(약 제 학 회 지
J. Korean Pharm. Sci.
6 (3) 58~69 (1976))

Dissolution Characteristics of Hydrophobic Drug-Soluble Carrier Coprecipitates (III)

Dissolution Behaviour of Indomethacin from Several Fast Release Solid Dispersions of Indomethacin

*In Koo Jeon, **Min Hwa Lee, and **Shin Keun Kim

(Received Nov. 29, 1975)

It is well established that dissolution is freruently the rate limiting step in the gastrointestinal absorpton of a drug from a solid dosage from. The relationship between the dissolution rate and absorption is particularly distinct when considering drugs of low solubility. Consequently, numerous attempts have been made to modify the dissolution characteristics of poorly water soluble drugs.

Since dissolution rate is directly proportional to surface area[1], one may increase the rate by decreasing the particle size of the drug.

Levy[2] has considered a number of methods by which a drug may be presented to the GI fludids in finely divided from. The direct method is the utilization of microcrystalline or micronized particles. A second method involves the administration of solutions from which, upon dilution with gastric fluids, the dissolved drug will precipitate in the form of very fine particles.

A more unique way of obtaining microcrystalline dispersions of a drug has been ercently suggested by Sekiguchi *et al*[3-4]. They have first proposed the formation of a eutectic mixture of a poorly water soruble drug with a physiologically inert, easily soluble carrier.

When such systems are exposed to water or GI fluids, the soluble carrier will dissolve rapidly and the finely dispersed drug particles will then be released.

* Baik Su Pharmaceutical Co., Ltd
** College of Pharmacy, Seoul National University

It has been suggested by Shefter and Higuchi[5] that the formation of crystalline solvate could be a powerful tool in affecting rapid disslution of highly insoluble substances.

Goldberg *et al.*[6-8] have noted that the formation of solid solution could reduce the particle size to a minimum and increase the dissolution rate as well as the solubility of the durgs.

It has also been shown that the rates of solution of drugs were appreciably increased by coprectipitating the drug with soluble polymers[9-11]. The increase was found to be sensitive to the method of preparation, the molecular weight of polymer and the particular ratio of drug to polymer.

Although several investigations[9,10,12-14] have demontrated that the solubility and/or dissolution rates of drugs can be increased in this manner, little information is available in the literature related to the *in vivo* absorption pattern of drugs orally administered as PVP coprecipitates. Recently, however, it was demonstrated [14-16] that both the rate and extent of absorption of the insoluble drug could be markedly enhanced when orally administered to rats in the form of a coprecipitate with PVP.

The purpose of the present investigation was to ascertain the general appility of soluble polymer coprectation technique as a method for enhancing the *in vitro* dissolution rate of hydrophobic indomethacin.

To accomplish this aim, the dissolution characteristics of pure indomethacin, indomethacin-polymer physical mixtures and indomethacin-polymer coprecipitates were quantitatively studied by comparing their relative dissolution rates. The solubility and dissolution behaviour of these systems were also examined.

EXBERIMENTAL

Materials and Reagents——The indomethacin(BP 1973), polyvinylpyrrolidone (PVP), polyethylene glycol(PEG) 4000 and polyethylene glycol(PEG) 6000 employed in this study were pharmaceutical grade. The polyvinylpyrrolidone had an average molecular weight of 25000. All other chemicals were commercially available reagent grade.

Apparatus——A contant temperature incubator, set at 37±0.1°, Hitachi-Horiba M-5 pH meter, Hitachi 139 spectrophotometer, Melting point apparatus(K.P. Ⅱ), Thin layer plate(5×20cm), covered with silica gel B-5 in 0.5mm in thickness.

Methods of Test Preparation——*Direct melting method* (fusion method)—Fine

powders of indomethacin and different water soluble carriers such as PEG 4000 and PEG 6000 were accurately weighed in certain ratios (1 : 4, 1 : 9 and 1 : 19 w/w). They were physically mixed and transferred to beakers of a suitable size. These physical mixtures were heated directly and quickly with constant stirring on the water bath until they all melted. The melts were quickly solidified by pouring onto stainless stell plates. The indomethacin-PEG 4000 coprecipitates repuired storage for a few days in a desiccator to harden. The final solid masses were pulverized in a mortar. The powders were sieve-sized to 20—70 mesh range, and the indomethacin -PEG weight ratios were analytically confirmed.

