International Journal of Pharmaceutics, 24 (1985) 275–286
Elsevier

IJP 00827

Enhanced in vitro release of indomethacin from non-aqueous suspensions using indomethacin–polyvinylpyrrolidone coprecipitate

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(Received October 29th, 1984)
(Modified version received December 9th, 1984)
(Accepted December 14th, 1984)

Key words: non-aqueous suspension – indomethacin – coprecipitate – polyvinylpyrrolidone – dissolution rate – release rate – partition coefficient – differential dialysis

Summary

The release of indomethacin and indomethacin–polyvinylpyrrolidone (PVP) coprecipitate (1 : 1) from non-aqueous suspensions to aqueous phase has been investigated. The coprecipitation with polyvinylpyrrolidone increases the solubility and the intrinsic dissolution rate of the drug. The release rate from non-aqueous suspension is significantly enhanced when the coprecipitate form is used and that at any pH and concentrations. The use of indomethacin–PVP coprecipitate avoids the formation of a cake at the oil/water interface due to an increase of the solubility and wetting of the drug included in the coprecipitate. The partition coefficient of indomethacin is not significantly reduced by the presence of PVP in the medium. The dialysis studies show that indomethacin is only weakly bound to PVP and therefore, PVP might only interfere weakly in the resorption process of the free drug through the biological membrane.

Introduction

Indomethacin (Ind) is a poorly water-soluble, non-steroidal anti-inflammatory drug. The rectal route of administration is commonly used for patients with ulcers or

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for those who are unable to tolerate the drug. Vidras et al. (1982) and Gueurten et al. (1983) have shown that the bioavailability of indomethacin after rectal administration is better with polyethylene glycol (PEG) base than with fatty bases. Unfortunately, various patients using PEG bases complain of irritations and colics (Gueurten et al., 1983). As Wilson and Thomas (1984) reported, PEG are powerful dehydrating agents that at high concentrations dehydrate the rectum mucosa and induce epithelium cell shedding and irritation. Greene et al. (1980) have also shown a potential toxicity of PEG after a long period of utilization.

In this study, we were interested in increasing the release of indomethacin from non-aqueous suspension through the use of a coprecipitate with polyvinylpyrrolidone (PVP). Many reports have shown that coprecipitation with PVP can enhance the dissolution rate of poorly water-soluble drugs (Simonelli et al., 1969; Chiou and Riegelman, 1971; Corrigan and Timoney, 1975; Sekikawa et al., 1978). PVP inhibits the crystallization of drugs during the coprecipitate formation when the cosolvent is removed in vacuum (Sekikawa et al., 1978; Simonelli et al., 1970). The inclusion of PVP leads to an amorphous solid state with a very high degree of randomness (Simonelli et al., 1976; Corrigan et al., 1984). Other authors explain the increase of solubility through formation of hydrogen bonding with PVP (Shefter and Cheng, 1980) or through coacervate formation (Sekikawa et al., 1979).

The release of indomethacin pure drug and coprecipitate from non-aqueous suspensions has been studied using the model apparatus that has already been extensively described, as have the theoretical concepts (Schoonen et al., 1979, 1980; Crommelin and De Blaey, 1980a and b; Fokkens, 1983). The variables which might influence the release process from a non-aqueous suspension are especially the solubility of the solid in water and in the lipid phase, the interface transport, the particle size and concentration of the solid in apolar media as well as the effect of adjuvants.

Materials and Methods

Materials

Indomethacin (B.P. 80), Plasdone K29-32 (Gaf) and Witepsol H15 (Dynamit Nobel) were used as supplied. Other chemicals were of reagent grade.

Methods

Preparation of Ind/PVP coprecipitate. Ind and PVP in a suitable weight ratio were dissolved in dichloromethane or isopropanol, then the solvent was removed under vacuum in a rotary evaporator at 45°C or 60°C, respectively. The residue was dried for 24 h under vacuum at room temperature, ground and stored in a desiccator protected from light.

Analysis of the sample. Samples were assayed for Ind using spectroscopy analysis at 322 nm or 260 nm. PVP does not interfere with the assay.

X-Ray analysis. Powder X-Ray diffractometry was carried out with a Philips X-Ray Diffractometer, CuKα radiation (40 kV, 16 MA, slit 1°-1°).

