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The effect of wetting agents on the dissolution of indomethacin solid dispersion systems

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Summary

Solid dispersion systems containing indomethacin and polyvinylpyrrolidone (PVP) 17 or 90 were prepared in drug: PVP ratios of 70 : 30, 80 : 20 and 90 : 10 by co-precipitation and spray drying. The polymorphic form of indomethacin in the systems was identified and physical mixtures containing the polymorphic form and the corresponding drug: PVP ratios were prepared for comparative purposes. Dissolution rates of indomethacin from the powdered systems were compared with that of the pure drug in water, in an aqueous polyethylene glycol (PEG) 300 solution and in 40 mM sodium cholate solution. Dissolution into PEG solution showed the drug dissolution rate from the systems depended upon the availability of drug to complex with PEG. In 40 mM sodium cholate solution, the dissolution rates of indomethacin from the systems were markedly enhanced due to favourable pH conditions, and were similar to one another, except for the indomethacin: PVP 17 co-precipitate which exhibited the fastest dissolution rate. The PVP 90 systems exhibited slightly slower dissolution rates in sodium cholate solution than the PVP 17 systems probably as a result of an increase in viscosity of the diffusion layer.

Introduction

Many studies have been carried out on the enhancement of the solubility and dissolution rates of poorly water-soluble drugs by the utilization of a solid dispersion or molecular dispersion containing low concentrations of drug dispersed in water-soluble polymers such as polyvinylpyrrolidone (PVP) (Bogdanova et al., 1981; Sekikawa et al., 1979). A slow release of some poorly water-soluble drugs may be preferred when their presence in high concentrations in the gastrointestinal tract causes irritation and ulceration with long-term use, such as with the anti-inflammatory drug, indomethacin (Shack, 1966). Because absorption is limited by the rate of dissolution, the accumulation of a drug near the mucosa from a slow release preparation would be reduced and subsequently the incidence of gastrointestinal effects could be reduced or eliminated altogether unless these effects were determined by the drug serum levels.

The aim of this study was to characterize solid dispersion systems containing indomethacin with polyvinylpyrrolidone 17 or 90 in high drug: PVP ratios in the form of co-precipitates and spray dried products prior to their use in vivo in an

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attempt to reduce intestinal ulceration caused by this drug. PVP was chosen because Lipman (1982) has previously shown a decrease in the dissolution rate of paracetamol in the presence of PVP.

Materials and Methods

Materials

Indomethacin (Nicholas Labs., Slough, U.K.), polyvinylpyrrolidone (Kollidon-17 and Kollidon-90, BASF, supplied by Blagden Campbell Chemicals, Surrey, U.K.), Cholic acid in the form of the sodium salt (Sigma Chemical Co., Poole, U.K.), L-tryptophan, acetonitrile for liquid chromatography, glacial acetic acid (B.D.H. Chemicals, Poole, U.K.), absolute alcohol (ethanol, James Burrough (F.A.D.), London, U.K.), polyethylene glycol, m.wt. 300, pure (Koch-Light Labs., Berks, U.K.) were used as received.

Methods

Preparation of the solid dispersion systems

Co-precipitates containing indomethacin and PVP 17 or 90 were prepared by the solvent method of Chiou and Riegelman (1971) in drug: PVP ratios of 80 : 20 and 70 : 30.

Spray dried products were prepared from a suspension of 15 g of the physical mixture in 4 litres of distilled water using a Buchi 190 Mini Spray Drier (Buchi Laboratories, Technik, Switzerland). The suspension was fed through a peristaltic pump at a flow rate of 8 $ml \cdot min^{-1}$. The inlet and outlet temperatures were 190°C and 80°C, respectively. Atomization was achieved at an airflow of 4 kg/cm^2 using a 0.7 mm diameter nozzle. The product was dried at 40°C under vacuum until constant weight was obtained. The final compositions of the products were 90 : 10 and 80 : 20 (drug : PVP).

Physical mixtures of drug and PVP were prepared in ratios corresponding to those in the co-precipitates and spray dried products and containing either form α or form γ of indomethacin.

Characterization of the polymorphic forms of indomethacin

Three polymorphic forms were prepared for characterization. Forms α and β were prepared according to the methods of Pakula et al. (1977), and form γ according to Borka (1974).

