were recorded using the X-ray diffractometer with Kα radiation. The settings used with the instrument were: 1°beam slit, 1° detector slit, copper tube Kα radiation and nickel filter.

Results and Discussion

IR Spectroscopy—The IR absorption spectra of the various coprecipitates and physical mixtures are shown in Figures 1.

It has been already reported that sulpiride has two crystal forms(Form I and Form II)[6].

IR absorption spectra of the two forms showed recognizable differences in the detailed structures and intensities of some major absorption band, in the amide stretching vibration region, specifically from 1,620 to 1,640 m^{-1} and Form I transformed to

Form Ⅱ in aqueous suspension resulting that 1,620cm^{-1} amide stretching band in Form I shift to 1,640 cm^{-1} in Form Ⅱ[6].

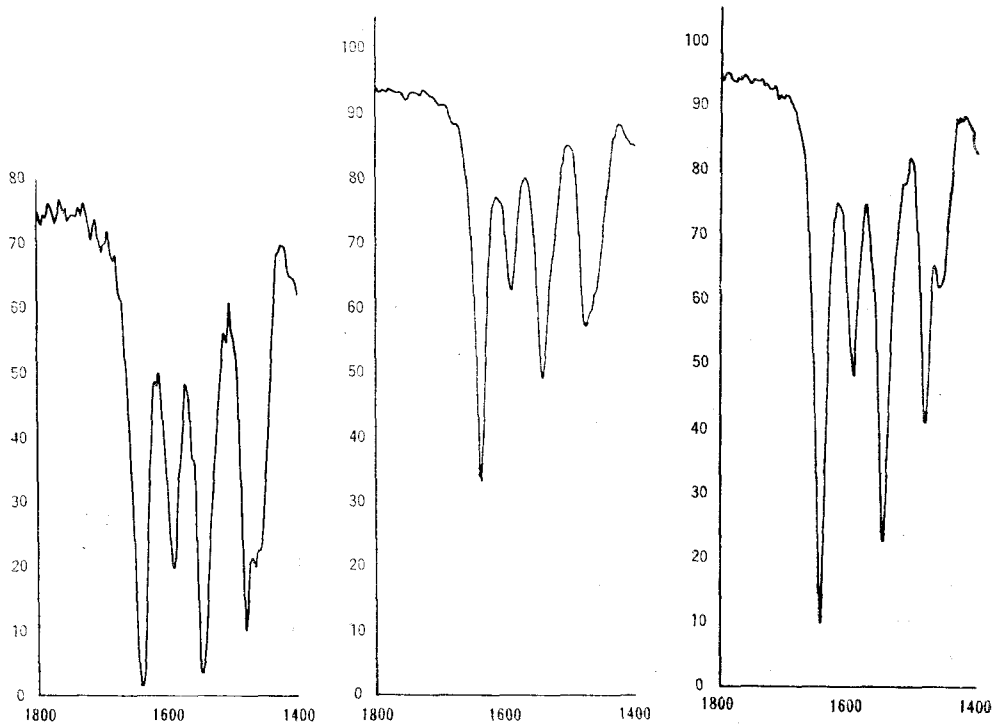

Figure 1a, 1b, 1c—IR spectra of sulpiride-PEG physical mixtures (from left to right)
Key: 1a, S : PEG 4000 = 1 : 1 ; 1b, S : PEG 6000 = 1 : 1 ; 1c, S : PEG 20000 = 1 : 1

In figures 1a, 1b, and 1c it is revealed that physical mixtures have absorption band at 1,640 cm^{-1} but coprecipitates have absorption band at 1,620cm^{-1} and 1,640 cm^{-1} simultaneously or only at 1,620 cm^{-1}(Fig. 1d, 1e, and 1f).

It shows that during coprecipitating with polyethylene glycol the sulpiride transformed to Form I. Transformation rates are different with the molecular size of polyethylene glycol and the coprecipitating ratios of sulpiride and polyethylene glycol.

