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Characteristics of the in vitro release of ibuprofen from polyvinylpyrrolidone solid dispersions

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Summary

This work examines the release of ibuprofen from various molecular weight fractions of polyvinylpyrrolidone (PVP) solid dispersions. The release characteristics were determined as a function of the solvent used, carrier-to-drug ratio, surface-active agents incorporated such as sodium lauryl sulphate (SLS), cetrimide and sorbitan monopalmitate (span 60) and the pH of the dissolution medium. It was found that higher release rates were obtained as the molecular weight was decreased and as the weight fraction of the polymer was increased. The dissolution rate constant (K) was found to vary linearly with the logarithm of the PVP molecular weight and the PVP weight fraction. Incorporation of surface-active agents in the solid dispersion preparations resulted in a dramatic increase in the release in the order: span 60 < cetrimide < SLS. K was also found to be pH-dependent having higher values in strong acid and alkaline media than in weakly acidic or neutral media. The increased release of the PVP drug dispersion as compared to the PVP–drug physical mix was attributed to the formation of a salt-like complex resulting from the interaction of the drug and the polymer.

Introduction

Drug dissolution from a solid dispersion is influenced by various factors such as the technology employed to prepare the dispersion, the proportion and properties of the carrier used, the pH of the dissolution medium, temperature and the surface properties of the solid dispersion particles. In general, the main interest in such systems has been focused on attempts to increase the dissolution rates of hydrophobic drugs by incorporating them in a water-soluble polymer matrix (Chiou and Riegelman, 1971). It has been shown that the same approach can be used to delay dissolution, thereby yielding a slow or sustained release of drugs (Higuchi, 1963; Patel and Jarowski, 1975; Najib and Suleiman, 1985a).

Several carrier systems have been used in the preparation of fast release solid dispersions. Polyvinylpyrrolidone (PVP) was used to enhance the dissolution rate of a number of drugs such as griseofulvin, cholesterol and 4-amino antipyrine (Shefter and Cheng, 1980), sulphathiazole (Simonelli et al., 1969, 1976; Corrigan et al., 1980), reserpine (Bates, 1969), hydroflumethiazide (Corrigan and Timoney, 1975), steroids (Resetarits et al., 1979), and indomethacin (Oth and Moes, 1985). Dissolution of prednisolone, methyltestosterone, hydrocortisone and digitoxin has been enhanced

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by polyethylene glycol (PEG) fusion dispersions (Chiou and Riegelman, 1971), as well as dicumarol (Ravis and Chen, 1981), and indomethacin (Ford and Elliott, 1985). Other carriers were used to a lesser extent than either PVP or PEG. These include β-cyclodextrin (Corrigan and Stanley, 1982) and phospholipids (Venkataram and Rogers, 1985).

In this work an attempt was made to characterize the release of ibuprofen from PVP–ibuprofen solid dispersion systems. This was done by determining the dissolution profiles and dissolution rate constants of solid dispersions prepared by different solvent techniques as a function of PVP molecular weight, weight fraction, pH of the dissolution medium and inclusion of surface-active agents in the dispersion preparation.

Materials and Methods

Materials

Ethanol Analar grade was obtained from B.D.H. Chemicals U.K. Chloroform, ibuprofen, PVP 10,000, PVP 40,000, sodium hydroxide, hydrochloric acid, cetrimide and span 60 were obtained from Sigma Chemical Co., U.K. Sodium lauryl sulphate (SLS) was obtained from Aldrich Chemical Co., U.S.A. PVP 24,500 was purchased from Karl-Kolb, U.K. The water used was double-distilled water with a surface tension of 71–72 $mN \cdot m^{-1}$ at 25°C.

Methods

Preparation of drug: PVP dispersions. Solid dispersions were prepared by the solvent method. The required amounts of PVP and drug were weighed, dissolved in the appropriate solvent, then the solvent was evaporated over a warm water bath. Further drying was carried out under anhydrous calcium sulphate. All samples were examined within 24 h of preparation following sieving at 80/120 mesh for size uniformity. Each batch of the prepared dispersions was tested for content uniformity before use. This was done by dissolving 0.1 g of the dispersion in 0.1 N NaOH. 1.0 ml of this solution was appropriately diluted with water and the amount of drug present was determined spectrophotometrically at 263 nm by reference to a suitable calibration curve. This was repeated 3 times for every batch. The 3 determinations resulted in 98.5–100.3% of the theoretical value.