Solvent method——The indomethacin-PVP coprecipitate systems(1 : 1, 1 : 5 and 1 : 9 w/w) were prepared by dissolving both components in chloroform and subseqeuently evaporating off the organic solvent. The resulting cloudy and colloid-like suspensions were further concentrated at 105° for 1 hr., until the formation of chloroform vapor bubbles were no longer observed. Semitransparant, viscous liquids were obtained and were allowed to solidify by cooling. The residues were than dried to constant weight in vacuo, and screened to 20—70 mesh range. The indomethacin-PVP weight ratios were analytically confirmed.

Stability Studies on the Indomethacin-Solid Dispersions—Thermal and chromatographic methods have been used to study the pure components and the components of the final dispersions to attempt to verify their chemical stability after processing.

Thermal Study——The melting point of indomethacin is 158—162°. The micronized powder was melted quickly to 170°, and the melting point of the rapidly solidified mass was measured by the capillary method to ascertain the effect of the heating process.

Thin Layer Chromatography——The pure and processed indomethacin samples were dissolved in chroform and spotted on the plates. The plates were developed by a solvent system of chloroform-acetic acid (95 : 5 v/v)[17] and visualized in a chamber of iodine.

Dissolution Rate Studies——The dissolution apparatus consisted of a 1 liter three necked round bottom flask, containing 900 ml of pH 6.0 or 6.5 phosphate buffer (BP 1975). The solution was maintained at 37±1° and agitated at 180 RPM by means of a stainless steel stirrer with stainnless propeller blades(37mm. diameter) connected to a constant speed motor. At frequent time intervals subsequent to the introduction of a quantity of test preparation equivalent to 300 mg. Of indomethacin into the dissolution medium, a 3.0 ml sample was withdrawn with the aid of a

filter pipette and replaced with 3.0ml. of fresh dissolution medium. All samples were run at least in triplicate.

Method of Analysis——To 3.0 ml sample was added fresh dissolution medium to produce 50 ml. The amount of indomethacin in solution at each time interval was determined spectrophotometrically in 1 cm. cells at 318 nm, using the dissolution medium as the blank. PEG 4000, PEG 6000, PVP, in the concentrations present in the assay samples, were found not to interfere with the determination of indomethacin.

Equilibrium Solubility Determinations——The equilibrium solubility of indomethacin was determined at 37° in pH 6.0 buffer, pH 6.5 buffer, and pH 6.0 buffer containing PEG 4000, PEG 6000 and PVP in varing concentrations. An excess amount of pure drug was placed in 50 ml. test tubes equipped with stoppers and containing 30 ml of an aqueous solution.

After the the thermostatic agitation with a magnetic stirrer at 37° for 24 hours, the content of each tube was equilibrated at 37° for 72 hours. The equilibrated samples were subjected to filtration at 37°. The filtrates were suitably diluted when necessary, and the concentration of drug in solution of drug in solution was determined spectrophotometrically at 318 nm, using the aqueous solution as the blank.

RESELTS AND DISCUSSION

Selection of Hydrophobic Drug and Water Soluble Polymer——A study was initiated to find a poorly soluble drug that would form a simple solid dispersion with a water soluble polymero Indomethacin and water soluble polymer, such as PEG 4000, PEG 6000 and PVP, were employed according to the criteria described in the report[7].

Indomethacin is soluble even in high molecular weight PEG melts, which viscosity increases markedly with the decrease in temperature. During the preparation of indomethacin-PEG solid dispersion forms, the durg will only nucleate with extreme differiculty due to the extremely high viscosity of the medium at low temperature and the short time interval for the completion of solidification. Therefore the solidification time may play an important factor especially in obtaining a metastable solid solution. Polyethylene glycols may well be ideal matrices foremost water insoluble durgs(assuming they are soluble in the PEG melts), whether they form stable or meta-stable solid solutions or fine

particles of pure drugs dispersed in the matrix.

PEG polymers were used as indomethacin supporitory bases[18-20]. The PEG bases may be made from polyethylene glycol or mixtures therof of various molecular weights which are used to prepare suppositories that are soluble in water and in the excretions of mucous membranes. It is known, however, that in the preparation of suppositories, discoloration, esterification and other undesirable conditions may result due to the to the excessive time required for crystallization to occur.

Therefore Dempski *et al.*[19-20] invented pharmaceutically acceptable crystalline material, which acts as a nucleating agent to prevent undesirable conditions such as discoloration and esterification.