Figures 2a, 2b, 2c, and 2d shows the transformation rate with the molecular size of polyethylene glycol and it is known that the transformation rate is increased in proportion to the molecular size of polyethylene glycol.

Figure 3a, 3b, 3c, 3d and 3e shows the relation between the transformation rate and the coprecipitating ratios of sulpiride and polyethylene glycol 4000 and it is known that the increase of the transformation rate is proportional to increase of polyethylene glycol ratios.

Form I in mixture of Form I and Form II was determined according to the method previously reported.[7]

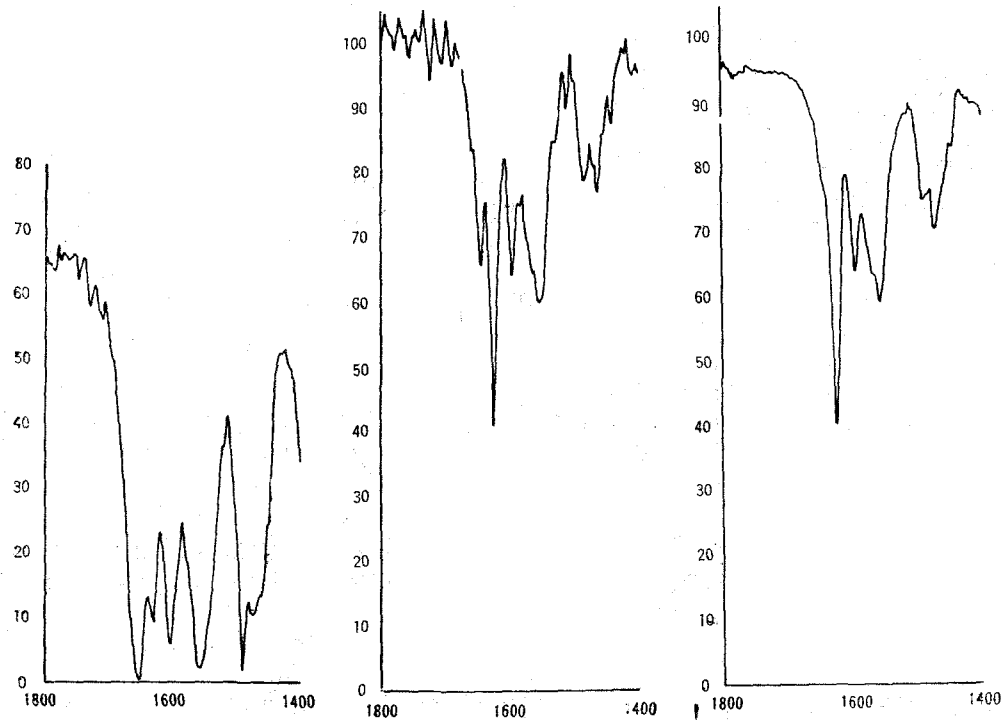

Figure 1d, 1e, 1f—IR spectra of sulpiride-PEG systems (from left to right).
Key: 1d, S : PEG 4000 = 1 : 1 ; 1e, S : PEG 6000 = 1 : 1 ; 1f, S : PEG 20000 = 1 : 1.

