Special Communication

THE USE OF POLYVINYLPYRROLIDONE (PVP) IN COPRECIPITATION

Najma Sultana, Saeed M. Arayne and Z.S. Saify

Abstract

The solubility of some of the potent drug has always been a significant problem for the pharmacologists in order to assess the biological activity of that particular compound. Various complementary products have been tried to overcome this problem. One of the important chemical agents in this respect is PVP. The importance of co-precipitation is emphasized with special reference to cardiac drugs such as reserpine, digitoxine, anti-tumor agent, acronine and hexyl resorcinol.

Polyvinylpyrrolidone (PVP) is known to increase the solubility of armatic compounds (Molyneax and Frank, 1961; Higuchi and Kuramoto, 1954; Higuchi and Kuramoto, 1954a). This has been explained (Molyneux and Frank, 1961) as a result of hydrophobic bonding and an exothermic interaction between the solubilized compound and PVP. In this paper application of this phenomenon to pharmaceuticals and the advantages of PVP drug coprecipitates are discussed (Mayersohn and Gibaldi, 1966; Simonelli et al., 1969).

The *physio-chemical modification* of drugs (PVP coprecipitation technique) for enhancing the gastro intestinal absorption of orally administered hydrophobic drugs offers advantages of possibly enabling one to administer the drug orally in a form from which it is most available for gastro intestinal absorption.

Among the techniques that can potentially enhance the dissolution rate and, hence the extent of absorption of hydrophobic drugs in the formation of coprecipitates with pharmacologically inert, polymeric materials such as PVP, several investigations (Stone, 1963; Mayersohn and Gibaldi, 1966; Bates, 1969; Simonelli et al., 1969; Svoboda et al., 1971; Stupak and Bates, 1972) have demonstrated in vitro, that the solubility and 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 polyvinylpyrrolidone coprecipitates. Recently (Stupak and Bates, 1972) it was demonstrated that both the rate and extent of absorption of water insoluble drug reserpine could be markedly enhanced when orally administered to rats in the form of 1:5 (w/w) coprecipitate with PVP.

The data obtained in a study (Stupak and Bates, 1973) demonstrate that coprecipitation with PVP increases the solubility and dissolution rate of digitoxin, and thereby significantly enhances the 'in vivo' absorption of this hydrophobic drug. These observations as well as those noted previously with reserpine (Stupak and Bates, 1972; Bates and Gibaldi, 1970; White and Gisvold, 1952; Dittert et al., 1968; Gibaldi, 1971; PVP-Polyvinylpyrrolidon, 1964; Shefter and Higuchi, 1963; The Merck Index, 1968; Stupak, 1972) indicate that it is quite possible that this technique might have general applicability to wide variety of relatively water insoluble drug entities whose absorption from gastrointestinal tract can be characterized as slow erratic, and incomplete. The advantages of utilizing this technique in the pharmacological screening of new drugs for oral activity are numerous and self evident.

In the study of digitoxin alone or as 1:9 (w/w) physical mixture or coprecipitate with PVP, it was orally administered at various drug dosage levels to fasted rats and the mortality was determined as a means of comparing the absorption characteristics of the drug from the various test systems. The markedly lower LD_{50} value observed for the coprecipitated drug as compared to the pure drug does not necessarily imply that digitoxin, when administered alone, is less available to the body than when administered in the form of PVP coprecipitate. However, it strongly suggests that the peak levels of digitoxin in the body after oral administration of the coprecipitate is far higher than that achieved following an equal dose of pure drug. This conclusion can be readily appreciated if one considers the case of a hydrophobic drug whose passive absorption rate is limited by the rate at which solution is affected within gastrointestinal fluids. In this type of absorption pattern, any change in the rate of solution of the drug in the gastro-intestinal fluids would produce a corresponding change in its absorption rate. Since dissolution must precede absorption, a faster dissolving form of the drug should be absorbed at a more rapid rate and possibly accumulate in the body to a greater extent than an equal dose of a slowly dissolving form of the same pharmacological agent (Gibaldi 1971).