Characterization of the polymorphic forms and identification of the form(s) present in the systems was carried out by differential scanning calorimetry, infra-red spectroscopy and X-ray diffraction as described by Tuladhar et al. (1983).

TLC studies

The Pharmaceutical Codex (1979, p. 937), Method 3a for analgesic and anti-inflammatory compounds was used to detect possible degradation products of the drugs in the preparation of the co-precipitates and spray dried products. The systems were compared against a decomposed drug sample obtained by heating the pure drug.

Surface area measurement

The Fisher Sub Sieve Sizer (K.E.K., Manchester, U.K.) was used to determine the surface area of the pure drug and powdered systems using the weight of powder equivalent to its true density. The true density of a powdered sample was determined using an Air Comparison Pycnometer (Beckman Model 930, Beckman RIIC, U.K.).

Solubility studies

The equilibrium solubility of indomethacin was determined in water, 0–10% w/v aqueous PVP solutions, phosphate buffer at pH 7.35 and 40 mM sodium cholate at pH 7.35 using a rotating wheel assembly (rotation at 10 rpm) immersed in a water bath at 37 ± 0.5°C. Excess amounts of solute were suspended in 20 ml of solvent in Sovirel tubes and rotated for 48 h after previously demonstrating that equilibrium was attained in this time. Samples were withdrawn, filtered through a 0.45 μm membrane filter and then diluted appropriately before being assayed for drug content using the reverse phase HPLC methods.

Dissolution studies

The dissolution apparatus consisted of a 1 litre vessel similar to that used in the B.P. dissolution test. This contained 600 ml of deaerated dissolution medium at 37 ± 0.5°C. The solution was agitated at 100 rpm by a teflon stirrer situated 3

cm above the base of the vessel and connected via a pulley to a variable speed motor (Citenco). The rotational speed was checked at selected time intervals using a tachometer (Smiths Industrial Division, London).

A weight of powder equivalent to a surface area of 300 cm^2 was placed on the vessel base at the beginning of the experiment. When PEG 300 was used as a wetting agent 0.5 ml of PEG 300 was mixed with the powder using a fine brush. The vessel top and stirrer were replaced and after the stirrer motor was started, the dissolution medium was added. 5 ml samples were withdrawn at selected intervals via a syringe attached to a length of plastic tubing placed directly in line with the stirrer and 3 cm away. Previous experimentation showed that there was no adsorption of drug onto the plastic. The samples were filtered through a 0.45 μm membrane filter, diluted appropriately and assayed for drug content using the reverse-phase HPLC methods. 5 ml of dissolution medium at 37 ± 0.5°C was replaced after each withdrawal.

Statistical evaluation of the dissolution profiles was carried out by first using a curve-fitting computer programme. The programme used was "Datafit", version 2.05 and designed by R. Gee (School of Pharmacy, University of London). The equation:

$$y = C_0 x + C_1[1 - e^{-(C_2 x)}]$$

was found to give the best fit to the results. C_0, C_1 and C_2 are the coefficients used. The 95% confidence limits of each fitted curve were calculated and overlap between the two curves meant they were not significantly different from each other.

Reverse phase HPLC methods

Method 1

The system consisted of a reciprocating pump (Metering Pumps, London) fitted with a 10 μl injection valve, a Cecil Instruments UV variable detector (Model CE212) connected to a Servogor 120 pen-recorder (John Minister Instruments). A Partisil 10 ODS-3 column (Whatman U.K.) and a precolumn packed with Pellicular Media (CO : PELL, ODS, Whatman U.K.) were used. The mobile phase consisting of 0.1% v/v aqueous acetic acid : acetonitrile (60 : 40) was pumped at a rate of 1.2 ml/min at a pressure of 8.273×10^6 Pa and the wavelength of analysis was 270 nm. The internal standard was L-tryptophan and each sample contained 0.0005% w/v L-tryptophan in the final dilution. The retention times for L-tryptophan and indomethacin were 5 and 14 min, respectively.

Method 2

An alternative procedure was required for drug samples in sodium cholate solution because the retention time of the sodium cholate peak was the same as that of indomethacin in Method 1. The same apparatus was used but the mobile phase was changed to 0.1% v/v aqueous acetic acid : acetonitrile (40 : 60). L-Tryptophan was retained as the internal standard and the final dilution of L-tryptophan contained 0.002% w/v. The retention times for L-tryptophan and indomethacin were 3 and 5 min, respectively.

