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Dissolution Characteristics of Hydrophobic Drug—Soluble Carrier Coprecipitate (I)

Enhanced Dissolution Rates of Furosemide from Furosemide Polymer Coprecipitates

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An enhancement in the dissolution rate of the drug should facilitate its GI absorption if the absorption process is dissolution rate limited.

One of the need for the techniques that can potentially enhance the dissolution rate and extent of absorption of hydrophobic drugs is the formation of coprecipitates with pharmacologically inert, polymeric materials.

The physicochemical modification offers the advantage of possibly enabling one to administer the drug orally in a form from which it is most available for GI absorption.

Several investigation[1-15] demonstrated that the formation of solid dispersions or coprecipitates of relatively water-insoluble drugs with various pharmacologically inert carriers can increase singnificantly their *in vitro* dissolution rates.

However, little information is available in the literature related to the dissolution rate patterns of furosemide, a water-insoluble diurectices, with respect to the sort of copolymer and the ratio of coprecipitates as a function of time, respectively.

The purpose of the present investigation was to ascertain, the general applicability of the copolymers to use fore more fast, enhanced dissolution techniques of furosemide.

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To accomplish the need for enhancement in the dissolution rate of furosemide, varying ratio coprecipitates with different water-soluble polymers, such as Polyvinylpyrrolidone (PVP), polyethylene glycol 4000(PEG 4000), and polyethylene glycol 6000 (PEG 6000), were quantitatively studied by comparing their dissolution characteristics of furosemide.

The dissolution patterns of pure furosemide, varying ratio furosemide-PVP coprecipitates, (1 : 2, 1 : 5, and 1 : 9(w/w)), furosemide-PEG 4000 coprecipitates (1 : 4, 1 : 9, and 1 : 19(w/w), furosemide-PEG 6000 coprecipitates(1 : 4, 1 : 9, and 1 : 19(w/w)), and the same ratio physical mixtures, respectively, were compared by the amount dissolved as a function of time.

EXPERIMENTAL

Materials——The furosemide (USP-XIX) (Teva middle east pharm. & chemical works), polyvinylpyrrolidone (average mol. wt. 40000), polyethylene glycol 4000, and polyethylene glycol 6000 were phamraceutical grade. All other chemicals used were reagent grade and used as received.

Apparatus——Dissolution tester (USP-XIX) (150 RPM, 37°), Beckmann DU spectrophotometer.

Test Preparation of Furosemide-PVP Coprecipitates——The 1 : 2, 1 : 5, and 1 : 9(w/w) ratio furosemide-PVP coprecipitates were prepared by dissolving both components in methanol and subsequently evaporating off the organic solvent under reduced pressure. The residue was then dried to constant weight in a desiccator(H_2SO_4, reduced pressure) and screened between 150—200 mech size (74—105μ) and the furosemide-PVP weight ratio was analytically confirmed. The 1 : 2, 1 : 5, and 1 : 9 (w/w) physical mixtures were prepared by gently triturating of furosemide(74—105μ) and PVP (74—105μ). The pure furosemide, possessing a particle size of 150—200mech sieve sized (74—105μ), served as all test preparations.

Test Preparation of Furosemide-PEG Coprecipitates——Furosemide and water-soluble carriers such as PEG 4000 and PEG 6000 were accurately wighed in 1 : 4, 1 : 9, and 1 : 19 ratios. First, PEG were heated on water bath with frequent stirring until they are melted. Later, furosemide was added to PEG part with frequent stirring on water bath until they are dissolved. The melts were quickly solidified by pouring onto stainless steel plates, facilitated by blowing cold air onto the oposite side of the plates. The furosemide-PEG mixtures were storaged in a desicc-

ator to harden. The final solid masses were pulverized in a mortar or by use of a samll ball mill and then powderes were sieve-sized to 150—200 mesh range.

Particulate Dissolution Rate Studies——The dissolution rate test method descrised in USP-XIX was used to assess the dissolution characteristics of the test prepartaion at 37. The 500ml of 0.05M acetic acid (pH 3.05) was added to the 1000 ml, three neck round bottom flask, maintained at 37°, and agitated at 150 RPM. The quantity of test preparation, 150—200 mesh powder (74—105μ) equivalent to 500mg of furosemide was transferred directly into the dissolution medium. At frequent time intervals subsequent to the introduction of test preparation, a 3.0ml sample was removed with the aid of a filter pipette and replaced with 3.0ml of fresh dissolution medium. The samples were subjected to Millipore filtration (0.45μ pore size) at 37°, the filtrates were diluted, if necessary, and the concentration of drug in solution was determined spectrophotometrically at 274nm, using Beckmann DU spectrophotometer. PVP, PEG 4000, and PEG 6000 in the concentrations present in the assay samples were found not to interfere with the determination of furosemide. All particulate dissolution rate experiments were perfomed in duplicate.