Stability Studies——When indomethacin dissolved in organic solvents and polyethylene glycol metls, the solution turned to yellow or greenish yellow color. All the indomethacin-PVP coprecipitates varied in yellow color according to the drug to polymer ratios, and indomethacin-PEG coprecipitates changed from greenish yellow to slightly greenish white with the pass of time. This means the crystal-growth of indomethacin in the matrices of PEG polymers.

Pure Indomethacin——The melting point of indomethacin after heating process was identical to that of unheated indomethacin. No spots were detected by TLC.

Indomethacin Dispersed in PEG and PVP Polymers——New spots could be detected on the thin layer plate.

On the basis of these facts, it seems that indomethacin is thermally stable and is not decomposed by the processing.

Dissolution Rate Studies——Since indomethacin is an dcidic erug (pKa 4.2)[17], it is important to determine how the dissolution rate of indomethacin in aqueous solution is affected by the change of the pH. As shown in Figure 1, the dissolution rate of 100—200 mesh pure indomethacin varied considerably with a varation of the pH. At 60 minutes, the dissolution rate of pure drug is 5.6 times faster at pH 7.0 than at pH 5.5.

It is assumed that the dissocition of indomethacin may be accelerated, thereby increasing its solubility, when the pH becomes higher. Therefore it seems that the increased dissolution rate of indomethacin is due to the higher solubility at the higher pH.

Also the rate of solution of indomethacin according to the particle size reduction is shown in Figure 2. The increased dissolution rate of above 200 mesh pure drug

in comparison to the 70—100 mesh pure drug can be related to only one factor, decreased particle size and increased surface area.

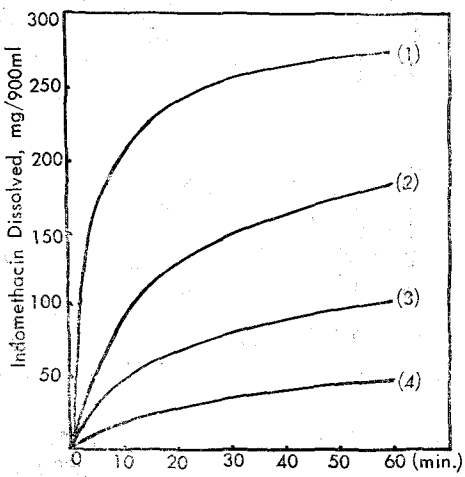


Figure 1—Dissolution rates of indomethacin at various pH buffer systems, 300mg/900ml at 37°. Key : (1), pH7.0; (2), pH6.5; (3), pH6.0; (4), pH5.5

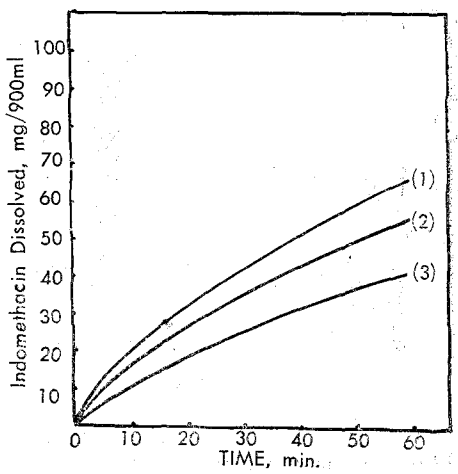


Figure 2—Milligrams of indomethacin released from pure drug of various particle size distribution, 300mg/900ml, pH6.0 at 37°. Key: (1), above 200 mesh; (2), 100—200 mesh; (3), 70—100 mesh.

Table I and Figures 3—13 include data obtained in the 1 liter dissolution apparatus under conditions in which in all cases the sample size was adjusted so as to contain 300 mg of indomethacin in 900ml phosphate buffer. In all indomethacin-polymer coprecipitates, the particles were screend to approximately the same size (20—70 mesh). Table I compares the studies utilizing the time it took for each preparation to reach 20% dissolution(T_{20}), 50% eissolution (T_{50}) and 70% dissolution (T_{70}). The data in table I were determined by the log-probit method suggested by Wagner[21].

As shown in Figure 3 the dissolution rate of the nonwetted, 100—200 mesh indomethacin is significantly slower than that of the same powder when wetted first prior to study(with 1 ml of 0.2% polysorbate 20 solution). As shown in Figure 3,4 and 6, the dissolution rates of the 1 : 9(w/w) in domethacin-PEG 4000, PFG 6000 and-PVP physical mixtures which were prepared in the manner previously described[14] were significantly faster than nonwetted 100—200 mesh pure drug.