Equilibrium solubility determinations. Equilibrium solubility of the drug and the drug : PVP dispersions was determined by a method similar to that of Najib and Suleiman (1985b).

Differential scanning calorimetry (DSC). Samples weighing approximately 10 mg were placed in aluminum pans and analyzed using a Stanton Redcroft DSC model 785 using dried alumina as a reference. The scanning speed was 10°C/min in the range of 20–300°C.

Conductivity determination. The conductivity of 1% colloidal dispersions of SLS, cetrimide and span 60 in water was determined at 25°C using a Karl-Kolb model 6072 conductivity meter.

Release studies. Release from constant area dispersion was carried out from discs prepared by compressing 0.50 g of the dispersion in a 1.0 cm diameter die in a hydraulic press using a force of 58.8×10^6 $N \cdot m^{-2}$. The disc surrounded by the die was centralized at the bottom of a 1 litre beaker in a USP dissolution apparatus (Erweka DT-D6 F.R.G.) maintained at 37 ± 0.1°C. A previously boiled and cooled 250 ml of the dissolution medium at the required pH was introduced into the beaker. A stirring rate of 60 rpm was maintained throughout the experiment. 5 ml samples were withdrawn at the designated time intervals and immediately replaced with a similar volume of fresh dissolution medium. The sample was transferred to a syringe and rapidly filtered through a 0.30 μm membrane filter unit (Millipore U.K., London). The samples were then assayed for their drug content spectrophotometrically at 263 nm. Each experiment was repeated 3 times and the average values were taken.

Results and Discussion

Fig. 1 shows the effect of the solvent used in the preparation of the solid dispersion on the release of ibuprofen from 1 : 3 drug : PVP disper-

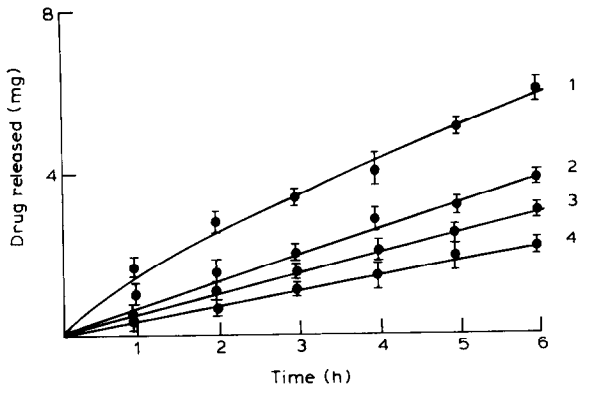

Fig. 1. The release of ibuprofen from different systems: (1) from 1:3 drug:PVP 24,500 solid dispersion using chloroform as a common solvent; (2) from 1:3 drug:PVP solid dispersion using ethanol as a common solvent; (3) from 1:3 drug:PVP physical mixture; and (4) from pure drug.

sion. It is evident from Fig. 1 that the use of chloroform as a solvent has a greater effect on increasing the release of the drug than ethanol. In both cases, however, the release was greater than when dissolution was carried out on the drug alone or drug–PVP physical mix. The difference in the dissolution of the dispersions obtained with different solvents could be due to the different crystalline structures and hence energies of the dispersions obtained from these solvents (Shefter and Higuchi, 1963; Goldberg et al., 1965).

The increase in release of the drug from the dispersion as compared to the physical mixture can be explained as follows: in a non-aqueous solvent such as chloroform, ibuprofen, being an acidic drug, could donate the proton of the carboxylic acid group to the basic nitrogen of the amide group in the pyrrolidone moiety of the polymer. This would probably result in the formation of a weak acid and a weak base salt like complex. As the drug is poorly water-soluble, this type of interaction does not take place to an appreciable extent in water. Therefore this would result in a greater dissolution of the dispersion as compared to the physical mix.