The inherent toxicity of PVP (Najma et al., 1978) can be readily eliminated as a factor contributing to the marked decrease in the oral LD_{50} value for digitoxin form the coprecipitate. In this connection, it has been demonstrated that pure PVP elicits no untoward effects when orally administered to rats in doses of upto 100 gm/Kg. The intravenous LD_{50} value for PVP is also very high, being 12-15 gm/Kg (PVP-

Polyvinylpyrrolidone 1964). This information, coupled with the results obtained following the oral administration of the physical mixture, indicates that the toxicity of digitoxin from the 1:9 (w/w) coprecipitate is not due to the presence of PVP but to an increase in the amount of drug in the body produced by a marked enhancement in the rate at which drug absorption occurs from this test system.

The interaction of polymers such as PVP with chemical compounds to increase solubility has been reported for some time (Higuchi and Kuramoto, 1954; Guttman and Higuchi, 1956). More recently it has been shown that the rates of solution of drugs were appreciably increased by coprecipitating the drug with polymers (Stone 1963; Mayersohn and Gibaldi, 1966). This increase in dissolution rate of some systems, however appears to be significantly greater than the expected increase calculated from the solubility increase due to the presence of polymer. Moreover the increase was found to be sensitive to the method of preparation and the ratio of drug to polymer utilized in the experiment regardless the potential value of any of them. There have been many suggestions (Higuchi and Kuramoto, 1954a) of why these interactions occur and include the presence of compounds and solutions, colloidal dispersion etc.

Sulphathiazole-PVP coprecipitate system has been extensively studied for a number of reasons. It has several well characterized crystalline forms and rates of solution which are significantly different for each form (Milosovich, 1964; Higuchi et al., 1967). The presence of polymorphism may in itself add several interesting possibilities and serve to further generalize the results. The crystal growth inhibition studies showed that PVP strongly interacted with sulphathiazole and inhibited crystal growth at low concentrations. It seems then logical to extend these studies to include co-precipitated mixture studies. PVP on the other hand, has been widely reported as generally interacting with a wide range of organic compounds (Higuchi and Kuramoto, 1954; Molyneux and Frank, 1961; Guttman and Higuchi, 1956) and, therefore, the results of any investigation involving PVP should be more generally applicable to other drugs as well.

The apparent solubility and rate of solution of sulphathiazole from compressed tablets containing (PVP) were found to be greatly increased if sulphathiazole was previously coprecipitated with PVP. The increase noted was found to be a function of the chain length of the PVP used as a coprecipitate and the sulphathiazole to PVP weight ratio of the coprecipitate powder mixture used to compress the tablets. The 10,000 molecular weight PVP yielded the most rapid sulphathiazole dissolution rate. The sulphathiazole rate of solution was (a) independent of the PVP weight fraction in the coprecipitated mixture at low PVP weight fractions (b) increased with increasing PVP weight fractions at intermediate weight fractions and (c) decreased with increasing PVP weight fractions at high PVP weight fractions (Higuchi et al., 1969). These results indicate that as the sulphathiazole to PVP ratio in the tablet decreases, the PVP boundary movement relative to the sulphathiazole boundary is also decreased. It appears safe to assume that at the higher PVP weight fractions the PVP is close enough to the unbound sulphathiazole layer to significantly contribute to the release profile and cause sulphathiazole release rates to be greater than those of the plateau region, i.e., the increase in rate can be attributed in part to the presence of sufficiently high concentrations of PVP at the interface to increase the effective solubility of sulphathiazole, and hence its apparent dissolution rate. The carrier effect of PVP (i.e. the sulphathiazole transported as PVP complex) can be significant, as the apparent solubility of sulphathiazole should be doubled with each increase of 3% in case of PVP concentration in solution.