Solubility determinations. An excess of drug was placed in a 15 ml test tube with 10 ml of acetic phosphate buffer at various pH. After an agitation for 24 h at 37°C, a sample was withdrawn and filtered through a 0.22 μm membrane filter and the filtrate was analyzed for Ind content. Buffer composition: acetic acid 0.05 M, monopotassium phosphate 0.05 M, hydrochloric acid or sodium hydroxide to pH, polysorbate 20 0.05%.

Solubility in Witepsol H15. A known excess of drug was placed in a 15 ml test tube with 10 g of Witepsol H15. After agitation for 24 h at 37°C, the suspension was filtrated through a 0.45 μm membrane filter. The fraction retained on the filter was washed with hexane and after dissolution in phosphate buffer 0.1 M, pH 7.20, was analyzed for Ind content.

Dissolution study. (a) Powder method: an excess of powder, corresponding to 3.8 g of Ind was dispersed in 100 ml pH 7.20 phosphate buffer 0.1 M. At appropriate intervals 2 ml samples were withdrawn, filtrated through a 0.22 μm membrane filter and the filtrate was analyzed for Ind content. The experiment was carried out at 37°C in the USP XX no. 2 dissolution vessel with a four-blade stirrer and the stirring rate was 150 rpm.

(b) Disc method: 500 mg of powder was compressed into a disc using a 1.273 cm diameter die in an IR press (Perkin Elmer) at a force of 10 tons. The disc was placed in a stainless steel holder, so that only one surface was exposed to the dissolution medium. The holder (thickness 0.7 cm; inner diameter 1.40 cm: outer diameter 2.0 cm) was then introduced like a tablet into the USP XX no. 2 dissolution apparatus with the disc surface facing the paddle stirrer. 500 ml of previously boiled pH 7.20 phosphate buffer 0.1 M was used as dissolution medium at 37°C. The stirring rate was 50 rpm. At appropriate intervals 10-ml samples were removed and analyzed for Ind content. Since the polymer is a part of the active surface, the results obtained were corrected taking into account the drug : polymer ratio according to the method of Graf et al. (1982).

Release from oily suspensions. Various amounts of Ind or Ind : PVP coprecipitate (1 : 1) were dispersed in melted Witepsol H15. The release of Ind from the oily suspensions into an aqueous phase was determined according to the method described by Crommelin and de Blaey (1980a). A one liter round-bottom beaker containing 850 ml various pH phosphate buffer 0.1 M was used with a four-blade stainless steel propeller (50 rpm) placed at 2.5 cm from the bottom of the beaker. 5 ml of the suspension was poured on the top of the aqueous phase in a 3 cm inner diameter siliconed open glass tube. The tube was mounted in such a way that the distance between the bottom of the tube and the suspension/aqueous phase interface was 1 cm. Samples of 10 ml were withdrawn at pre-set intervals and replaced by fresh test fluid. Samples were analyzed for Ind content. All the experiments were carried out at 37°C.

Partition coefficients. Glass-stoppered centrifuge tubes containing 10 ml *n*-octanol and 10 ml of various solutions of Ind (50–500 μg/ml) in pH 7.20 McIlvaine buffer 0.5 M ($Na_2HPO_4 \cdot 12\ H_2O$, Citric acid, KCl) were shaken in a water-bath at 37°C during 24 h. The concentration of Ind was determined in the aqueous phase after centrifugation.

Differential dialysis. The method used has already been described elsewhere (Polderman et al., 1974). A cellulosic membrane (1-7/8 DM Union Carbide) was clamped between the two compartments of a dialysis cell. One side of the cell was filled with 25 ml of pH 7.20 phosphate buffer 0.1 M containing 0.5 mg/ml PVP and 0.5 mg/ml Ind or 1.0 mg/ml coprecipitate 1 : 1; the other side was filled with 25 ml of various Ind solutions with concentrations higher and lower than 0.5 mg/ml. The dialysis cells were rotated in a water-bath at 37°C during 6 h, the solutions of both sides were analyzed for Ind content. The decrease or increase of the Ind (ΔC) concentration in the solution free of PVP was plotted against the starting concentration (C_{in}). A straight line is obtained whose intersection with the C_{in}-axis indicates the free drug concentration in the PVP-Ind solution.