In order to get further evidence on the possible interaction of the drug with PVP, DSC studies were performed on ibuprofen, PVP and ibuprofen–PVP dispersion. The results obtained are shown in Fig. 2. The ibuprofen curve shows two endothermic peaks. The first peak at about 75.5°C and corresponds to the melting point of ibuprofen. The second endothermic peak at about 230°C and corresponds to the evaporation of ibuprofen which occurs after melting. The PVP curve shows a shallow, broad endothermic peak at about 60°C which is thought to represent the vaporization of

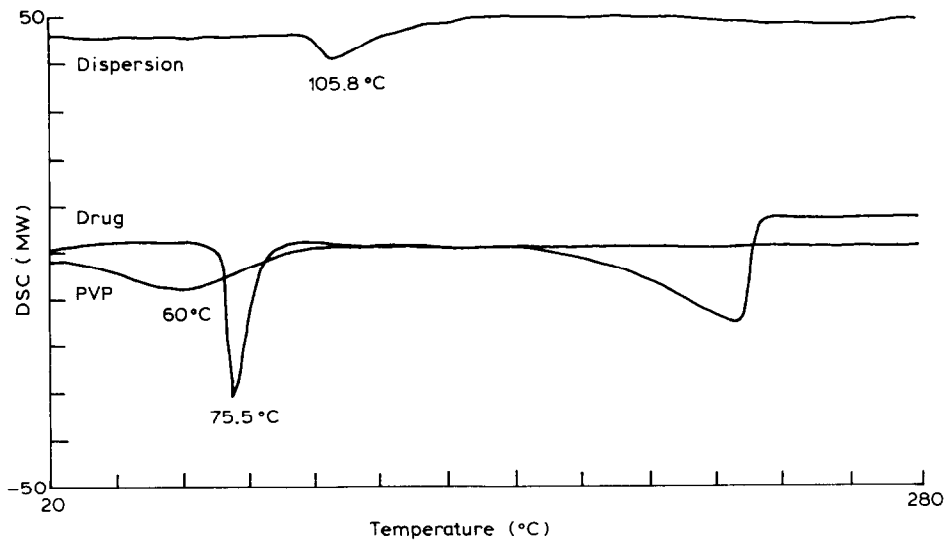

Fig. 2. The DSC thermograms of ibuprofen, PVP and ibuprofen–PVP (1:3) dispersion.

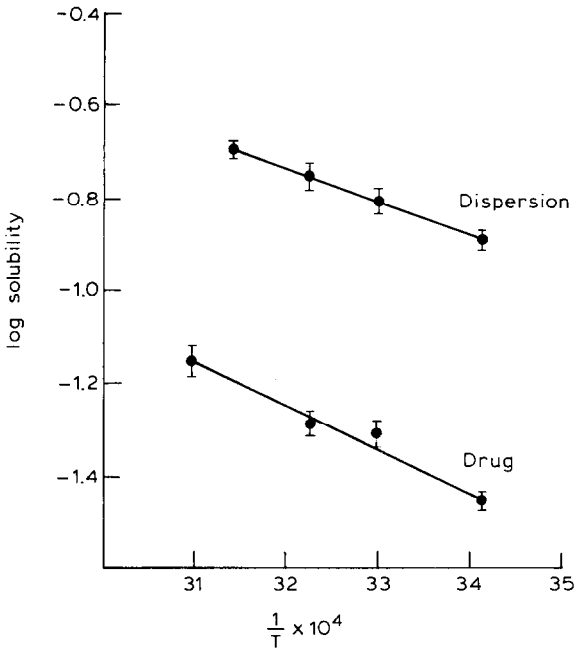

Fig. 3. The van't Hoff plot of ibuprofen and ibuprofen : PVP (1 : 3) dispersion.

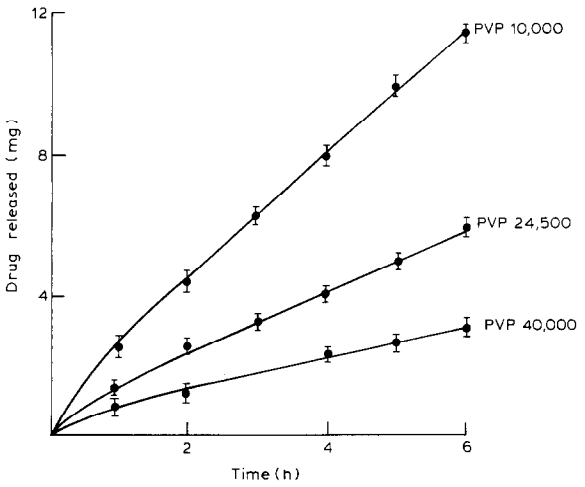

Fig. 4. The effect of PVP molecular weight on the release of ibuprofen.

moisture from the PVP sample. The ibuprofen–PVP curve shows only one peak at 105.8°C. This peak is thought to be the melting point of the complex formed by the suggested interaction between the drug and the polymer. The disappearance of the drug peak from the drug–polymer curve indicates that all of the drug has interacted with the polymer and this excludes the presence of a crystalline drug in the dispersion.

