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Studies on Hydrophobic Drug - Soluble Carrier Coprecipitates(I)

Dissolution Characteristics of Furosemide–Polymer Coprecipitates

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Abstract□In order to increase the dissolution rate of furosemide(4-chloro-N-furfuryl-5-sulfamoyl anthranilic acid), various ratio coprecipitates with water-soluble polymers, such as polyvinylpyrrolidone and polyethylene glycol, of different molecular weight, were prepared and quantitatively studied by comparing their dissolution characteristics of furosemide at powder state and at non-disintegrating disk state containing constant surface area at various temperatures and rotating velocities. The dissolution characteristics of furosemide from pure furosemide disks and 1:2(w/w) furosemide-PVP coprecipitate disks were in accordance with Noyes-Nernst equation and the rate constant of dissolution was proportional to the square root of rotating velocity of the disks. The intrinsic rate of dissolution at 150 rpm, 37°C was 2.21×10^{-7} for the PVP 10,000 coprecipitate, 1.64×10^{-7} for the PVP 40,000 coprecipitate, and 1.44×10^{-7} for the PVP 360,000 coprecipitate, while the rate was 1.27×10^{-8} M/cm^2 min for pure furosemide, respectively. The activation energy of dissolution was about 17,000 for furosemide and about 7,300 cal/mole for the 1:2 furosemide-PVP 40,000 coprecipitate, respectively.

Keyphrases□furosemide—a sulfamoyl derivative of anthranilic acid—its coprecipitates with PVP and PEG—dissolution rate—intrinsic rate of dissolution—activation energy of dissolution—Noyes-Nernst equation.

When solid preparations are administered orally, the rate-determining step of an appearance of their medicinal effect is very important and it has been often observed on the dissolution rate.

If the absorption process of a drug is dissolution rate limited, an enhancement in the dissolution rate should facilitate its gastrointestinal absorption and it is considered to be very important to increase the dissolution rate of hydrophobic drugs. Thus, the dissolution characteristics of a pure drug alone[1~28] and of hydrophobic drug-soluble carrier systems[29~70] have been widely investigated.

One of the techniques that can potentially enhance the dissolution rate of hydrophobic drugs is the formation of coprecipitate with pharmacologically inert, polymeric materials. A number of investigations demonstrated that the formation of solid dispersions or coprecipitates of relatively water-insoluble drugs with various water-soluble polymers can increase significantly their *in vitro* dissolution rates and/or *in vivo* absorption.

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 and there have

been many suggestions on why these increases in dissolution rate and in solubility occur.

In the previous studies from this laboratory, polyvinylpyrrolidone, a water-soluble polymer, in the form of coprecipitate with allobarbital[64], phenobarbital[65], and furosemide[66] was shown to enhance markedly the rate of solution of these water-insoluble drugs. On the basis of these *in vitro* findings, it was decided to characterize dissolution rate of furosemide under the constant surface area, diuretic effects, and physicochemical modifications upon coprecipitating. To accomplish an enhancement in the dissolution rate of furosemide (4-choloro-N-furfuryl-5-sulfamoyl anthranilic acid), various ratio coprecipitates with water-soluble polymers, such as polyvinylpyrrolidone (PVP), polyethylene glycol (PEG) of different molecular weights were prepared and quantitatively studied by comparing their dissolution characteristics of furosemide at powder state and at non-disintegrating disk state.

The purpose of the present investigation was to ascertain general applicability of the polymer to be used for more enhanced dissolution of furosemide, to investigate factors affecting the dissolution rate of furosemide, and to establish a relationship between the gradients such as physicochemical modification, temperature, and rotating velocity.

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 were reagent grade and used as received.

Apparatus

Dissolution tester (conditioned with varying temperature and rotating velocity), spectrophotometer (Schimadzu UV 210-4).