Results and Discussion

The powder X-ray diffraction patterns of coprecipitates show no diffraction peaks attributed to indomethacin. This implies the absence of apparent crystallinity for Ind in coprecipitate systems. When the intrinsic dissolution rates have been measured by the disc method, the coprecipitate exhibited faster drug dissolution rate than the physical mixture as shown in Fig. 1. The intrinsic dissolution rate of coprecipitates increases when the PVP content increases in the solid dispersion until a 4 : 3 ratio is reached (Fig. 2). A 1 : 1 ratio has been used in all further studies. Intrinsic dissolution rates of the physical mixtures are much lower than those exhibited by the corresponding coprecipitates. When dissolution experiments were

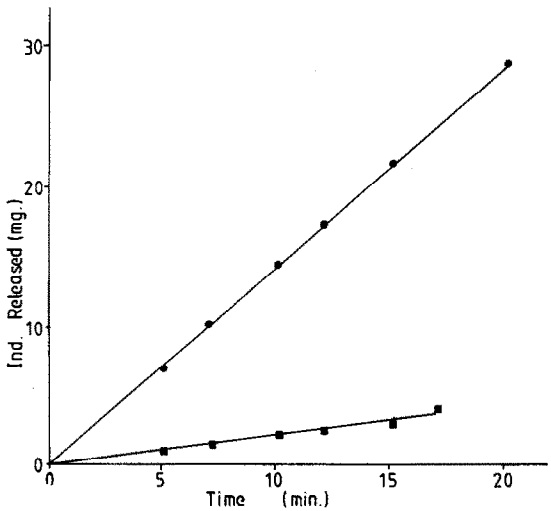

Fig. 1. Dissolution profiles of Ind/PVP coprecipitate 1 : 1 (●) and Ind/PVP physical mixture 1 : 1 (■), determined by the disk method.

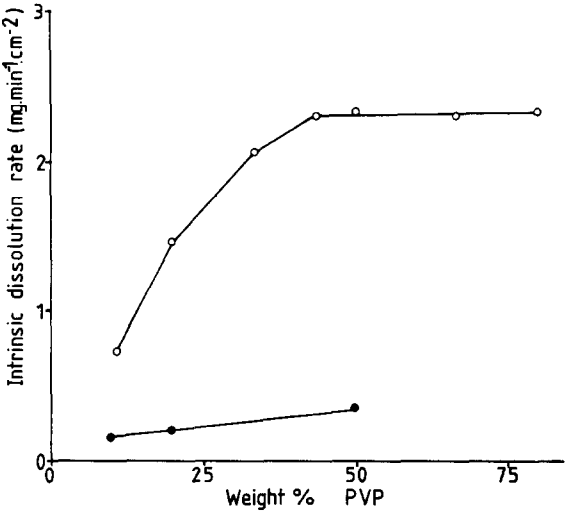

Fig. 2. Intrinsic dissolution rate of Ind as a function of PVP weight percentage in the disk. Coprecipitate Ind/PVP (○), physical mixture Ind/PVP (●).

carried out on Ind/PVP physical mixtures with discs containing more than 50% PVP, the exposed surface of the disc releases fragments of solid into the dissolution medium, therefore the condition of constant surface area was no longer fulfilled. Discs of pure drug could not be prepared because capping occurred dramatically.

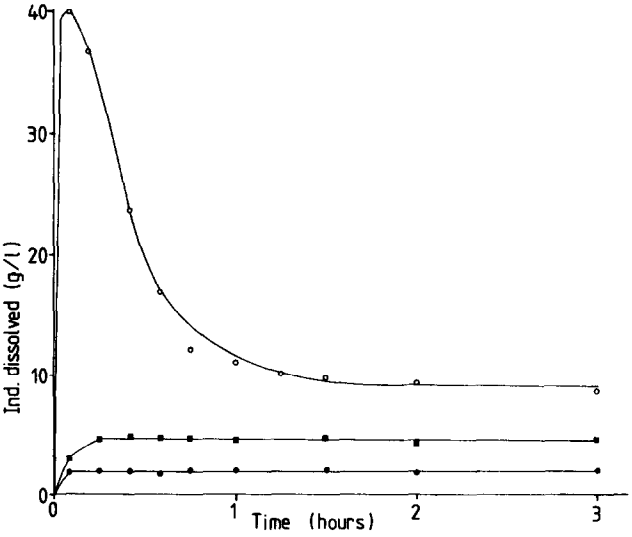

Fig. 3. Dissolution profiles of Ind pure drug (●), Ind/PVP physical mixture 1:1 (■) and Ind/PVP coprecipitate 1:1 (○), determined by the powder method.