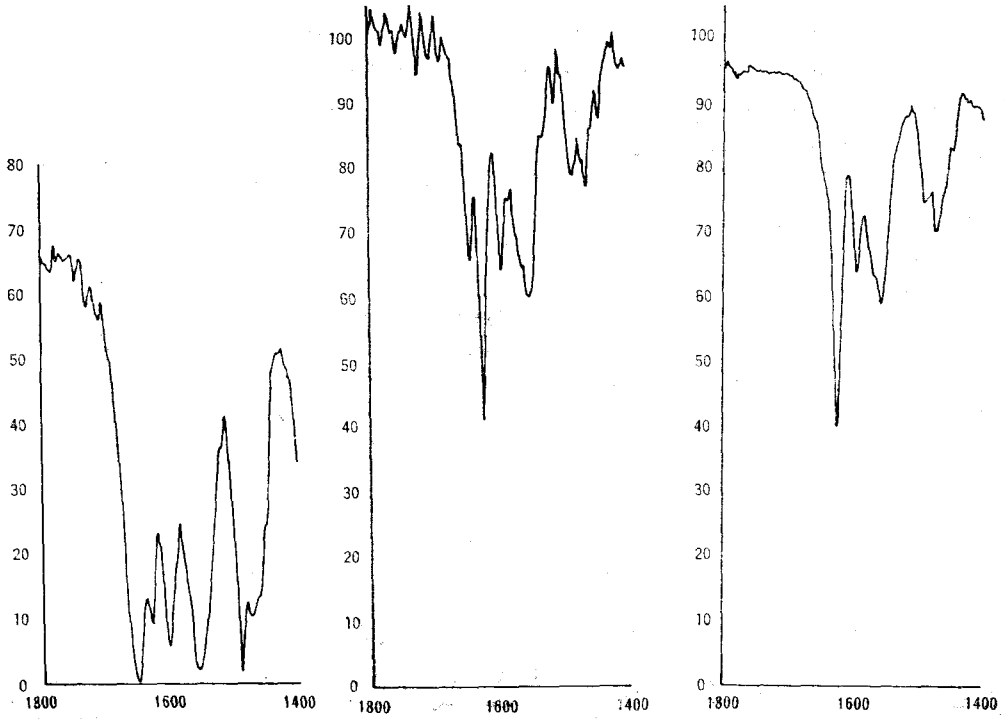

Figure 2a, 2b, 2c—IR spectra of sulpiride-PEG systems(from left to right)
Key: a; 2a, S : PEG 4000 = 1 : 0.5 ; 2b, S : PEG 6000 = 1 : 0.5 ; 2c, S : PEG 20000 = 1 : 0.5

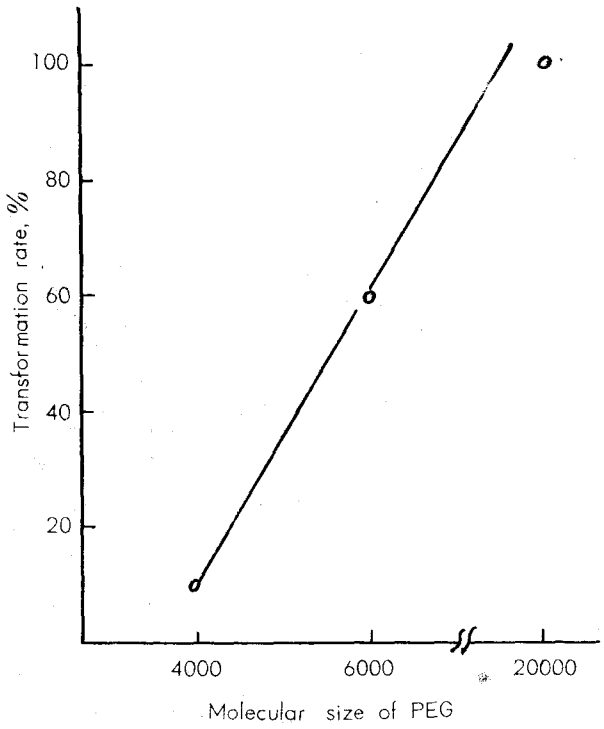

Figure 2d—Transformation rate with the molecular size of polyethylene glycols.