Preparation of Furosemide Test Systems

The 1:2 (w/w) ratio furosemide-PVP coprecipitates were prepared by the solvent method[69] using PVP of different mol. wt., i.e., 10,000, 40,000 and 360,000, respectively, and the physical mixtures at same ratio were also prepared. The 1:2, 1:4, and 1:9 ratio furosemide-PEG coprecipitates were prepared by the melting method[66] using PEG of mol. wt., 4,000 and 6,000. The 1.5-cm in diameter, flat-faced, non-disintegrating disks containing constant surface area of pure furosemide, of furosemide-PVP 10,000 coprecipitate, of furosemide-PVP 40,000 coprecipitate, of furosemide-PVP 360,000 coprecipitate, of furosemide-PEG 4,000 coprecipitate, and of furosemide-PEG 6,000 coprecipitate, respectively, were prepared by the method described in the previous paper[64, 65].

Particulate Dissolution Rate Studies

The dissolution rate tests from the powder and disk preparation were carried out by the experimental conditions described in the previous paper[64, 65].

Determination of Equilibrium Solubility

The equilibrium solubility of furosemide test preparations were determined by the method described in the previous paper[64, 66].

RESULTS AND DISCUSSION

Stability of Furosemide in Dissolution Medium

The pure furosemide in the dissolution medium was used to verify its chemical stability during dissolution rate experiment. The change in furosemide concentration was not found when the pure furosemide solution in 0.005M HAc was kept at 37°C for seven days. The furosemide in 0.005M HAc medium was stable in dissolution medium.

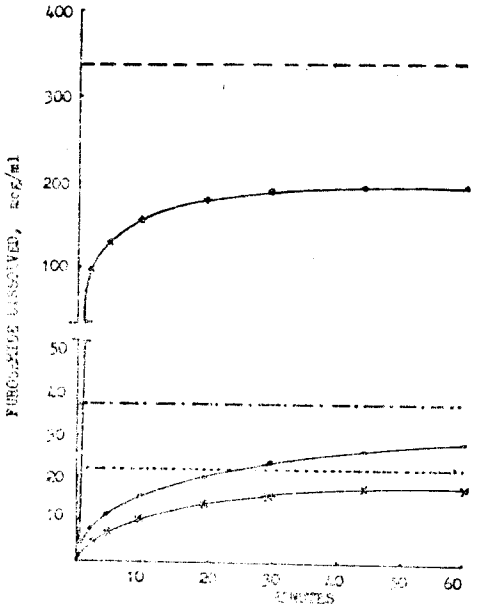

Fig. 1: Dissolution rates of furosemide in powder state at 37°, 150 rpm.

Key: ×=pure furosemide;
●=1:2 furosemide-PVP 40,000 physical mixture;
▲=1:2 furosemide-PVP 40,000 coprecipitate;
····=equilibrium solubility of furosemide;
-·-=equilibrium solubility of 1:2 furosemide-PVP 40,000 physical mixture;
– –=equilibrium solubility of 1:2 furosemide-PVP 40,000 coprecipitate.

Dissolution Rates of the Furosemide-PVP coprecipitate at the powder state

The effect of PVP on the dissolution of furosemide was investigated for the furosemide test preparations at the powder state.

The dissolved amount of furosemide, microgram per milliliter against time, and the equilibrium solubility for the 1:1 furosemide-PVP 40,000 coprecipitate and the same ratio physical mixture are shown in Fig. 1, while pure furosemide is included as a point of reference. The amount of furosemide in solution from the physical mixture was slightly increased comparing with pure furosemide and that from the 1:2 furosemide-PVP 40,000 coprecipitate was rapidly and markedly exceeded than the same ratio physical mixture.

The considerable interest is the fact that even though the particle size of the drug available for dissolution was the same condition, the dissolution rate of furosemide from the pure furosemide and physical mixture was different. This suggests that a simple particle size reduction is not responsible for the enhanced dissolution of furosemide experienced with the coprecipitate system. The slight increase noted in the rate of solution of furosemide from the physical mixture as compared with the pure drug is almost likely due to the ability of the water-soluble polymer to enhance the wettability of the hydrophobic furosemide particles.