TABLE 1

SOLUBILITIES (mg/ml) AT VARIOUS pH

pH	Indomethacin (mg/ml)	Coprecipitate Ind/PVP 1 : 1 (mg/ml)	Physical mixture Ind/PVP 1 : 1 (mg/ml)
5.10	0.025	0.044	0.033
5.70	0.109	0.192	0.120
6.00	0.187	0.320	0.232
6.30	0.360	0.580	0.407
6.60	0.660	1.50	0.844
7.20	1.56	9.27	2.16

In solubility studies, a typical supersaturation phenomenon is observed for the coprecipitate (Fig. 3). The recrystallization has been extensively described by Takayama et al. (1980) who studied the crystallization of indomethacin coprecipitate under non-sink conditions. Solubilities at equilibria of different forms of Ind at different pH are listed in Table 1. At pH 7.20, the solubilities measured for the coprecipitate (1 : 1) and the physical mixture (1 : 1) are 5.94 and 1.38 times higher, respectively, than that of the pure drug.

Release from non-aqueous suspension

The solubility of Ind, Ind/PVP 1 : 1 coprecipitate and Ind/PVP 1 : 1 physical mixture in Witepsol H15 at 37°C is 2.9 ± 0.5 mg/g (n = 5), 1.2 ± 0.1 mg/g (n = 4)

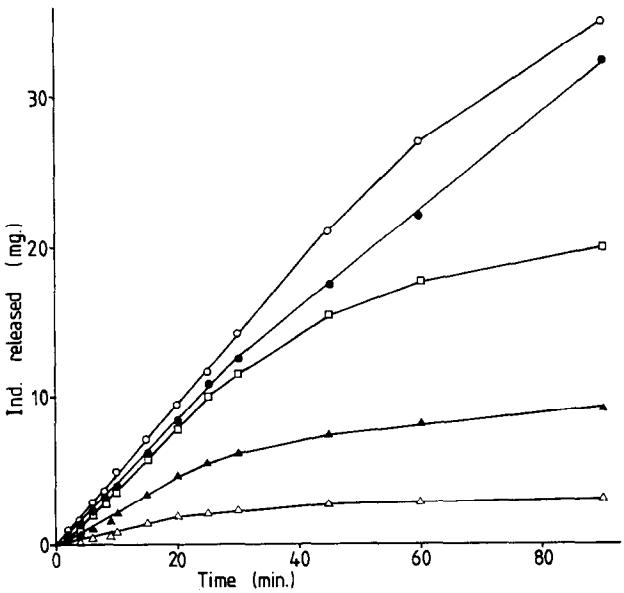

Fig. 4. Release of indomethacin from suspensions in Witepsol H15 with various concentrations of Ind pure drug to pH 7.20 phosphate buffer 0.1 M. △, 0.25%, ▲, 0.50%; □, 1.0%; ○, 2.0%; ●, 3.0%.

Fig. 5.

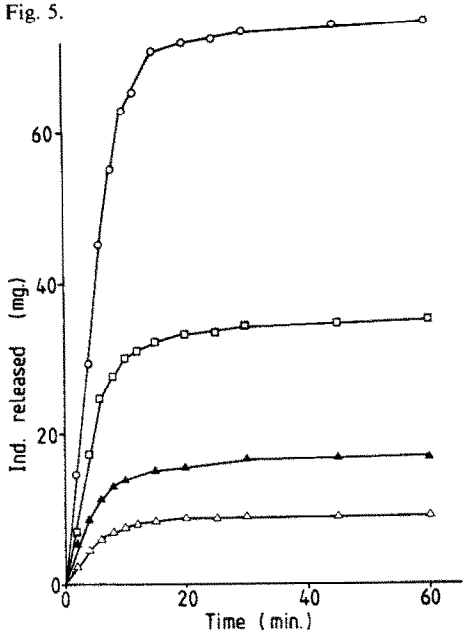

Fig. 6.