The solubility of pure drug in pH 6.0 buffer containing 1% PEG 4000, PEG 6000 and PVP is approximately 1.09, 1.24, and 1.36 times greater respectively than in pH 6.0 buffer itself. The equilibrium solububilities of indomethacin in pH 6.0 and 6.5 buffer at 37° were 14.1mg/100 ml and 41.3mg/100ml respectively. The results

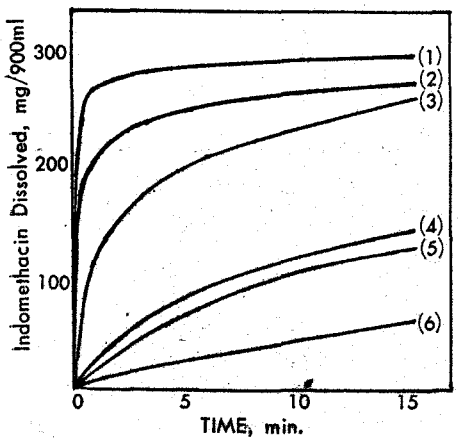


Figure 3—Dissolution rates of indomethacin -PEG 4000 solid dispersions, 300mg/900ml, pH9.5 at 37°. Key (1), 5%—; (2), 10%—, (3), 20%—; (4), 5% indomethacine PEG 4000 physical mixture; (5), wetted, 100—200 mesh pure durg; (6), nonwetted, 100—200 mesh pure drug.

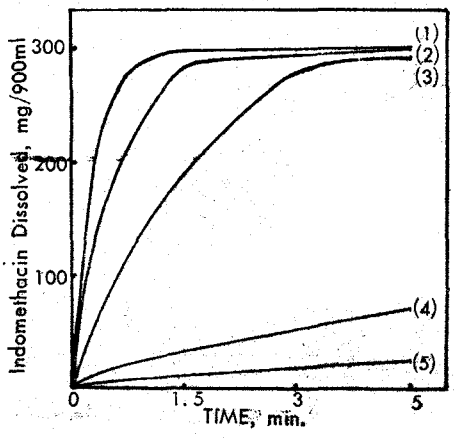


Figure 4—Dissolution rates of indomethacin -PEG 6000 solid dispersions, 300/mg/900ml, pH6.5 at 37°. Key: (1), 5%—:(2), 10%—; (3), 20%—; (4), 5% indomethacin-PEG600 physical mixture; (5), nonwetted, 100—200 mesh pure drug.

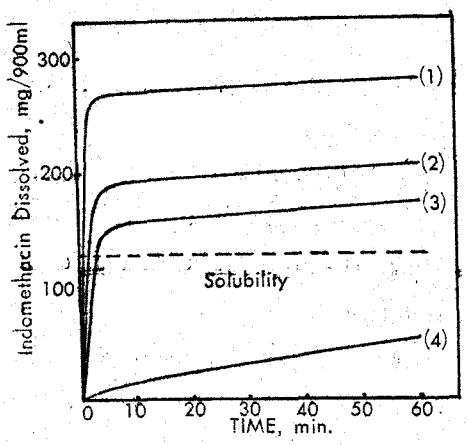


Figure 5—Dissolution rates of indomethacin -PEG 6000 solid dispersions, 300mg-900ml. pH 6.0 at 37°. Key; (1), 5%—; (2), 10%—; (3), 20%—; (4), nonwetted, 100—200 mesh pure drug.

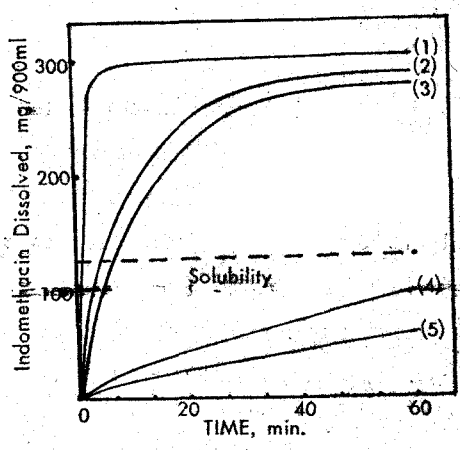


Figure 6—Indomethacin dissolution rate studies, on the 5th day after test sysetm prepared, 300mg/900ml, pH 6.0 phosphate buffer at37°. Key: (1), 1 : 9 w/w indomethacin-PVP coprecipitate; (2), 1 : 1 w/w indomethacin-PVP coprecitate; (3), 1 : 5 w/w indomethacin-PVP coprecipitate; (4), 1 : 9 w/w indomethacin-PVP physical mixture; (5), nonwetted, 100—200 mesh pure drug.