A comparison of dissolution characteristics of the 1:2 furosemide-PVP 40,000 coprecipitate with those of the same ratio physical mixture indicates that the coprecipitate pre-

paration goes into solution at faster rate than the physical mixture. This result indicates that the mere presence of PVP is not responsible for the enhanced dissolution rate of furosemide. In addition, the role of PVP in the different enhancement of the furosemide dissolution rate among the coprecipitate system and the physical mixture is quite interesting. Also, the equilibrium solubility studied indicates that there might be different characteristics in the coprecipitate system.

Dissolution Rates on Furosemide-PEG Coprecipitates at the powder state

In order to study the effect of chain length in PEG, the 1:4 ratio coprecipitates with PEG 4,000 and PEG 6,000 were prepared using direct melting method and the dissolution rates were determined. The micrograms per milliliter of furosemide dissolved against time, and the equilibrium solubility of furosemide from 1:4 furosemide-PEG coprecipitate system are shown in Fig. 2. The equilibrium solubility of furosemide from the 1:4 furosemide-PEG coprecipitate was increased about 1.6-fold in PEG 6,000 coprecipitate and about 1.3-fold in PEG 4,000 coprecipitate, and the dissolution rates in 60 minutes from those coprecipitates, were increased slightly when compared with pure furosemide.

Owing to similar physical properties of PEG 4,000 and PEG 6,000, it is understandable that the furosemide dispersed in these two carriers all exhibited approximately the similar dissolution characteristics. It is also seen that the chain length of PEG indeed slightly changes the dissolution rate of furosemide,

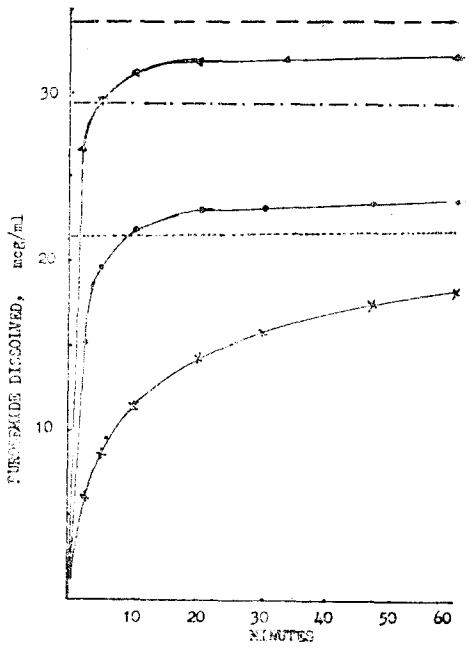

Fig. 2: Dissolution rates of furosemide in powder state at 37°, 150 rpm.

Key: ×=pure furosemide;
●=1:4 furosemide-PEG 4,000 coprecipitate;
▲=1:4 furosemide-PEG 6,000 coprecipitate;
····=equilibrium solubility of furosemide;
-·-=equilibrium solubility of 1:4 furosemide-PEG 4,000 coprecipitate;
- -=equilibrium solubility of 1:4 furosemide-PEG 6,000 coprecipitate.

the PEG 6,000 polymer coprecipitate being faster than PEG 4,000 polymer coprecipitate[54].

From this result, the high molecular weight copolymer of PEG appears to produce more increase in solubility and to be useful for coprecipitation.

Basic Consideration for the Dissolution Rates

Two types of dissolution are usually taken into consideration, transport controlled dis-

solution and chemically controlled one[20, 21]. However, dissolution of pharmaceutical preparations is usually a transport controlled reaction except a few cases[6]. A simple method for the dissolution rate experiment is to measure the dissolution from the static solid in the static liquid. In the static state, the transport of the substance dissolved does not depend on diffusion only because of the free convection of liquid caused by the influence of the gradient of temperature, and density of liquid. One of the methods to cover the influence of free convection is to give a forced convection to the solid-liquid interface. The rotating disk method attempted in this study is advantageous in such fact and the surface area of solid is kept constant in the progress of dissolution, since it takes shorter time for the experiments. The dissolution rate of solid particles in fluid media is generally represented by Noyes-Nernst equation:

$$\frac{dC}{dt} = \frac{S}{V} \cdot \frac{D}{h} (Cs - C)$$

Under the carefully controlled conditions, the surface area of dissolving particles remains constant during the dissolution process, and D, Cs, and h all will be constants, and C becomes very small comparing with Cs[19, 27], hence the intrinsic rate of dissolution, G, will be constant.