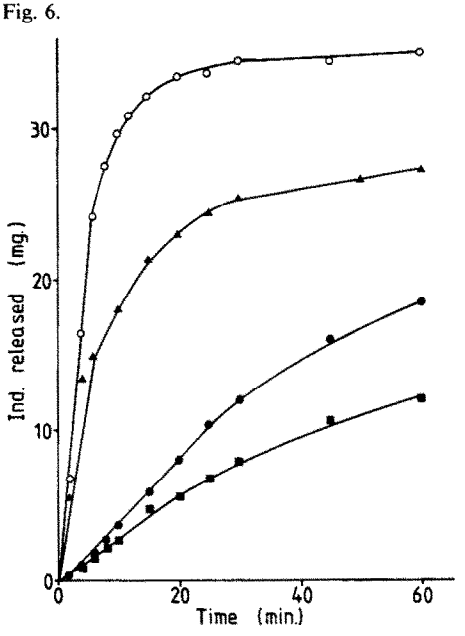

Fig. 5. Release of indomethacin from suspensions in Witepsol H15 with various concentrations of Ind/PVP coprecipitate 1:1, △, 0.25%; ▲, 0.50%; □, 1.0%; ○, 2.0%.

Fig. 6. The release of indomethacin (1%) from suspensions in Witepsol H15 containing various adjuvants to pH 7.20 phosphate buffer 0.1 M. ●, pure drug; ■, physical mixture Ind/PVP 1:1; ○, coprecipitate Ind/PVP 1:1; ▲, Ind + 0.2% Tween 80.

and 3.0 ± 0.4 mg/g ($n = 4$), respectively. The drug will be present at a concentration that is higher than its saturated concentration in all experiments. Thus the driving force for release from non-aqueous suspension will be sedimentation more than diffusion (Schoonen et al., 1979).

The release from 5 ml Witepsol H15 suspensions containing concentrations ranging from 0.25 to 3.0% w/v Ind are shown in Fig. 4 for the pure drug and in Fig. 5 for the coprecipitate. A sediment appears readily at the lipid/water interface for the pure solution. As listed in Table 2, the initial release rate increases with concentration until a value is reached above which it is nearly constant. This critical concentration lies around 1% w/v. The limiting process of release must then be the interfacial transfer or the poor solubility of the drug in water. The lack of reproducibility of the release process for pure drug, after 30 min is due to the release of large agglomerates from the interface prior to dissolution. If 0.2% w/v of Tween 80 is added to the pure drug suspension, the release increases as shown in Fig. 6; particles of Ind fall undissolved through the interface. This is due to a change in wetting and/or interfacial tension; so the dissolution surface area becomes larger and is less reproducible. A more extensive study of the effect of Tween 80 on the release from Ind oily suspensions had been reported previously (Gueurten et al., 1983). As

TABLE 2

INITIAL RELEASE RATE OF INDOMETHACIN FROM WITEPSOL H15 SUSPENSIONS AT VARIOUS CONCENTRATIONS

Concentration (% w/v)	Coprecipitate 1 : 1		Indomethacin	
	Release rate (mg/min)	r	Release rate (mg/min)	r
0.25	0.78 ± 0.04	0.997	0.08 ± 0.02	0.997
0.50	1.31 ± 0.07	0.983	0.26 ± 0.01	0.999
1.0	3.46 ± 0.09	0.978	0.41 ± 0.02	0.999
2.0	7.07 ± 0.21	0.993	0.48 ± 0.01	0.998
3.0	10.3 ± 0.1	0.996	0.45 ± 0.01	0.999

particles of Ind fall through the interface prior to dissolution, it is not the interfacial passage but the dissolution rate that seems to be the rate-limiting process.

The release from various suspensions of coprecipitate 1 : 1 is shown in Fig. 5. The plateau (i.e. the exhaustion of the suspension) is always reached in less than 15 min and no sediment forms at the interface. When the concentration of Ind/PVP coprecipitate 1 : 1 in the suspension increases the initial rate of release increases, as shown in Table 2. This increase is linear and can be described by the following empirical equation:

$$V = 3.54\,A - 0.195 \qquad (r = 0.999)$$

where V = release rate of Ind (mg/min); A = concentration of Ind equivalent in the suspension (%w/v).

Here again particles of coprecipitate leave the interface prior to dissolution, but they dissolved then readily in the buffered medium. Thus it is obvious that the coprecipitation of Ind with PVP has the advantage to improve the release rate of the drug from non-aqueous suspensions by increasing significantly the solubility in the aqueous medium as well as the wetting of the drug. It is to be noted also that with the physical mixture (1 : 1), the release rate of Ind from non-aqueous suspension is reduced as shown in Fig. 6. Fokkens et al. (1984) reported that the addition of PVP leads to a decreased release of zomepirac and has no effect on the liberation of zomepirac sodium.