Equilibruim Solubility Determinations——The equilibrium solubility of furosemide was determined at 37° in 0.05M HAc (pH 3.05) and 0.05M HAc containing 1% (w/w) PVP. Excess of furosemide were placed into 200ml of glass-stoppered flask together with 100ml portions of the solvent system listed. All flasks were closed securely and mechanically shaken at 37° until equilibrium was attained. Equilibrium was established by repetitive sampling and was found to occur within 12—24 hrs. The equilibrated samples were subjected to Millipore filtration(0.45μ pore size) at 37°, the filtrates were suitably diluted when necessary, and the concentration of drug in solution was determined spectrophotometrically at 274nm, using Beckmann DU spectrophotcmeter.

RESULTS AND DISCUSSION

Stability of Furosemide during Experiment——The pure furosemide in the final solution was used to verify the chemical stability during dissolution rate experiment. The pure furosemide solution in 0.05M HAc was kept at 37° for a day, no detectable change in furosemide concentration was found. Therefore, the furosemide in 0.05M HAc was stable during experiment.

Studies on the PVP Coprecipitate System——The effect of PVP ratio to furosemide on the dissolution rate was investigated, to determine whether a greater concentration of polymer could effect the dissolution rate of furosemide, the varying ratio coprecipitates with PVP were studied in the dissolution medium. The methanol coprecipitates composed of furosemide to PVP of 1 : 2, 1 : 5, and 1 : 9 (w/w) ratio were prepared and their dissolution rate patterns were obtained.

Figure 1 shows the microgram per ml of furosemide, dissolution amounts as a function of time for all coprecipitates, while, the pure furosemide is included as a point of reference. The dissolution rates in 60 min. for the 1 : 2, 1 : 5, and 1 : 9 (w/w) ratio furosmide PVP coprecipitates were increased about 11—, 30—, and 38-fold by comparing with pure furosemide. It should be noted that the furosemide coprecipitate with high concentration of PVP exhibits marked increase in the dissolution rate as compared with pure furosemide. The result of this experiment indicates, as one would expect, that the enhanced dissolution of furosemide is apparently dependent on the PVP content used in coprecipitating(Figure 1).

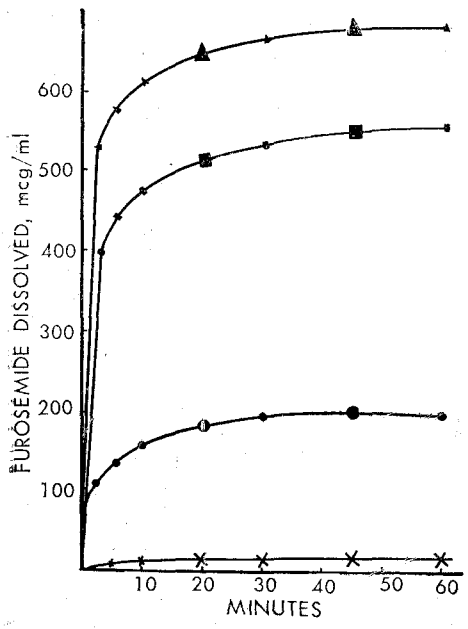

Figure 1—Dissolution rates of furosemide in furosemide-PVP coprecipitates. Key: ×, pure furosemide; ●, 1 : 2 ratio; ■, 1 : 5 ratio; ▲, 1 ; 9 ratio

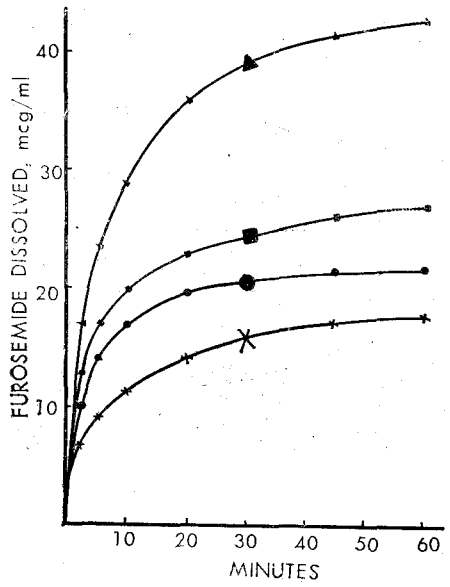

Figure 2—Disslution rates of furosemide in furosdmide-PVP physical mixtures Key: ×, pure furoemide; ●, 1 : 2 artio; ■, 1 : 5 ratio; ▲. 1 : 9 ratio.