Characteristics under the Constant Surface Area

In the powder state, the surface area of the dissolving particles might be changed as the dissolution time passes and the dissolution characteristics could be altered. In order to overcome this problem, the dissolution characteristics of furosemide from constant surface area, and non-disintegrating disks of the drug alone and of coprecipitate with PVP were evaluated.

The dissolved amounts of furosemide are shown in Fig. 3 as mole concentration against time under the constant surface area. The apparent zero order dissolution rate constants were determined from the least square slopes of these plots. The rate constants reveal that furosemide from the coprecipitate disk goes into solution at markedly faster rate than it does from the pure furosemide disk.

However, in case of the physical mixture disk, the disintegration of the disk was followed after short time during the experiment and the surface area of the dissolving particles was not held constant and the dissolution rate experiments could not be carried on. The disintegration of the disk was brought about in the physical mixture, but not in the coprecipitate. In another words, furosemide and PVP act independently in the physical mixture, while the two components act as one unit in the coprecipitate. Apparently, the role of PVP alters the physical characteristics and solubility of furosemide. Therefore, one can postulate that there may be some binding forces between furosemide and PVP molecules.

Effect of Molecular Weight of PVP

PVP polymers with a wide range of molecular weights are available, and it is important to determine if any behavioral differences exist with molecular weight of PVP. If a difference did exist, the polymer with different molcular weights might show different dissolution.

Toward this end, the non-disintegrating disks of 1:2 furosemide-PVP coprecipitates

were prepared with PVP of different molecular weights such as about 10,000, 40,000 and 360,000. The dissolution rates of 1:2 furosemide-PVP disks, with three different molecular weights of PVP are shown in Fig. 9 including the furosemide disk for reference. The rate constants of dissolution, k, of furosemide from the 1:2 furosemide-PVP coprecipitate disks at 150 rpm, 37°C were about 15.62×10^{-7} for PVP 10,000 coprecipitate, 11.62×10^{-7} for PVP 40,000 coprecipitate, 10.2×10^{-7} for PVP 360,000 coprecipitate, and 8.95×10^{-8} M/min for pure furosemide, respectively.

From these results, the dissolution rate from the PVP 10,000 coprecipitate showed faster rate than that from the PVP 40,000 coprecipitate and that from the PVP 360,000 coprecipitate.

The greater effectiveness of the lower molecular weight polymer in enhancing drug release from coprecipitate systems was reported also for sulfathiazole by Simonelli, Metha, and Highuchi[39], and for hydrochlorothiazide by Corrigan, Thimoney, and Whelan[50].

As expected, higher molecular weight PVP dissolves more slowly, while their solution is of course more viscous. Owing to such different physical properties, it is supposed that the dissolution rates of furosemide from furosemide-PVP coprecipitates with different molecular weights became quite different. Concerning the molecular weight of PVP, the low

Table I: Intrinsic Rate of Dissolution, G, at 37°C, 150rpm.

Test Systems	Intrinsic Rate of Dissolution, M/cm², min.
Furosemide	1.27×10^{-8}
1:2 Coprecipitate	
Furosemide-PVP 10,000	2.21×10^{-7}
Furosemide-PVP 40,000	1.64×10^{-7}
Furosemide-PVP 360,000	1.44×10^{-7}

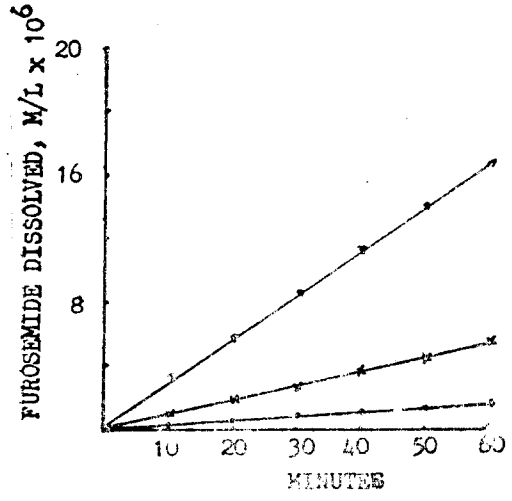

Fig. 3: Dissolution rates of furosemide from furosemide disks at 150 rpm.
Key: ● = at 25°; × = at 37°; ▲ = at 50°