Indomethacin is a weak acid, with a pK_a value around 4.4 ± 0.1 (Inagi et al., 1981; Herzfeldt and Kümmel, 1983), whose dissolution rate and solubility is depending on pH (Table 1 and Gueurten and Dubois, 1980). Fokkens (1983) has shown the influence of pH on the release of a weak acid (phenobarbital) from non-aqueous suspensions.

The release of indomethacin from 1% Ind w/v suspension prepared either with the pure drug or the 1 : 1 coprecipitate was studied at three different pHs. The results are summarized in Fig. 7 and the calculated initial dissolution rates are reported in Table 3. The release depends strongly on pH for the pure drug and increases when the pH becomes higher than the pK_a value. Here again, we observed the formation of a sediment at the oil/water interface for the pure drug.

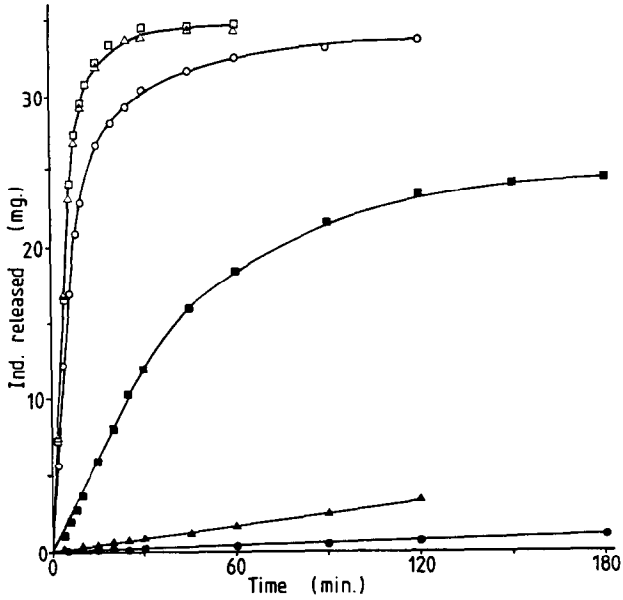

Fig. 7. Release of indomethacin from suspensions in Witepsol H15 to phosphate buffer 0.1 M at various pH. ●, pH 5.10; ▲, pH 6.00; ■, pH 7.20. Open symbols Ind/PVP coprecipitate 1:1; closed symbols indomethacin pure drug.

As it can be noticed from Fig. 7, the liberation rate measured with the coprecipitate form is much higher than that obtained with the pure drug at any pH. The pH dependency is less pronounced for the coprecipitate than for the drug alone. At pH 5.10, almost all the drug has been released from the coprecipitate suspension after 2 h, this will never be the case with the pure drug. Here again the dissolution behaviour of the coprecipitate could be described in a two-step model: drug particles pass through the interface and dissolved readily in the aqueous medium.

Till now, it has been shown that the release of indomethacin in the coprecipitate form from non-aqueous suspensions is faster, completed in a very short time and is much less influenced by the pH of the aqueous phase. On the other hand, it has been

TABLE 3

INITIAL RELEASE RATE OF INDOMETHACIN AND IND/PVP COPRECIPITATE 1:1 FROM WITEPSOL H15 SUSPENSIONS TO 0.1 M PHOSPHATE BUFFER AT VARIOUS pH

pH	Release rate (mg/min)	
	Indomethacin	Coprecipitate 1:1
5.1	0.0061 ± 2.10^{-4}	2.40 ± 0.15
6.0	0.280 ± 1.10^{-4}	3.26 ± 0.01
7.2	0.41 ± 0.02	3.46 ± 0.09

TABLE 4

PARTITION COEFFICIENT OF INDOMETHACIN AND IND/PVP COPRECIPITATE 1:1 AS A FUNCTION OF THE INITIAL CONCENTRATION IN THE AQUEOUS PHASE

Indomethacin initial conc. (mg/ml)	PC o/w	Ind/PVP coprecipitate initial conc. of Ind (mg/ml)	PC o/w
0.0492	20.8	0.0492	21.0
0.110	22.7	0.0982	20.0
0.502	22.5	0.489	21.0

already reported that an increase of the release rate does not always mean a better bioavailability.