Solubility of the drug and drug–polymer dispersions were studied as a function of temperature. This was done in order to calculate the heat of solution of both the drug and the complex. Fig. 3 shows the van't Hoff plot of these systems. ΔH as calculated from these plots is 19.128 $kJ \cdot K^{-1} \cdot mol^{-1}$ for the drug and 14.199 $kJ \cdot K^{-1} \cdot mol^{-1}$ for the complex. The lower heat of solution of the complex as compared to that of the drug indicate that the complex is more energetic and hence more soluble than the drug.

The release of ibuprofen from dispersions prepared with PVP of different molecular weights is shown in Fig. 4. It is evident from Fig. 4 that dissolution of the drug increased with decreasing polymer molecular weight. Similar findings have been reported for the release of hydroflumethiazide from PEG melt systems (Corrigan and Timoney, 1975) and for the release of sulphathiazole from PVP dispersions (Simonelli et al., 1969). The effect of the molecular weight of the polymer on the release of the drug from solid dispersions is multi-factorial; lower molecular weight fractions of PVP were reported to have a greater dissolution rate than the higher ones (Nogami et al., 1970; Heyd et al., 1969). This would result in a greater rate of exposure of the drug to the aqueous media and hence a greater dissolution rate. Also for equal weights the lower the molecular weight fraction used the greater is the number of polymer molecules that are available for the formation of a more soluble complex with the drug and hence the dissolution rate of the drug is increased. Improved dissolution rates obtained with the lower molecular weight fractions as compared to the higher ones could also be due to the higher porosity of the mass, which would result from the faster dissolution of a larger number of molecules which are present in the case of the lower molecular weight fractions. In an attempt to show the dependency of the drug release on the molecular weight of the carrier, K was calculated by the method described by Florence et al. (1973) and

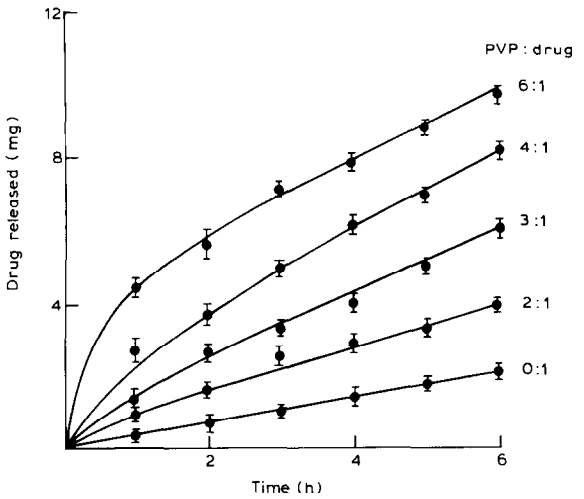

Fig. 5. The effect of PVP 24,500 weight fraction in the solid dispersion on the release of ibuprofen.

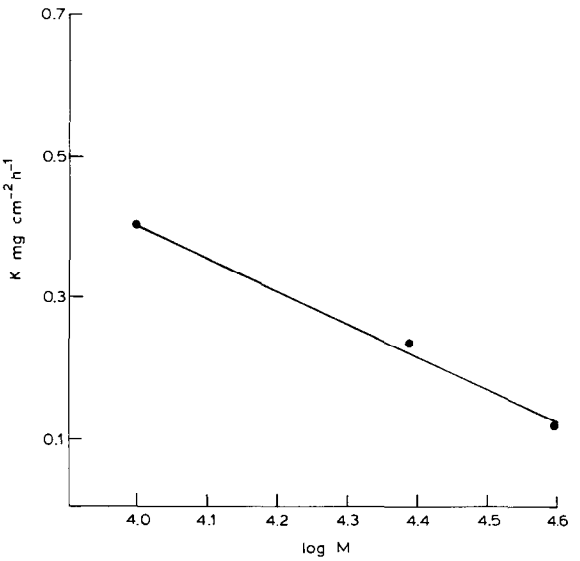

Fig. 6. The relationship between the logarithm of PVP molecular weight and dissolution rate constant (K).

plotted as a function of the logarithm of the PVP molecular weight (M). Fig. 5 shows that a linear relationship was obtained suggesting that K is decreased as M was increased.