Studies on the Physical Mixture System——The dissolution pattern of furosemide in the presence of PVP as the same ratio with above coprecipiatde system, the amounts dissolved in the 1 : 2, 1 : 5, and 1 : 9(w/w) ratio physical mixture are denoted in Figure 2.

A comparison of the dissolution characteristics of furosemide-PVP physical mixture with those of the pure furosemide indicates that the durg goes into solution at faster rate from the former preparation. Unlike the coprecipitated systems, the physical mixture systems did not show so much high amounts dissolved and unexpectedly there was no appreciable enhancement of furosemide dissolved due to the presence of PVP. Apparently, the presence of PVP either alters the surface characteristics of the furosemide and solubility of furosemide.

Effect of Solvent Used in Coprecipitate System——The formation of drug solvates has been shown to affect the dissolution rate of hydrophobic drugs significantly[13-16]. Since methanol was used to prepare the furosemide coprecipitate system with PVP, PEG 4000, or PEG 6000, the possibility existed that the enhanced dissolution characteristics of furosemide from this system, resulted from the for-

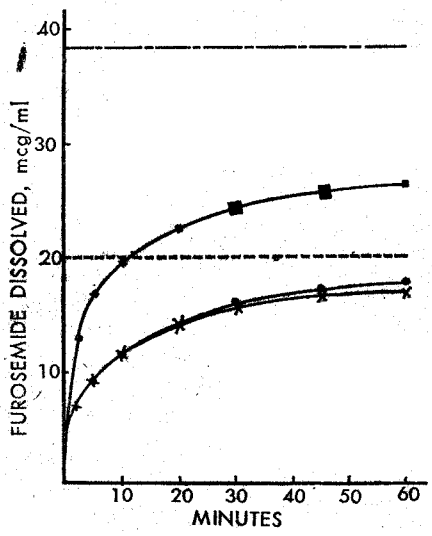

Figure 3—Dissolution rates of furosemide. Key: ×, pure furosemide; ●, furosemide recrystallized from methanol; ■, 1:5 ratio furosemide-PVP physical mixture; ·····, equilibrium solubility of furosemide in dissolution medium containing no PVP: ---, equilibrium solubility of furosemide in disolution medium containing 1% PVP.

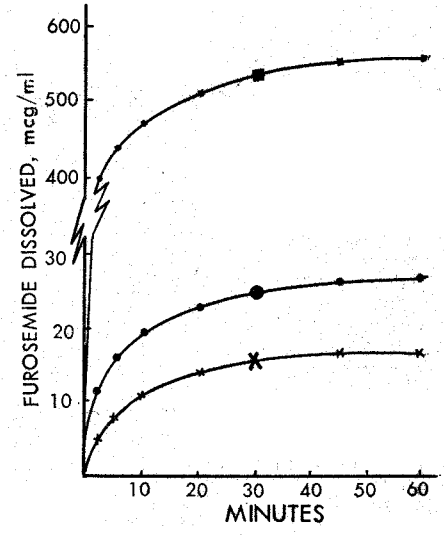

Figure 4—Dissolution rates of furosemide. Key: ×, pure furosemide; ●, 1 : 5 ratio furosemide-PVP physical mixture; ■, 1:5 ratio furosemide-PVP coprecipitate.

mation of a methanol solvate. To explore this possibility, the dissolution rate of furosemide only, recrystallized from methanol was investigated. The disslution rates for pure furosemide(74—105μ) and recrystallized furosemide(74—105μ) are depicted in Figure 3.

The rates of solution of furosemide from these systems are quite similar in magnitudes between pure furosemide and recrystallized furosemide from methanol. The result of this experiment suggests that the increase noted in the dissolution of furosemide from 1 : 5(w/w) PVP coprecipitate cannot be due to the formation of a durg-methanol solvate during the preparation of the coprecipitate system.