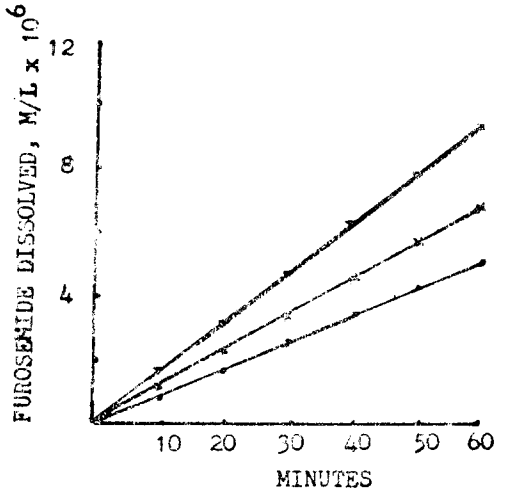

Fig. 4: Dissolution rates of furosemide from furosemide disks at 37°.
Key: ● = at 150 rpm; × = at 300 rpm; ▲ = at 600 rpm.

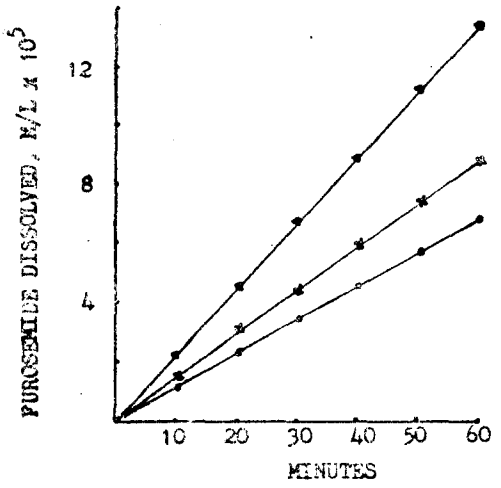

Fig. 5: Dissolution rates of furosemide from 1:2 furosemide-PVP 40,000 coprecipitate disks at 150 rpm.
Key: ●=at 25°; ×=at 37°; ▲=at 50°.

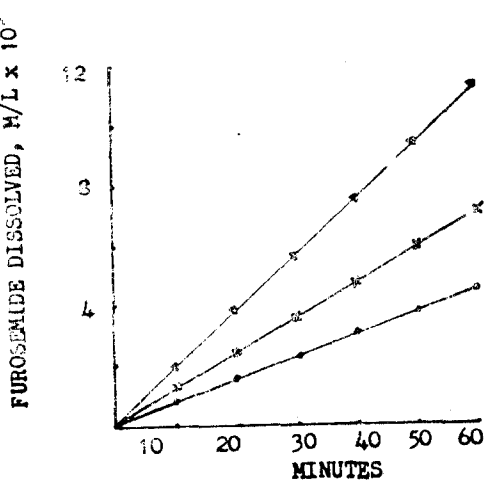

Fig. 6: Dissolution rates of furosemide from 1:2 furosemide-PVP 40,000 coprecipitate disks at 37°.
Key: ●=at 150 rpm; ×=at 300 rpm. ▲=at 600 rpm.

molecular weight PVP 10,000 coprecipitate showed the fastest dissolution rate than the PVP 40,000 coprecipitate and the PVP 360,000 coprecipitate[39, 40, 50, 62].

Intrinsic Rate of Dissolution

Under sink conditions, a percent value of dissolved drug at time 't' may simply be equivalent to the percent surface area generated to time 't'[19].

However, under the experimental conditions of 200 ml of 0.005M HAc medium, 37°C, 150 rpm, it is appropriate for the sink conditions ($C \leq 0.1$ Cs) in some particular time during the dissolution process. The intrinisic rates of dissolution of furosemide from furosemide test systems are described in Table I.