The release of ibuprofen from dispersions containing different weight fraction of PVP 24,500 is shown in Fig. 6. It is clear from Fig. 6 that increasing the proportion of PVP in the dispersion resulted in an increase in the dissolution rate. This could be due to the fact that as the proportion of the PVP is increased, the proportion of PVP unreacted with the drug is increased. Therefore the PVP coat thickness around the particles is increased. As the PVP is highly water-soluble, it dissolves rapidly upon exposure to the aqueous medium thus improving the wettability and hence dissolution of the dispersed drug.

Fig. 7 shows the relationship between PVP weight fraction and K. A linear relationship was obtained showing that for the dispersions studied K, increased as the polymer weight fraction is increased. It has been reported, however, (Simonelli et al., 1969) that at very high polymer weight fractions — greater than those used in this study — a decrease in K is obtained with increase in polymer weight fraction.

Fig. 8. shows the release of ibuprofen from 1 : 3 drug : PVP dispersions as a function of pH. The relationship between K and pH is shown in Fig. 9. From Figs. 8 and 9 it can be noted that the release and the dissolution rate constant (K) were higher in strongly acidic and alkaline media than in the intermediate region. This can be attributed to the effect of pH on the degree of ionization and hence solubility of the complex formed from the interaction of PVP with the drug. Under strong acid

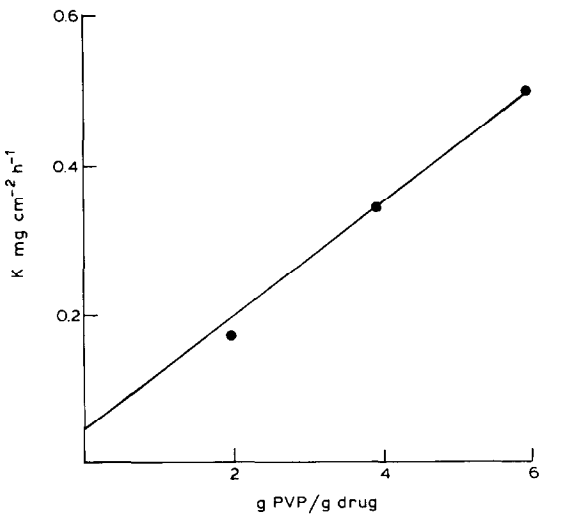

Fig. 7. The relationship between the PVP 24,500 weight fraction and the dissolution rate constant (K).

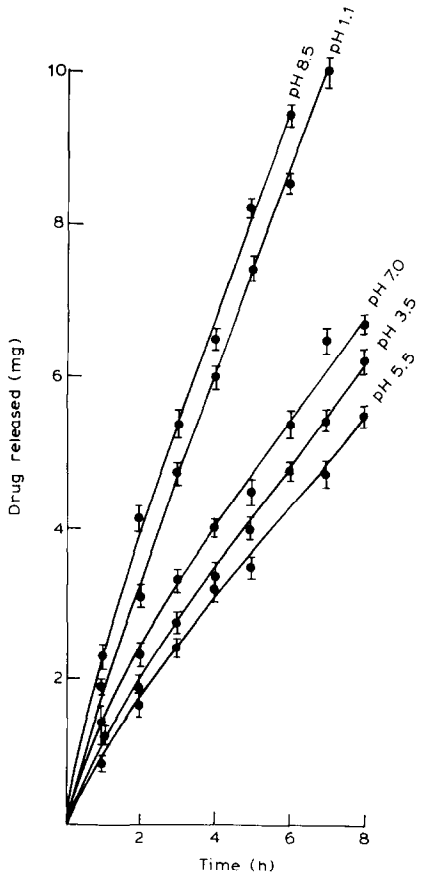

Fig. 8. The effect of pH of the dissolution medium on the release of ibuprofen from 1 : 3 drug : PVP solid dispersions.