Iwaoku et al. (1982) showed that the release from a lipidic suspension of phenobarbital–β-cyclodextrin complex is much better than that of the free drug but as the complex presents a poor permeability through membrane, its absorption rate is not significantly higher than that of the pure drug. Gueurten et al. (1983) did not notice any significant difference between blood levels of Ind released from suppositories including Tween 80 or not even if the liberation rate from non-aqueous suspension in vitro, was higher in presence of Tween 80. Obviously, the increase of the dissolution rate and the solubility in the aqueous phase is useless if the drug cannot penetrate the membrane phase. The determination of the oil/water partition coefficient as well as the permeation through a dialysis membrane will then be of value to predict the bioavailability.

The apparent partition coefficients (PC o/w) of the pure drug and the coprecipi-

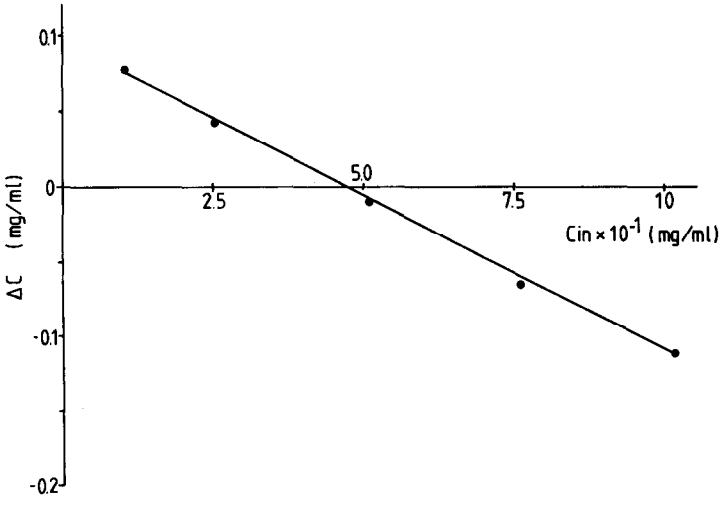

Fig. 8. Determination of free Ind in Ind/PVP coprecipitate 1:1 solution using the differential dialysis method.

tate 1 : 1 are listed in Table 4. There is no significant difference between PC o/w of the pure drug and the coprecipitate when the concentration of PVP is in the same range than the Ind concentration. A more complete study of Ind partitioning between *n*-octanol and water has already been reported (Inagi et al., 1981).

The interaction between PVP and the drug has been studied by a differential dialysis method. The percentage of free indomethacin is $93 \pm 2\%$ for the coprecipitate 1 : 1 (Fig. 8) and $89 \pm 3\%$ for the physical mixture 1 : 1. This means that PVP interacts only slightly with indomethacin. Only the free portion of drug will pass through the biological membrane, as the fraction of bound drug is low (7% of coprecipitate), PVP might not prevent the resorption.

In further studies the interfacial transfer, the passage through biological membrane as well as in vivo test will be realized on coprecipitate, but already a good bioavailability from non-aqueous suspension of Ind coprecipitate forms might be expected.

Acknowledgements

M. O., as Research Assistant of the 'Fonds National de la Recherche Scientifique', thanks F.N.R.S. for financial support.

References

Chiou, W.L. and Riegelman, S., Pharmaceutical applications of solid dispersion systems. J. Pharm. Sci., 60 (1971) 1281–1302.

Corrigan, O.I. and Timoney, R.F., The influence of PVP on the dissolution properties of hydroflumethiazide. J. Pharm. Pharmacol., 27 (1975) 759–764.

Corrigan, O.I. and Holohan, E.M,. Amorphous spray-dried hydroflumethiazide–PVP systems: physicochemical properties. J. Pharm. Pharmacol., 36 (1984) 217–221.

Crommelin, D.J.A. and de Blaey, C.J., In vitro release studies on drugs suspended in non-polar media. I. Release of sodium chloride from suspensions in liquid paraffin. Int. J. Pharm., 5 (1980a) 305–316.

Crommelin, D.J.A. and de Blaey, C.J., In vitro release studies on drugs suspended in non-polar media. II. The release of paracetamol and chloramphenicol from suspensions in liquid paraffin. Int. J. Pharm., 6 (1980b) 29–42.