Results and Discussion

Polymorphic characterization

The three polymorphic forms of indomethacin exhibited characteristic melting points shown in Table 1. Their characteristic infra-red spectra were in agreement with those of Spychala et al. (1977) and X-ray diffraction patterns agreed with those obtained by Rowe (1980).

Polymorphic characterization of indomethacin in the dispersion systems identified the presence of form α or form γ (Table 2). Form α was present in the co-precipitates as this is the form obtained after recrystallization from ethanol. Form γ was present in the spray dried products showing

TABLE 1

INDOMETHACIN CRYSTAL MELTING POINTS OBTAINED BY DSC AT A SCAN SPEED OF 8°C·min $^{-1}$

Nomenclature	Crystal melting point (°C)
α	153.2
β	158.5
γ	160.0

TABLE 2

THERMAL ANALYSIS OF INDOMETHACIN: PVP SOLID DISPERSION SYSTEMS USING DSC AT A SCAN SPEED OF $8°C \cdot min^{-1}$

System	PVP	% Drug content	Onset of melt (°C)	Polymorph present
Co-precipitate	17	80	154.5	α
		70	151.0	α
	90	80	150.2	α
		70	150.5	α
Physical mixture (form γ)	17	90	159.2	γ
		80	159.5	γ
		70	159.5	γ
	90	90	159.3	γ
		80	159.4	γ
		70	159.0	γ
Spray dried product	17	90	160.0	γ
		80	160.1	γ
	90	90	160.0	γ
		80	159.8	γ
Physical mixture (form α)	17	80	154.2	α
		70	153.1	α
	90	80	152.7	α
		70	150.8	α

the polymorphic form had not altered during spray drying. Infra-red spectra and X-ray diffraction of the systems confirmed the results obtained from thermal analysis. The presence of PVP in the systems did not affect the identification of the polymorphic forms by these methods.

TLC studies

The TLC studies showed that indomethacin did not decompose during the preparation of the co-precipitates and the spray dried products. The R_f values for the decomposed drug were 0.7 and 0.9, whereas the R_f value for indomethacin in the systems was 0.7.

Equilibrium solubility

Fig. 1 shows the equilibrium solubility of in-

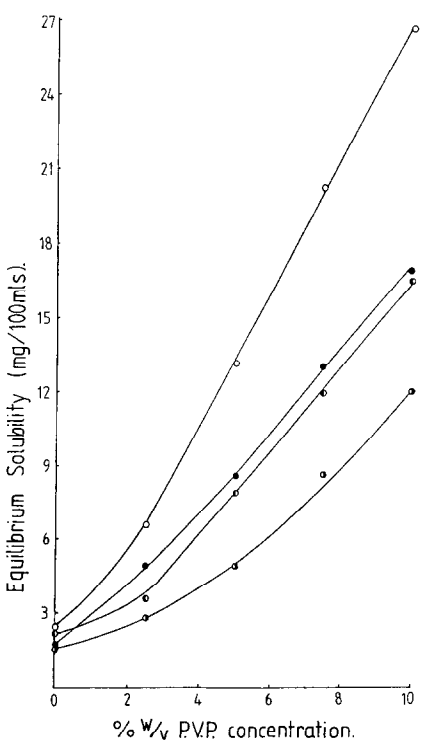

Fig. 1. Aqueous equilibrium solubility of indomethacin in PVP 17 and PVP 90 after 48 h at 37±0.5°C.
Key:
◑, indomethacin (form γ) in PVP 17 solutions (pH 3.6);
◐, indomethacin (form γ) in PVP 90 solutions (pH 4.0);
●, indomethacin (form α) in PVP 17 solutions (pH 3.6);
○, indomethacin (form α) in PVP 90 solutions (pH 4.0).

TABLE 3

EQUILIBRIUM SOLUBILITIES OF INDOMETHACIN IN 40 mM SODIUM CHOLATE SOLUTION (pH 7.35), 0.1 M PHOSPHATE BUFFER (pH 7.35) AND WATER (pH 5.6)

Solvent	Equilibrium solubilities of:	
	Form α (mg %)	Form γ (mg %)
40 mM sodium cholate solution (pH 7.35)	200.70	175.93
0.1 M phosphate buffer (pH 7.35)	173.27	136.55
Water (pH 5.6)	2.06	1.85

domethacin was greater in PVP 90 solutions and increased with increasing PVP concentrations. This suggests that indomethacin interacted with PVP in solution, probably via hydrogen bonding between the carboxylic acid group of indomethacin and the oxygen atom in the pyrrolidone ring of PVP.