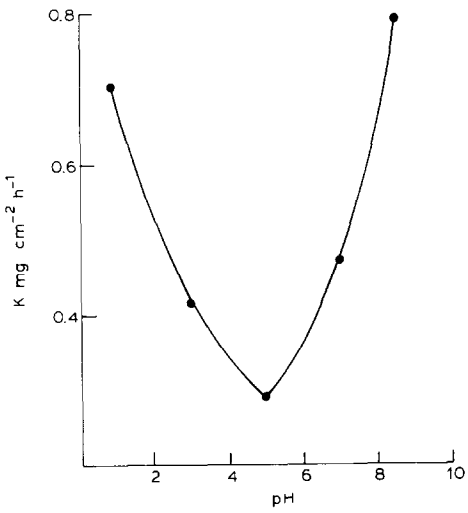

Fig. 9. The relationship between the pH of the dissolution medium and the dissolution rate constant (K).

conditions the basic amide group in the pyrrolidone moiety of the polymer is in a protonated form; this results in an increase in the dissolution rate of the complex. In alkaline media the acidic carboxylic group ionizes and this would result in an increased solubility of the complex. At intermediate pHs neither the acidic nor the basic group ionizes to an appreciable extent and the complex exists in an almost neutral charge form. Therefore the dissolution rate in this region is lower than that of the strongly acidic or alkaline media.

The effect of incorporating surface-active agents on the release of drug from dispersions composed of 1 : 1 : 3 drug : surface-active agent : PVP is shown in Fig. 10. It is evident from the graph that the anionic surface-active agent, SLS, exhibited a greater effect on the drug dissolution than cetrimide which had a greater effect than span 60. The greater SLS effect could be attributed to its higher hydrophilic character than cetrimide and span as indicated from the HLB values (Martin et al., 1983) and the conductivity values (Table 1). Therefore it would have a greater solubilizing action. Also the alkaline nature of SLS would enhance the dissolution of a weakly acidic drug such as ibuprofen. However, with all of the three surface-active agents the release obtained and the

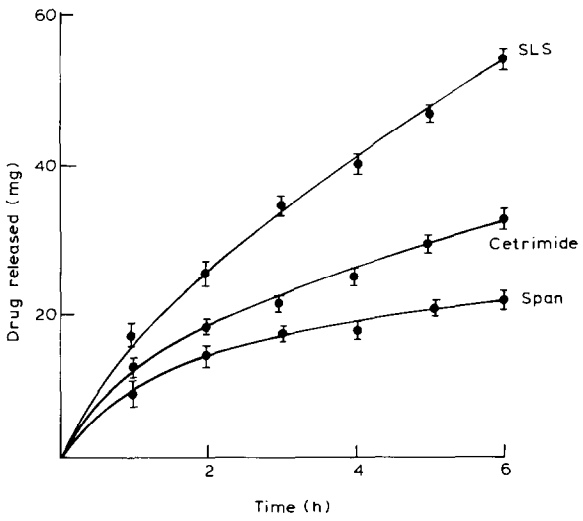

Fig. 10. The effect of the surface-active agents incorporated in the solid dispersion on the release of ibuprofen.

TABLE 1

THE CONDUCTIVITY OF 1% DISPERSIONS OF THE SURFACE-ACTIVE AGENTS USED

Surface-active agent	Conductivity $\times 10^4$ (mho/cm)
SLS	10
Cetrimide	6
Span 60	3

value of K (Table 2) was higher than that obtained in the absence of these surface-active agents. This could be attributed to their ability to reduce the interfacial tension between the solid and the dissolution medium and hence improves the wettability of the drug particles and enhances the diffusion of the dissolved drug molecules across the solvent hydrodynamic layer.

In conclusion it can be stated that ibuprofen seems to form a salt-like complex with PVP. This complex has a lower heat of solution than the original drug and hence a greater release rate. The dissolution rate of such a complex was dependent on the solvent used, weight fraction and molecular weight of PVP. Surface-active agents included in the solid dispersion preparations resulted in an enhanced dissolution. This effect was attributed to the reduction in the interfacial tension caused by the surface-active agents and to their solubilizing action. The release from the studied solid dispersions was pH-dependent; that is the higher release rates were obtained in strongly acidic or alkaline media than in the intermediate regions. This effect was attributed to the effect of pH on the degree of ionization of the complex formed as a result of the interaction between PVP and the drug. Finally work is now being undertaken to elucidate the mechanism of interaction between PVP and ibuprofen and to further characterize the complex formed.

TABLE 2

THE VALUE OF THE DISSOLUTION RATE CONSTANT (K) OBTAINED IN THE PRESENCE OF SURFACE-ACTIVE AGENTS

Drug : PVP : surface-active agent	k($mg \cdot cm^{-2} \cdot h^{-1}$)
1 : 0 : 0	0.07575
1 : 3 : 0	0.223
1 : 3 : 1 (span 60)	0.572
1 : 3 : 1 (Cetrimide)	0.659
1 : 3 : 1 (SLS)	1.052

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