of dissolution in pH 6.0 buffer, and pH 6.0 buffer containing 0.63% PEG 4000, 0.63 % PEG 6000 and 0.3% PVP are shown in Figure 13. And they are supported by the data in Figure 14. It is also conceivable that the presence of micelles could, through solubilization, affect the dissolution rate of indomethacin by increasing its

saturation concentration as shown in Figure 13. Therefore it can be concluded that the significantly increased dissolution rates of indomethacin from physical mixtures with comparison to pure drug may be attributed to the enhanced wettability and increased solubility of hydrophobic indomethacin by the presence of hydrophilic polymers, and additionally to the particle size reduction during the sample preparation.

The dissolution profiles for indomethacin recrystallized from 1% chloroform solution, wetted and nonwetted pure indomethacin are depicted in Figure 9.

The rates of solution of indomethacin from recrystallized indomethacin and wetted pure drug are quite similar in magnitue and about two times faster than nonwetted pure drug. The differences observe in Figure 9 can most probably be attributed to differances in the crystal lattice and particale size distribution of the two teste systems and/or some change in the rate of solution brought about by the presence of a minute amount of chloroform in the precinitated drug crystals. Since he dissolution rate of the recrystallized indomethacin is markedly different from that found for the coprecipitates, it may be assumed that the enhanced dissolution ate of indomethacin as a coprecipitate is not due to recrystallization, per se.

The strikingly fast dissolution rates of indomethacin dispersed in polymer systems are shown in Table I, Figure 3—8 and 15. And attainments of supersaturation of indomethacin were also found as shown in Figure 5—7. As compared to nonwetted pure brug, dissolution rates of indomethacin were increased respectively: 7.9, 10.9, and 12.9 times faster for the 1 : 4, 1 : 9, and 1 : 19(w/w) indomethacin-PEG 4000 coprecipitates, 12.8, 13.5, and 13.6 times faster for the 1 : 4 1 : 9, and 1 : 19(w/w) indomethacin-PEG 6000 coprecipitates, and 9.6, 4.6, and 11.0 times faster for the 1 : 1, 1 : 5, and 1 : 9(w/w) indomethacin-PVP ecoperecipitates. The dissolution rates of indomethacin dispersed in polymers were remarkably fast, as compared to pure drug and its physical mixture with polymer. This increase in dissolution rate of these systems appears to be markedly greater than the expected increase calculatee from the enhanced solubility and wettadility due to the presence of polymer. Hence this rapid dissolution may be attributed by the molecular and/or colloidal dispersion of indomethacin in the polymer matrix, in addition by the enhanced solubility and wettability of indomethacin brought about by the presence of polymer.

Table I—Twenty, Fifty, and Seventy Percent Dissolution Times for Various Forms of Indomethacin at pH 6.5

Physical Forms of Indomethacin Test System	T_{20}% min.	T_{50}% min.	T_{70}% min.
100—200mesh pure drug, nonwetted	10—20	50—60	—
100-200 mech pure drug, wetted	<5	20—25	50.0
5% Indomethacin-PEG 6000	≪1.0	0.2	0.4
10% Indomechacin-PEG 6000	≪1.0	0.3	0.6
20% Indomethacin-PEG 6000	≪1.0	0.8	1.3
5% Indomethacin-PEG 4000	≪1.0	0.3	0.4
10% Indomethacin-PEG 4000	≪1.0	0.5	1.5
20% Indomethacin-PEG 4000	≪1.0	2.0	6.0
1 : 1 w/w Indomethacin-PVP	≪1.0	2.0	3.0
1 : 5 w/w Indomethacin-PVP	2.0	5.0	9.0
1 : 9 w/w Indomethacin-PVP	≪1.0	1.2	2.2

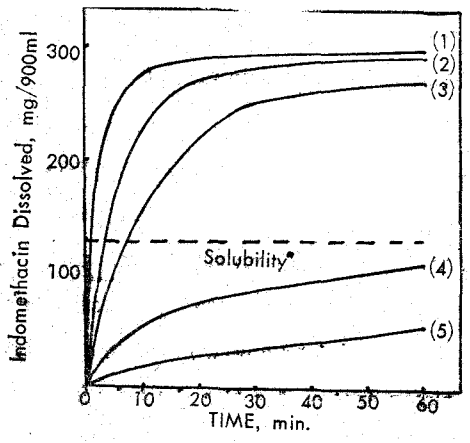


Figure 7—Dissolution rates of indomethacin -PVP coprecipitates, on the 15th day after test system prepared, 300mg/900ml, pH 6.0 buffer at 37°. Key: (1), 1 : 9 ratio; (2), 1 : 1 ratio; (3), 1 : 5 ratio; (4) wetted, 100—200 mesh pure drug; (5), nonwetted, 100—200 mesh pure drug.