Analysis of the above reveals that there are several possibilities which can occur. The drug in the solid phase can exist bound to the polymer, only in one of its unbound forms, or lastly as a combination of the above states. If the drug and polymer coexist as a complex, the dissolution of drug can occur by either of two methods, the bound drug can be removed from the polymer at the surface by solvent interaction and thereby precede the polymer into solution, or the drug polymeric complex can dissolve intact followed by dissolution of the drug polymeric complex in solution. The formation of drug solvates affect the dissolution rate of hydrophobic drugs significantly (Shefter and Higuchi, 1963). Digitoxin, forms solvates with ethanol and water, which are stable in vacuo at temperature upto 118°C (The Merck Index, 1968). Since chloroform has been used to prepare the digitoxin PVP-Coprecipitate system, the possibility existed that the enhanced absorption and dissolution characteristics of digitoxin from this system resulted from the formation of a 1:1 chloroform solvate.

The similarity between the dissolution and solubility behaviour of digitoxin from the 1:9 (w/w) drug-PVP coprecipitate and that previously observed with reserpine-PVP coprecipitate systems (Stupak 1972), coupled with the fact that both drugs form "glass solutions" with the polymer, strongly suggests that a similar mechanism is operable. Accordingly, it may be proposed that a high energy form of digitoxin, most probably amorphous in nature, is formed as a

result of coprecipitating the drug with PVP and that its increased solubility characteristics are responsible for the marked enhancement in drug dissolution and absorption experienced with the coprecipitate system.

The mechanism involving the dissolution of the drug-coprecipitate complex followed by dissociation lends itself to a simple solution if the assumption is made that the diffusion layer model is operative as the dissolution rate will be governed by the solubility of the complex and the diffusion coefficient of all polymeric species. The system can than be quantitical by consideration of the equations of the continuity existing in the diffusion layer. The mechanism which allows the drug to be removed from the polymer by solvent interaction will depend on the rate of interaction. To be operative this rate must obviously be faster than the rate of intact complex dissolution.

In another study pharmaceutical grade 40,000 molecular weight, PVP was coprecipitated with acronine from ethanol. The ratio of acronine to PVP was 1:5 (w/w). Solubility of acronine as the coprecipitate (75 mcg/ml. distilled water) was approximately 15 times that of non coprecipitated acronine (5 mcg/ml.) Acronine (Svoboda et al., 1971) a compound of known experimental antitumor activity (Svoboda et al., 1966) was compared with the acronine-polyvinylpyrrolidone (Ac-PVP) coprecipitate against two of the most sensitive tumors to acronine, X5563 plasma cell myeloma and C1498 myelogenous leukemia. These data indicate that PVP coprecipitated acronine is more active than acronine itself.

Hexylresorcinol, an alkylated dihydroxy benzene, shows oxidative decomposition characteristic of phenols, both as a solid and in aqueous solution. The observation that compressed tablets, which contained hexylresorcinol and polyvinylpyrrolidone (PVP) did not discolor after 19 weeks at 50°, resulted in an investigation of the role of PVP as a stabilizer and also an investigation of the effect of PVP on the microbiological activity of hexylresorcinol (Polli and Frost, 1969).

During an investigation of the role of PVP as a stabilizer for hexylresorcinol in a compressed tablets and its effect on the microbiological activity of the later, a molecular interaction between hexylresorcinol and PVP, of unusually strong complexing tendency, was identified by the solubility isotherm method and infra red spectroscopy. The stoichiometry of the complex was calculated to be one hexylresorcinol molecule per vinylpyrrolidone repeating unit. The antimicrobial activity of hexylresorcinol, evaluated by two different methods using both Gram-positive and Gram-negative bacteria was found to be reduced in the presence of PVP. This reduction in activity was apparently due to the molecular interaction between hexylresorcinol and PVP. The method of Klotz et al. (1946) was employed to determine the complexing of hexylresorcinol with PVP. If hexylresorcinol had not complexed with PVP, the hexylresorcinol concentrations would be equal on each side of the membrane. The total hexylresorcinol concentrations would be equal on each side of the membrane. The total hexylresorcinol concentration and the concentration of unbound hexylresorcinol thus would be equal and K would be 1. However if hexyl resorcinol complexed with PVP, the hexylresorcinol concentration would be unequal on each side of membrane. The concentration of unbound hexylresorcinol would be less than the total hexylresorcinol concentration and K would be greater than 1.