The results show that the intrinsic rate of dissolution, G, of furosemide was increased by the formation of coprecipitate.

Effect of Temperature on the Dissolution Rate

The effect of temperature on the dissolution rate of furosemide from the pure furosemide disk and the 1:2 furosemide-PVP 40,000 coprecipitate disk was investigated. The dissolved amount of furosemide from the pure furosemide disks at various temperatures (25, 37 and 50°C) is denoted as mole concentration against time in Fig. 3 and that from the 1:2 furosemide-PVP 40,000 coprecipitate is in Fig. 4. The rate constant of dissolution of furosemide at 150 rpm, 37°C from the furosemide disk was 8.95×10^{-8} and that from the furosemide-PVP 40,000 coprecipitate disk, 11.62×10^{-7} M/min., respectively.

The rate constant of dissolution of furosemide from the 1:2 furosemide-PVP 40,000 coprecipitate disk was increased about 13-fold by comparing from the pure furosemide disk. And

Table II: Activation Energy of Dissolution, Ea.

Test Systems	Activation Energy of Dissolution, cal/mol.
Furosemide	17,000
1:2 Furosemide-PVP 40,000 coprecipitate	7,300

the dissolution rate of furosemide was increased, as one would expect, at high temperature. Fig. 7 illustrates the dependence of rate of dissolution, k, of furosemide on the temperature at 150 rpm. The plot of log k against 1/T was supposed to be straight in the present temperature range[3, 11, 16, 20]. As shown in Fig. 7, the slightly sharp straight line from furosemide disk became dull in slope from the 1:2 the furosemide-PVP coprecipitate disk. The activation energy[3] calculated from the slope of straight line is described in Table II.

The result of this experiment indicates that the activation energy of dissolution decreases by the formation of the coprecipitates, indicating the increase in the dissolution rate.

Effect of Rotating Velocity on the Dissolution Rate

Both effects of temperature and rotating velocity are commonly used to aid in distinguishing the process controlling the dissolution rate[28]. Fig. 4 shows the dissolution rate of furosemide at various rotating velocities (150,

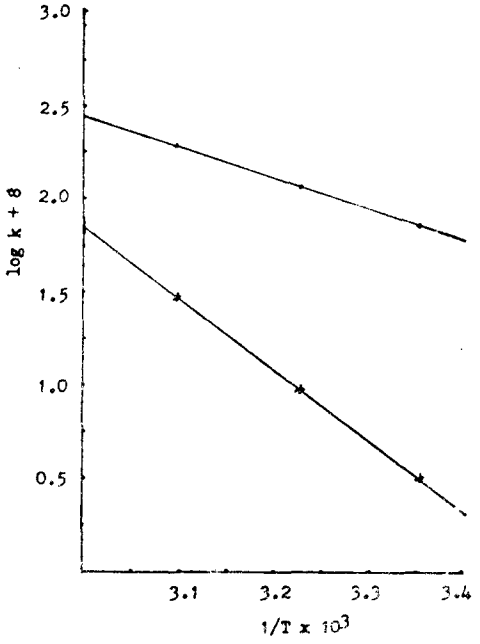

Fig. 7: Dependence of rate constant, k, of furosemide on the temperature at 150 rpm.
Key: × = pure furosemide;
● = 1:2 furosemide-PVP 40,000 coprecipitate.

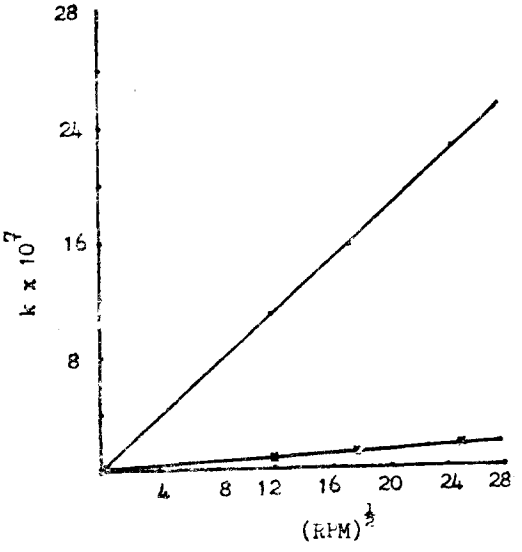

Fig. 8: Dependence of rate constant, k, of furosemide on the rotating velocity of disk at 37°.
Key: × = pure furosemide;
● = 1:2 furosemide-PVP 40,000 coprecipitate.