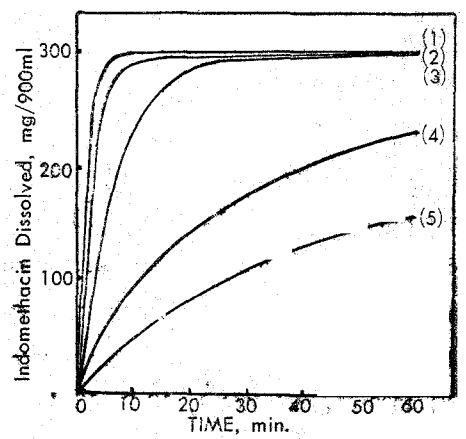


Figure 8—Dissolution rates of indomethacin -PVP coprecitates, on the 15th day after test system prepared, 300mg/900ml pH6.5 buffer at 37°. Key: (1), 1 : 9 ratio; (2), 1 : 1 ratio; (3), 1 : 5 ratio; (4), wetted, 100—200 meshpure drug; (5), nonwetted, 100—200 merh pure drug.

As shown in Figure 15, the rates of solution of indomethacin from the coprecipitates varied according to the polymer component used to form the coprecipitates. Thus the rank order of solution at pH 6.5 and 6.0 was PEG 6000>PEG 4000>PVP and PEG 6000>PVP>PEG 4000, respectively. Since very fine cloudy particles were suspended not to be filtered when the indomethacin-PEG 4000 coprecipitates were exposed to pH 6.0 buffer, the disselution test on them was omitted. Also since

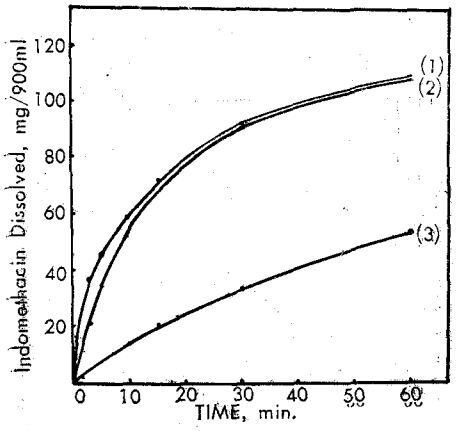
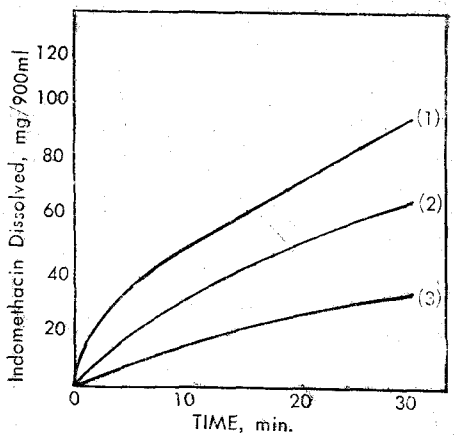


Figure 9—Indomethacin dissolution rate studies, 300mg/900ml pH 6.0 phosphate buffer at 37°. Key: (1), pure drug recrystallized from Chloroform; (2), 100—200 mesh pure drug, wetted; (3), 100—200 mesh pure drug, nonwetted.



Figuue 10—Effect of indomethacin to PVP ratio on the release profile of indomethacin from physical mixtures, at pH 6.0. Key: (1), 1 : 5 ratio; (2), 1 : 9 ratio; (3), 1 : 0 ratio.

indomethacin dispersed in PVP was dissolved clearly, and that dispersed in PEG 6000 was dissolved slightly suspended at pH 6.0. Thus, the increasing order of molecular/or colloidal dispersion in the matrices of polymers was PVP>PEG 6000> PEG 4000. It should also be noted that, as one would expect, the dissolutionrate ofindomethacin increases with increasing PEG weight fraction in coprecipitates forthe thisrange of PEG. The dissolution rateof indomethacin dispersed in PEG 6000 issignificantly faster than that dispersed inPEG 4000, as shown in Figure 15. This means some behavioral differences exist witha variation in chain length and that thecrystal gr owth of indomethacin is significantly faster in the matrices of PEG 4000 than in those of PEG 6000.