Physicochemical Studies——It is also obvious that the dissolution rate of furosemide is dependent on the particale size of the drug. The dissolution rate behavior of pure furosemide alone, 1 : 5(w/w) furosemide-PVP physical mixture, and the same ratio coprecipitate with PVP is shown in Figure 4. This figure depicts the solubility characteristics of the test systems only for 60 min. The dissolution characteristics of the 1 : 5(w/w) forosemide-PVP physical mixture were slightly increased dy those obtained with the pure drug. The considerable interest is the fact that even though the particle size of drug available for dissolution was held constant, the bissolution rate of furosemide from the pure furosemide and physical mixture system with PVP was differentiated. This suggests that simple particale 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 mixutre, as compared to the pure drug, is almost likely due to the sbility of the water-soluble polymer to enhance the wettability of the hydrophobic aurosemide particles. An examination of the dissolution rate for the pure furosemide, and 1 : 5(w/w) furosemide-PVP coprecipitate reveals that the amount of drug in solution from the coprecipitate system rapidly and markedly exceeds the equilibrum folubility of the drug (Figure 3 and 4). However, the dissolution rate of 1 : 5 (w/w) furosemide-PVP coprecipitate was 21 times greater than the same ratio furosemide-PVP physical mixture. This result indicates that the more presence of PVP is not responsible for the enhanced dissolution rate of furosemide. In addition the role of PVP in the differential apparent enhancement of the furosenide dissolution rate among the coprecipitate system and the physical mixture is quite interesting. Also, the equilibium solubility studied(Figure 3) indicates that the enhanced dissolution rate of furosemide from the 1 : 5(w/w) furosemide-PVP coprecipitate system is most probably not result of a water-soluble complex formation between

the drug and PVP. Based on these results, it appears that a form of furosemide possessing a high thermodynamic activity was produced during the preparation of the PVP coprecipitate[15-17]. Since the surface area of the dissolving particles was change as a function of time in the partculate dissolution rate experiments, the possibility exists that the PVP simply affects the physicochemical medification of furosemide crystals during the coprecipitation procedure and the particle size reduction was part of the mechanism responsible for the effectiveness of the coprecipitate system. The results obtained in the PVP coprecipitate systems suggest that a high energy, metastable form of furosemide is produced on its coprecipitation with PVP. When the coprecipitate is brought into contact with dissolution medium, the PVP carrier rapidly dissolves, thus releasing this highly energetic form of drug. Accordingly, it may be proposed that a high energy form of furosemide, most probably amorphous, as compared to the most thermodynamically stable form of drug, is formed during the coprecipitation process, and that the dissolution of furosemide is markedly enhanced from the coprecipitate.

Studies on the Effect of PEG Molecular Weight on the Furosemide Dissolution Rates——Since wide range of molecular weight polymers of PEG were available, it was important to determine if any behavioral differences existed with avariation in the chain length. If a difference did exist, the polymer chain length that appeared to produce the most significant solubility increase would be utilized for this study. Toward this end, 1 : 4, 1 : 9, and 1 : 19(w/w) ratio coprecipitates with PEG 4000 and with PEG 6000, were prepared using direct melting method, and dissolution rates were determined. The micrograms per milliliter of furosemide dissolved as a function of time for varying ratio coprecipitates are shown in Figures 5 and 6.

The dissolution rates in 60 min. for the 1 : 4, 1 : 9, and 1 : 19 ratio coprecipitates were increased about 3—, 5—, and 7-fold in furosemide-PEG 6000 test preparations and about 1.7-, 2-, 4-fold in the same ratio furosemide-PEG 4000 coprecipitates, respectively. Owing to the similar physical and chemical properties of PEG 4000 and PEG 6000, it is understandable that the furosemide dispersed in these two carriers all exhibit approximately the same dissolution characteristics. It is also seen that the chain length indeed significantly changes the dissolution rate of furosemide, the PEG 6000 polymer being faster than PEG 4000 polymer. For this result, the high molecular weight copolymer of PEG appears to produce significant solubility increase and available for coprecipitation.

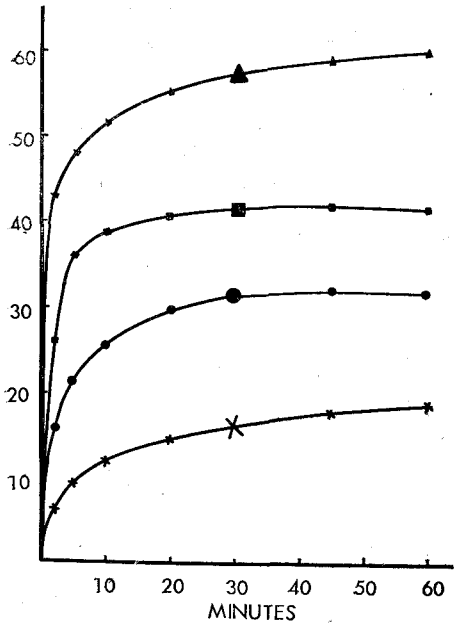

Figure 5—Dissolution rates of furosemide in furosemide-PEG 4000 coprecipitates.
Key: ×, pure furosemide; ●, 1:4 ratio; ■, 1:9 ratio; ▲, 1:19 ratio.