The equilibrium solubility of indomethacin was greater in 40 mM sodium cholate solution at pH 7.3 compared with its solubility in phosphate buffer at pH 7.3 (Table 3). This result confirms that of Miyazaki et al. (1981) who suggested the increase in indomethacin solubility in bile salt solution may be due to micellar solubilization as well as effects due to a favourable pH.

In all of the solvents tested, the metastable polymorphic form, form α was more soluble than the stable polymorphic form, form γ.

Dissolution studies

(i) In water

One of the problems with poorly water-soluble drugs like indomethacin is that they are often hydrophobic (Lerk et al., 1977) and tend to float on the surface of the dissolution medium preventing the exposure of the true surface area of the powder to the medium. During dissolution in water, the co-precipitates were well wetted but the spray dried products, physical mixtures and pure drug tended to float on the medium surface. Therefore, the dissolution profiles obtained from the systems could not be compared against one another, although the systems containing PVP exhibited faster dissolution rates than the pure drug (Fig. 2).

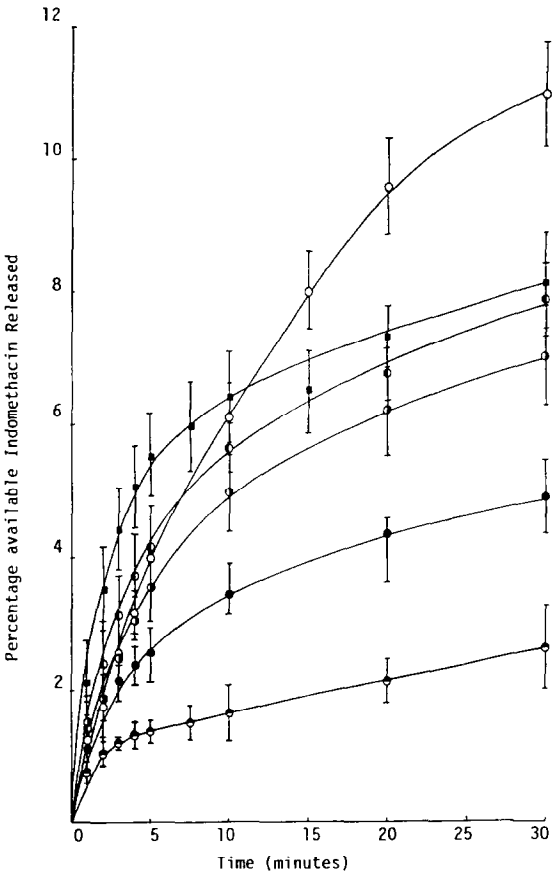

Fig. 2. Dissolution of indomethacin from powdered indomethacin:PVP 90 dispersion systems in water at 37 ± 0.5 °C (pH 5.6).
Key:

Symbol	System	Polymorphic form present	Drug: PVP ratio
●	Indomethacin	α	–
◓	Indomethacin	γ	–
■	Co-precipitate	α	80:20
◐	Physical mixture	α	80:20
◑	Physical mixture	γ	80:20
○	Spray dried product	γ	80:20

(ii) In PEG solution

To improve the wetting of the systems, PEG 300 was mixed with the powdered systems prior to dissolution. Fig. 3 shows the dissolution profiles from some of the dispersion systems. The dissolution rate order was pure drug > spray dried product = physical mixture > co-precipitate which is