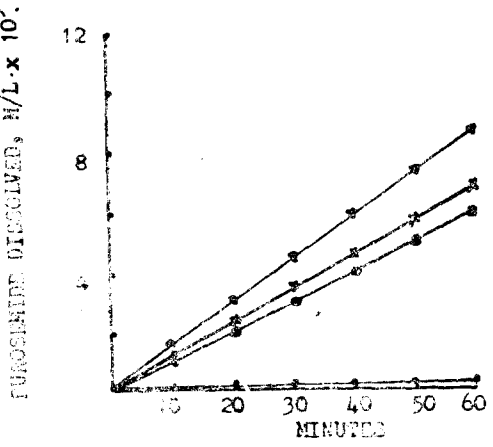

Fig. 9: Dissolution rates of furosemide in disk state at 37°, 150 rpm.
Key: ●=pure furosemide;
▲=1:2 furosemide-PVP 10,000 coprecipitate;
×=1:2 furosemide-PVP 40,000 coprecipitate;
■=1:2 furosemide-PVP 360,000 coprecipitate.

300 and 600 rpm) from the pure furosemide disks, and Fig. 6 shows that from the 1:2 furosemide-PVP 40,000 coprecipitate disks. The dissolution rate of furosemide, as one would expect, was increased at high rotating velocity. This result indicates that the dissolution is expected as transport-controlled reaction and that the disintegration of the disk does not take place. Fig. 8 shows the dependence of rate constant of dissolution, k, of furosemide on the rotating velocity of disk at 37°C. The plot of rate constant of dissolution, k, against the square root of the above rotating velocity was supposed to be straight line which passes through the original point. The results also verify that the rate constant of dissolution is proportional to the square root of rotating velocity of the disks[3, 20].

Studies on the PEG Coprecipitate System

As in case of PVP coprecipitate system in the powder state, the surface area of the dissolving particles might be changed as the dissolution time passes, and the dissolution characteristics of furosemide were determined from the non-disintegrating disk, under the constant surface area state. The coprecipitate disks with PEG 4,000 and with PEG 6,000 were disintegrated by melting at 37° of the dissolution medium and the dissolution rate experiments could not be carried on.

Application and Importance of Results

The observation obtained in the present study demonstrates that coprecipitation with polymer such as PVP and PEG increased the solubility and dissolution rate of furosemide and the coprecipitation technique might have general application to a wide variety of relatively water-insoluble drugs. The use of this techinque to the relatively water-insoluble drugs might increase bioavailability of drugs by increasing the dissolution, and the solution preparations of water-insoluble drugs could be made specifically for intravenous injections. The technical application in the pharmcological screening of new drugs might be self-evident.

CONCLUSIONS

The results of the studies on dissolution rate and equilibrium solubility demonstrate that the extent of furosemide in dissolution was significantly enhanced by the formation of the co-

precipites with polymers. 1) The dissolution chatacteristics of furosemide from the pure furosemide disks and the 1:2 (w/w) furosemide-PVP coprecipitate disks were in accordance with the Noyes-Nernst equation. 2) The rate constant of dissolution, k, was proportional to the square root of rotating velocity of the disks. 3) The intrinsic rate of dissolution, G, at 150 rpm, 37°C was 2.21×10^{-7} for the PVP 10,000 coprecipitate, 1.64×10^{-7} for the PVP 40,000 coprecipitate, and 1.44×10^{-7} for the PVP 360,000 coprecipitate, while it was 1.27×10^{-8} M/cm^2 min for pure furosemide, respectively. 4) The activation energy of dissolution, Ea, was about 17,000 for furosemide, and about 7,300 cal/mole for the 1:2 furosemide-PVP 40,000 coprecipitate, respectively, Thus it was decreased by the formation of coprecipitates.

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