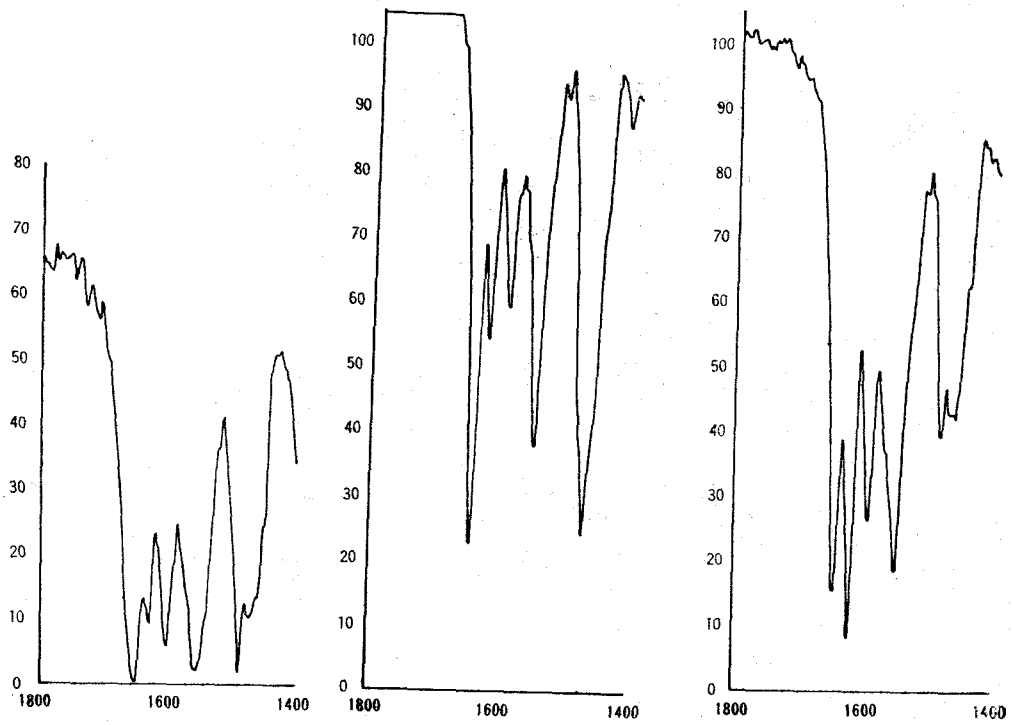

Figure 3a, 3b, 3c, 3d—IR spectra of sulpiride-PEG4000 systems (from left to right)
Key: 3a, S : PEG = 1 : 1 ; 3b, S : PEG = 1 : 2 ; 3c, S : PEG = 1 : 3 ; 3d, S : PEG = 1 : 4.

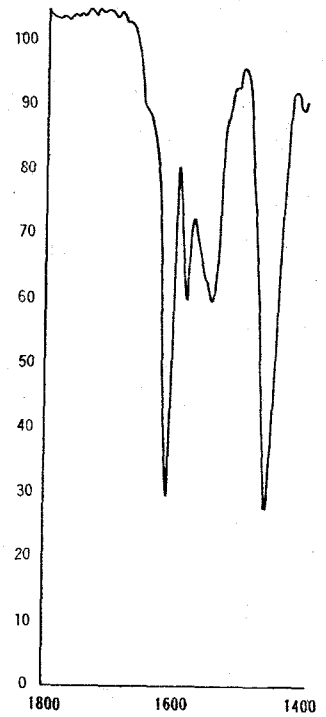

Figure 3d.

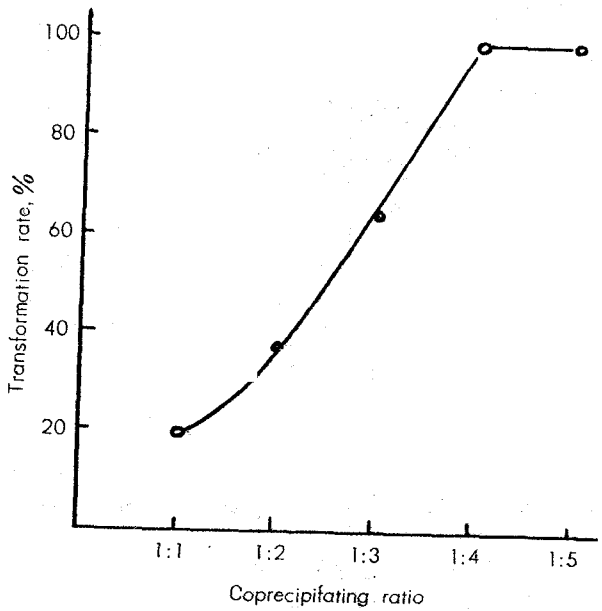

Figure 3e—The coprecipitating ratios of sulpiride and polyethylene glycol 4000.