The presence of PVP in the tablet was also shown to be responsible for the color stability of hexylresorcinol. After one week at 37°C and 50°C., the tablets without PVP were darker in color than the tablets containing PVP. After one month under the same temperature conditions, the tablets without PVP appeared as motled, brownish pink tablets whereas the PVP containing tablets remained white. Placebo tablets, containing neither hexylresorcinol nor PVP did not discolor. These observations indicated that the discoloration of the hexylresorcinol in the compressed tablet was prevented by the addition of PVP and it acted as a stabilizer, possible through complex formation.

The interaction between PVP and other pharmaceuticals gave evidence to support the existance of the formation of complexes in solution between PVP and p-aminobenzoic acid, salicylic acid, p-hydroxy benzoic acid, m-hydroxybenzoic acid, phenobarbital (Higuchi and Kuramoto, 1954), sodium salicylate, chloramphenical and mandelic acid (Higuchi and Kuramoto, 1954a). No evidence of the complex formation was detected between PVP and aminopyrine, citric acid (Higuchi and Kuramoto, 1954) procaine hydrochloride, benzyl penicillin, caffeine, theophylline and cortisone (Higuchi and Kuramoto, 1954a). The similarity of the influence of chemical structure on the stability of the PVP complexes as compared to the caffeine complexes indicated that a similar mechanism may be responsible for both series. The greatest K value of 1.2 was however for sulphathiazole at 0.05% PVP. Since the authors observed a K value of 3.0 for hexylresorcinol at 0.05% PVP, it appears that hexylresorcinol showed an unusually strong complexing tendency with PVP.

Previous evidence of the complexing behaviour of PVP in solution was based mainly on pharmacological data. Pellart et al. (as cited by

Higuchi and Kuramoto, 1954) made an extensive review of the literature and listed the drugs on which PVP had a retardant action pharmacologically. These drugs included penicillin, insulin, Novocaine(R), adrenocortical extracts (R), pituitary extracts, Neptal (R), prostigmine(R), mercury cyanide(R), hexobarbital and quinine. The sulphonamides are retarded in some cases but not appreciably. Signier et al (as cited by Higuchi and Kuramoto, 1954) reported the results of a study on the speed of dialysis of morphine dissolved in distilled water and in solutions of PVP (5-30%). Their data indicated that PVP had no real inhibiting action on the diffusion of morphine through a membrane unless the concentration of the polymer in the solution is 15% or greater. Their clinical tests on about 30 patients showed that 20% PVP prolongs the analgesic effect of morphine, but animal experiments were inconclusive. The mechanism of the pharmacological retarding action of PVP requires further investigations.

References

Bates, T.R. (1969) Dissolution characteristics of reserpine polyvinyl-pyrrolidone coprecipitates. J. Pharm. Pharmacol., 21:710.

Dittert, L.W., Adams, H.J., Alexander, F., Chong, C.W., Ellison, T. and Swintosky, J.V. (1968) 4-Acetamidophenyl 2, 2, 2-trichloroethyl carbonate, particle size studies in animals and man. J. Pharm. Sci., 57:1146.

Gibaldi, M. "Introduction to biopharmaceutics, Philadelphia, Lea and Febiger, 1971, pp 6-8.