Fokkens, J.G., In Vitro Drug Release from Non-Aqueous Suspensions, Ph. D. Thesis, Utrecht, February 1983.

Fokkens, J.G., de Blaey, C.J., Niederer, R.R. and Zulliger, H.W., Optimization of the in vitro release of zomepirac from suspensions and suppositories. Int. J. Pharm., 19 (1984) 177–187.

Graf, E., Beyer, C. and Ossama, A., Feststoff dispersion von Acetohexamid. Teil 2: Acetohexamid-PVP 25,000. Acta Pharm. Technol., 28 (1982) 131–135.

Greene, M.H., Young, T.I. and Eisenbarth, G.S., Polyethylene glycol in suppositories: carcinogenic? Ann. Internal Med., 93 (1980) 78.

Gueurten, D. and Dubois, D.M., Etude quantitative de l'influence du pH sur la vitesse de dissolution de l'indomethacin. Pharm. Acta. Helv., 55 (1980) 320–325.

Gueurten, D., Moës, A.J. and Yetimoglu, F., Libération de principes actifs à partir d'excipients gras pour suppositoires. Essais in vitro et in vivo. Proceedings 3rd International Conference Paris, Université de Paris Sud, A.P.G.I., 1983.

Herzfeldt, C.D. and Kümmel, R., Dissociation constants, solubilities and dissolution rates of some selected non steroidal antiinflammatories. Drug. Dev. Ind. Pharm., 9 (1983) 767–793.

Inagi, T., Muramatsu, T., Nagai, H. and Terada, H., Mechanism of indomethacin partition between *n*-octanol and water. Chem. Pharm. Bull., 29 (1981) 2330–2337.

Iwaoku, R., Arimori, K., Nakamo, M. and Uekama K., Enhanced absorption of phenobarbital from suppositories containing phenobarbital–β-cyclodextrin inclusion complex. Chem. Pharm. Bull., 30 (1982) 1416–1421.

Polderman, J., Basart-Westgeest, G.M. and Siemons, J.A.R., Preservation of creams and emulsions. II: Determination of the active part of a preservative. Pharm. Weekbl., 109 (1974) 325–328.

Schoonen, A.J.M., Moolenaar, F. and Huizinga, T., Release of drugs from fatty suppository bases. I. Mechanism. Int. J. Pharm., 4 (1979) 141–152.

Schoonen, A.J.M., Moolenaar, F., Reuvers, K.A. and Huizinga, T., Release of drugs from fatty suppository bases. II. A rate-limiting interfacial process. Int. J. Pharm., 7 (1980) 29–43.

Sekikawa, H., Nakano, M. and Arita, T., Inhibitory effect of PVP on the crystallization of drugs. Chem. Pharm. Bull., 26 (1978) 118–126.

Sekikawa, H., Nakano, M. and Arita, T., Dissolution mechanisms of drug–PVP coprecipitates in aqueous solution. Chem. Pharm. Bull., 27 (1979) 1223–1230.

Shefter, E. and Cheng, K.C., Drug–PVP dispersions. A differential scanning calorimetric study. Int. J. Pharm., 6 (1980) 179–182.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Dissolution rates of high energy PVP–sulfathiazole coprecipitates. J. Pharm. Sci., 58 (1969) 538–549.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Inhibition of sulfathiazole crystal growth by PVP. J. Pharm. Sci., 59 (1970) 633–637.

Simonelli, A.P., Mehta, S.C. and Higuchi, W.I., Dissolution rates of high energy sulfathiazole–povidone coprecipitates II: Characterization of form of drug controlling its dissolution rate via solubility studies. J. Pharm. Sci., 65 (1976) 355–361.

Takayama, K., Nambu, N. and Nagai, T., Dissolution kinetics for coprecipitates of indomethacin with PVP. Chem. Pharm. Bull., 28 (1980) 3304–3309.

Vidras, N.J., Reid, V.E., Bohidar, N.R. and Plakogiannis, F.M., Medicament release from suppository bases I: Physicochemical characteristics and bioavailability of indomethacin in rabbits. J. Pharm. Sci., 71 (1982) 945–949.

Wilson, C.G. and Thomas, N.W., Interaction of tissues with polyethylene glycol vehicles. Pharm. Int., 5 (1984) 94–97.