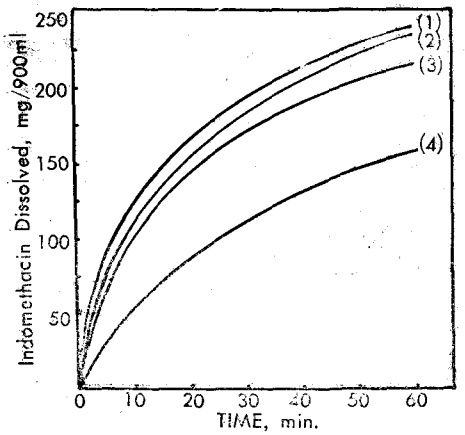


Figure 11—Effects of some physical mixtures on the release profile of indomethacin from 5%- indomethacin-PEG 4000 and -PEG 6000 physical mixtures at pH6.5, as compared to pure drug. Key: (1), 5% indomethacin-PEG 4000; (2), 5% indomethacin-PEG 6000; (3), wetted, 100—200 mesh pure drug; (4), nonwetted, 100—200 mesh pure drug.

Unexpectedly, however this trend was not observed as shown by the release profiles for the 1 : 1, 1 : 5 and 1 : 9 indomethacin to polymer ratios plotted Figures. 7 and 8. It seems that this is related to the different physico-chemical properties of

indomethacin-PVP coprecipitates and their relative abilities to facilitate the wetting and hence the dissolution rate of indomethacin.

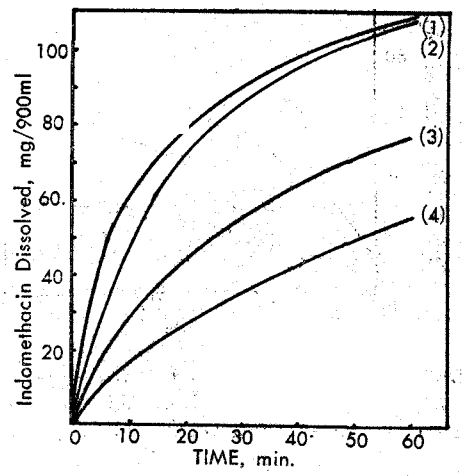


Figure 12—Effect of some physical mixtures on the release profile of indomethacin from 5% indomethacin-PEG 6000 and 1 : 9 w/w indomethacin-PVP at pH6.0 as compared to pure drug. Key: (1), wetted, 100—200 mesh pure drug; (2), 5% indomethacin-PEG 6000; (3), 1 : 9 w/w indomethacin-PVP; (4), nonwetted, 100—200 mesh mesh pure drug.

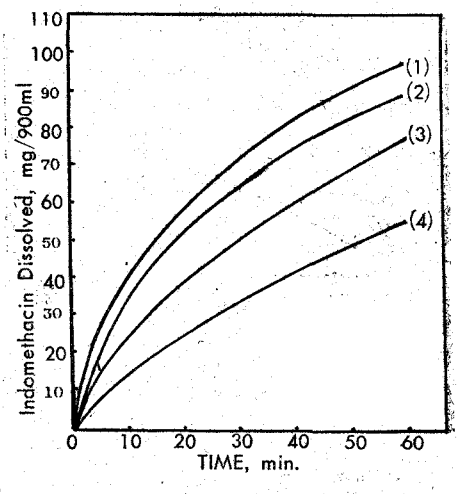


Figure 13—Milligrams of indomethacin released from 100—200 mesh pure drug as a function of time, using 0.63% PEG 4000, 0.63% PEG 6000, 0.3% PVP, and pH6.0 phosphate buffer as the release medium. Key: (1), 0.3% PVP; (2), 0.63% PEG 6000; (3), 0.63 PEG 4000; (4), pH6.0 buffer only.

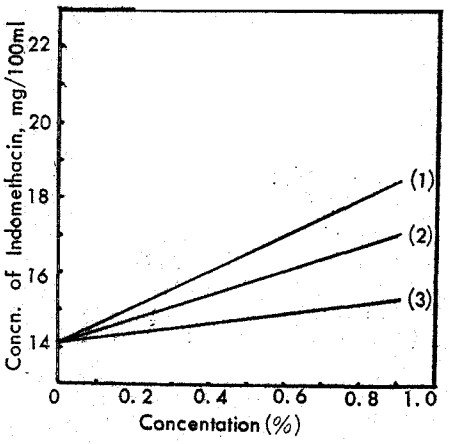


Figure 14—Effects of PEG 4000, PEG 6000 and PVP on the aqueous solubility of indomethacin at pH 6.0 phosphate buffer solution. Key: (1), PVP; (2), PEG 6000; (3), PEG 4000.