Guttman, D. and Higuchi, T. (1956) Possible complex formation between macromolecules and certain pharmaceuticals X: The Interaction of some phenolic compounds with polyethylene glycols, polypropylene glycols and Polyvinylpyrrolidone. J. Amer. Pharm. Assoc., 45:659

Higuchi, T. and Kuramoto, R. (1954) Study of possible complex formation between macromolecules and certain Pharmaceuticals. I. Polyvinylpyrrolidone with sulphathiazole, procaine hydrochloride, Sodium salicylate, Benzylpenicillin, Chloramphenicol, mandelic acid, Caffeine, theophylline and Cortisone. J. Amer. Pharm. Assoc., 43:393.

Higuchi, T. and Kuramoto, R. (1954a) Study of possible complex formation between macromolecules and certain Pharmaceuticals: II Polyvinylpyrrolidone with p-aminobenzoic acid, aminopyrine, benzoic acid, salicylic acid, p-hydroxybenzoic acid, m-hydroxybenzoic acid, citric acid and phenobarbital. J. Amer. Pharm. Assoc. 43:398.

Higuchi, W.I., Bernardo, P.D. and Mehta, S.C. (1967) Polymorphism and drug availability. II. Dissolution rate behavior of the polymorphic forms of sulphathiazole and methylprednisolone. J. Pharm. Sci., 56:200.

Klotz, I.M., Walker, M.F. and Pivan. (1946) The binding of organic ions by proteins. J. Amer. Chem. Soc., 68:1486.

Mayersohn, M. and Gibaldi, M. (1966) New method of solid state dispersion for increasing dissolution rates. J. Pharm. Sci., 55:1323.

Milosovich, G. (1964) Determination of solubility of a metastable polymorph. J. Pharm. Sci., 53:484.

Molyneux, P. and Frank, H. (1961) The interaction of polyvinylpyrrolidone with aromatic compounds in aqueous solution. Part I. Thermodynamics of the binding equilibria and interaction forces. J. Amer. Chem. Soc., 83:3169.

Najma, S. Arayne, M.S. and Saify, Z.S. (1978) Polyvinylpyrrolidone in gastroenterology. JPMA., Submitted for publication.

Polli, G.P. and Frost, B.M. (1969) Complexation between hexylresorcinol and polyvinylpyrrolidone and its microbiological evaluation. J. Pharm. Sci., 58:1543.

"PVP-Polyvinylpyrrolidone", General Aniline and Film Corp., New York, N.Y. (1964), p. 15.

Shefter, E. and Higuchi, T. (1963) Dissolution behaviour of crystalline solvated and nonsolvated forms of some Pharmaceuticals. J. Pharm. Sci., 52:781.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I. (1969) Dissolution rate of high energy polyvinylpyrrolidone (PVP)-Sulphathiazole coprecipitates. J. Pharm. Sci., 58:538.

Stupak, E.I. and Bates, T.R. (1972) Enhanced absorption and dissolution of reserpine from reserpine-polyvinylpyrrolidone coprecipitates. J. Pharm. Sci., 61:400.

Stupak, E.I. and Bates, T.R. (1973) Enhanced absorption of Digitoxin from orally administered Digitoxin-Polyvinylpyrrolidone coprecipitates. J. Pharm. Sci., 62:1806.

Swarbrick, J. Current concepts in the Pharmaceutical Sciences, biopharmaceutics, Philadelphia, Lea and Febiger, 1970, p. 95.

Svoboda, G.H., Poore, G.A., Simpson, P.J. and Boder, G.B. (1966) Alkaloids of Acronycha Baueri Schott I. Isolation of the alkaloids and a study of the antitumor and other biological properties of acronycine. J. Pharm. Sci., 55:758.

Svoboda, G.H., Sweeney, M.J. and Walkling, W.D. (1971) Antitumor activity of an Acronycine-polyvinylpyrrolidone coprecipitate. J. Pharm. Sci., 60:333

The Merck index of chemicals and drugs. 8th ed. Rahway, N.J., Merck, 1968, p. 364.

White, W.F. and Grsvold, O. (1952) Absorption rate studies of orally administered cardiac glycosides in cats. J. Amer. Pharm. Assoc., 41:42.