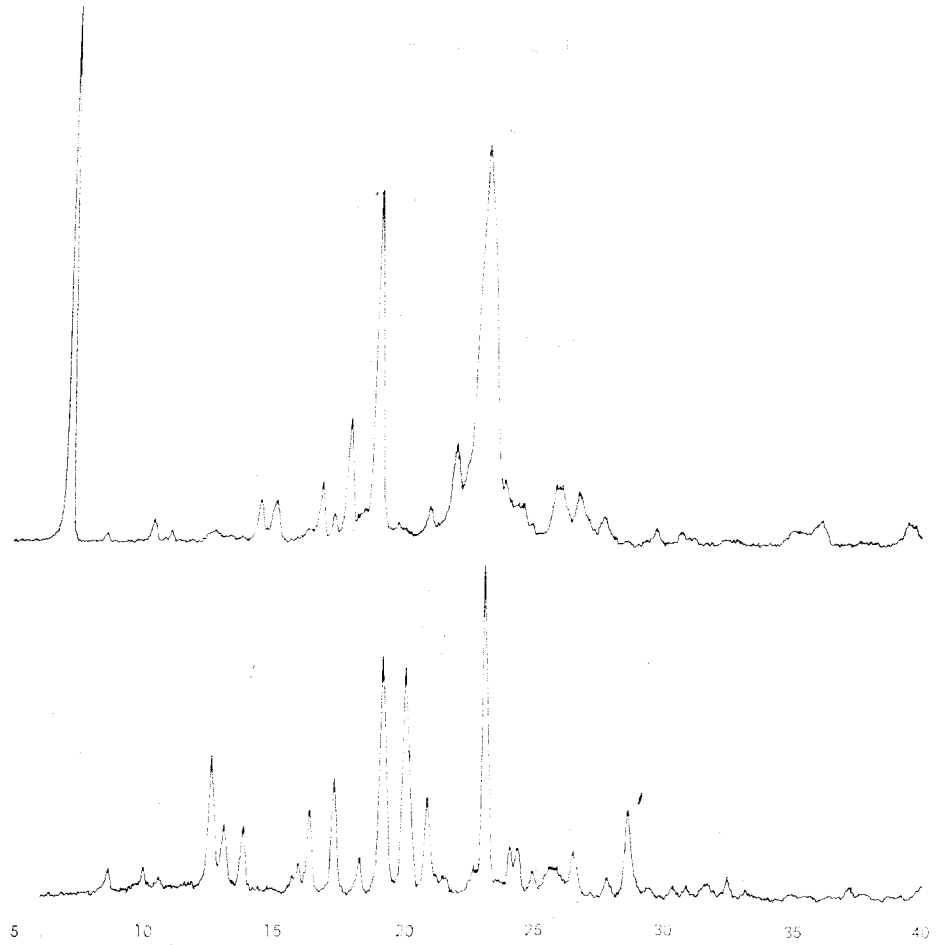

Figure 4—X-ray diffractogram of sulpiride-PEG 4000 system(ratio 1 : 3, top) and sulpiride Form Ⅱ.

X-Ray Diffractometry—Figure 4 shows the X-ray diffractogram of the coprecipitates with polyethylene glycol 4000 at 1 : 3 coprecipitating ratio. It reveals that no differences of crystallinity between coprecipitate and sulpiride Ⅱ is recognized but the change of 2θ degrees shows that sulpiride Form Ⅱ transformed to Form Ⅰ during coprecipitating.

Conclusion

1. Sulpiride Form Ⅱ transformed to Form Ⅰ during coprecipitating with polyethylene glycol by solvent method.

2. Transformation rate is increased in proportion to molecular size of polyethylene glycol and the coprecipitating ratios of polyethylene glycol in coprecipitate.

References

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