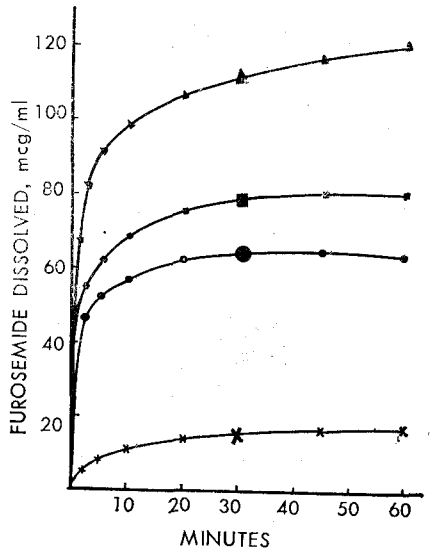

Figure 6—Dissolution rates of furosemide in furosemide-PEG 6000 coprecipitates.
Key: ×, pure furosemide; ●, 1:4 ratio; ■, 1:9 ratio; ▲, 1:19 ratio.

Application and Importance of Results——The results obtained in the present study demonstrate that coprecipitation with copolymer, such as PVP, PEG 4000, and PEG 6000 increased the solubility and dissolution rate of furosemide.

Figure 7 shows that dissolution rate difference by comparing the sort of polymer used in coprecipitaing. Even the 1 : 2 ratio coprecipitates with PVP possess better dissolution rate than 1 : 19 ratio coprecipitates with PEG 4000 or with PEG 6000. These observations indicate that the coprecipitation technique might have general application to a wide variety of the relatively water-insoluble drug. The advantage of utilizing this technique to the relatively water-insoluble drug might increase the absorption from the GI tract, following the increasing the dissolution, and the solution preparations of water-insoluble drugs could be made specifically for intravenous injections. The technical applications in the pharmacological screening of new drugs might be self-evident and hoped to explore in future.

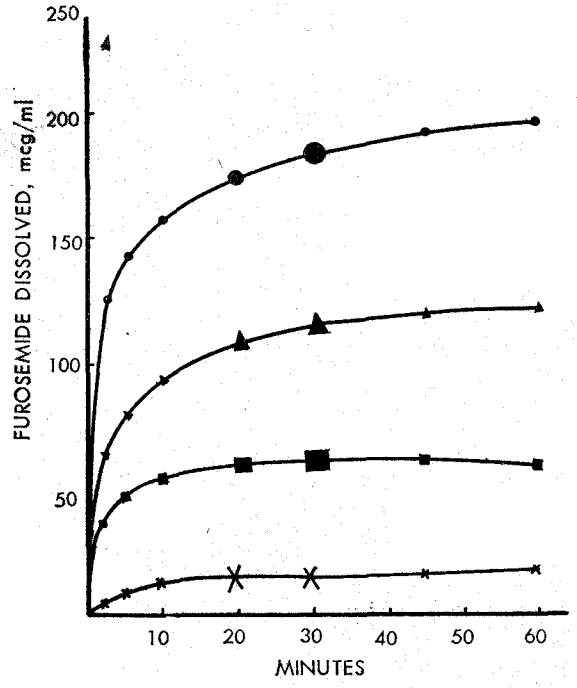

Figure 7—Dissolution rates of furosemide.
Key: ×, pure furosemide; ●, 1:2 ratio PVP coprecipitate; ■, 1:19 ratio PEG 4000 coprecipitate; ▲, 1:19ratio PEG 6000 coprecipitate.

CONCLUSIONS

From the data obtained in the present study, these results could be supported as following;

1. The result of dissolution rates of furosemide studied demonstrates that the extent of furosemide of dissolution is significantly enhanced, following the formation of the coprecipitates.
2. The enhanced dissolution of furosemide is apparently dependent on the polymer content, such as PVP, PEG 4000, and PEG 6000, used in coprecipitating.
3. The high molecular weight polymers appear to produce significant increase of dissolution rate.

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