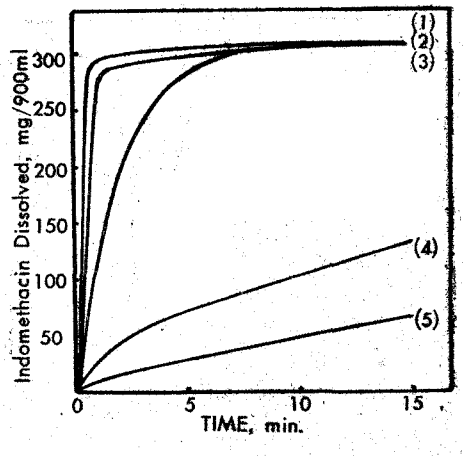


Figure 15—Dissolution rates of various indomethacin carrier coprecipitates, 300mg/900ml, pH 6.5 at 37°. Key: (1), 5% indomethacin-PEG 6000; (2), 5% indomethacin-PEG 4000; (3), 1 : 9w/w indomethacin-PVP; (4), wetted, 100—200 mesh pure drug; (5), nonwetted, 100—200 meshpure drug.

CONCLUSION

The results obtained in the present study demonstrate that the solubility and dissolution rate of indomethacin can be greatly increased by the use of coprecipitation techniques with PVP or PEG polymers. Since several reports have shown that similar results have been obtained with other hydrophobic drugs and soluble carriers it appears that the coprecipitation technique can be made generally applicable. Extrapolation of the *in vitro* findings suggests the possibility that this form will provide more rapid and complete absorption of the drug, permit a reduction in dosage, and conceivably provide a significant therapeutic application.

And we are planning to investigate the relationship between the enhanced *in vitro* dissolution rates of this drug and *in vitro* absorption characteristics.

REFERENCES

1) A.A. Noyes and W.R. Whitney, *J. Am. Chem. Soc.*, **19**, 930 (1897)
2) G. Levy, *Am. J. Pharm.*, **135**, 78 (1963)
3) K. Sekiguchi and N. Obi, *Chem. Pharm. Bull.* (Tokyo), **9**, 866 (1961)
4) K. Sekiguchi, N. Obi, and Y. Useda, *ibid.*, **12**, 134 (1964)
5) E. Shefter and T. Higuchi, *J. Pharm. Sci.*, **52**. 781 (1963)
6) A.H. Goldberg, M. Gibaldi, and J.L. Kanig, *ibid.*, **54**, 1145 (1965)
7) A.H. Goldberg, M. Gibaldi, and J.L. Kanig, *ibid.*, **55**, 482 (1966)
8) A.H. Goldberg, M. Gibaldi, and J.L. Kanig, *ibid.*, **55**, 487 (1966)
9) M. Mayersohn and M. Gibaldi, *ibid.*, **55**, 1323 (1966)
10) A.P. Simonelli, S.C. Mehta, and W.J. Hihuchi, *ibid.*, **58**, 538 (1969)
11) W.L. Chiou and S. Riegelman, *ibi.*, **58**, 1505 (1969)
12) T.R. Bates, *J. Pharmacol.*, **21**, 710 (1969)
13) G.V. Svoboda, M.J. Sweeney, and W.D. Walkling, *ibid.*, **60**, 333 (1971)
14) E.I. Stupak and T.R. Bates, *J. Pharm. Sci.*, **61**, 400 (1972)
15) E.I. Stupak and T.R. Bates, *ibid.*, **62**, 1806 (1973)
16)
17) S. Goto, W. Tseng, M. Kai, S. Aizawa. and S. Iguchi, *Yakuzaigaku*, **29**, 118 (1969)
18) D.J. Allen and J.V. Bondi, *Brit. pat.* 1,284,192 (1972)
19) D.J. Allen and J.V. Bondi, *Brit. pat.* 1,284,162 (1972)
19) R.E. Dempski and J.C. Saboe, *U.S. pat.* 3,849,549 (1974)
20) R.E. Dempski and J8C. Saboe, *Brit. pat.* 1,384,760 (1975)
21) J.G. Wagner, *J. Pharm. Sci.*, **58**, 1253 (1969)