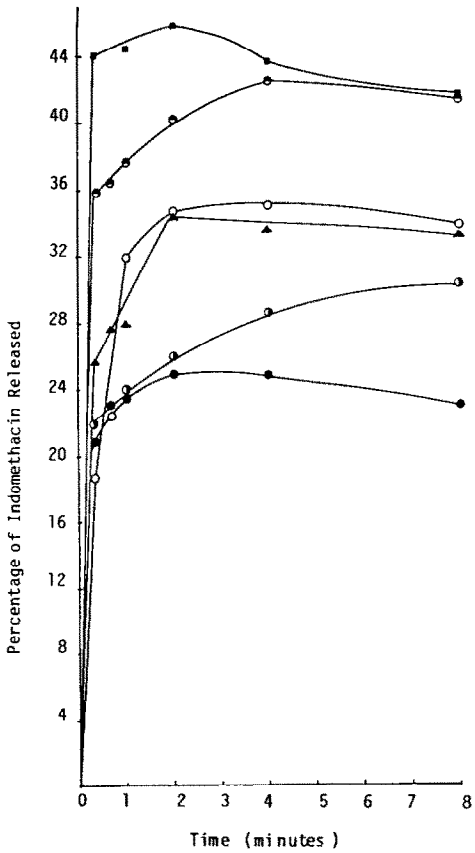

Fig. 3. Dissolution of indomethacin from powdered indomethacin:PVP 17 dispersion systems in the presence of PEG 300 (pH 5.5).
Key:

Symbol	System	Polymorphic form present	Drug: PVP ratio
■	Indomethacin	α	–
◓	Indomethacin	γ	–
○	Spray dried product	γ	80:20
▲	Physical mixture	γ	70:30
◑	Physical mixture	γ	80:20
●	Co-precipitate	α	80:20

approximately the reverse order obtained in aqueous dissolution. This order is due to the presence of PVP in the dispersion systems protecting the drug from complexation with PEG by differing degrees dependent upon the association between PVP and drug in the solid state. PEG therefore appears to have an inhibitory effect on the dissolution of PVP.

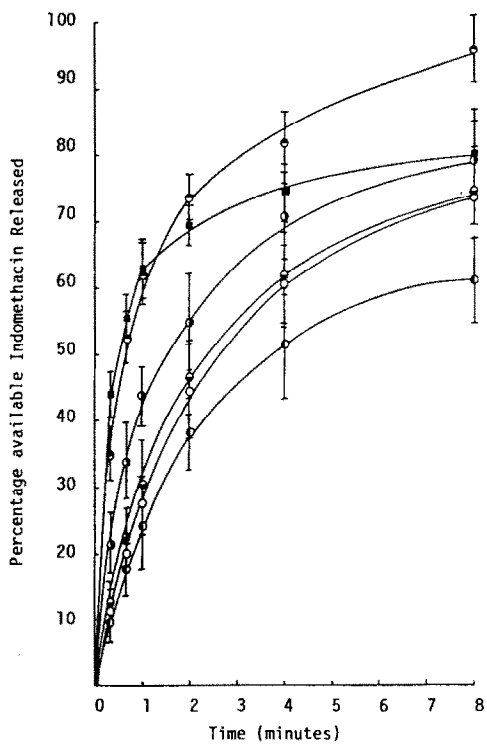

Fig. 4. Dissolution of indomethacin from powdered indomethacin:PVP 17 dispersion systems in 40 mM sodium cholate solution at 37 ± 0.5°C (pH 7.35).
Key:

Symbol	System	Polymorphic form present	Drug: PVP ratio
◓	Co-precipitate	α	70:30
◒	Physical mixture	γ	70:30
■	Physical mixture	α	70:30
◑	Spray dried product	γ	80:20
◐	Indomethacin	γ	–
○	Indomethacin	α	–

In the absence of PVP, the pure drug freely complexed with PEG and produced the fastest dissolution rates. The greatest protection of drug from complexation with PEG was provided by PVP in the co-precipitates since the drug was dispersed in a PVP matrix in the solid state. The spray dried products and physical mixtures produced slightly slower dissolution rates than the pure drug because there was some association between drug and PVP in the solid state so that upon dissolution, a PVP diffusion layer surrounded some of the dissolving drug particles.

(iii) In 40 mM sodium cholate solution

Bile salts have been shown to improve the solubility and dissolution of poorly water-soluble drugs (Bates et al., 1966a, 1966b and 1966c) and thus dissolution of the dispersion systems into sodium cholate solution was carried out to ensure complete wetting of the systems using a material present in vivo.

The dispersion systems and pure drug exhibited faster dissolution rates in sodium cholate solution than in water due to improved wetting, a slightly higher pH of the dissolution medium and possible complexation between indomethacin and sodium cholate.

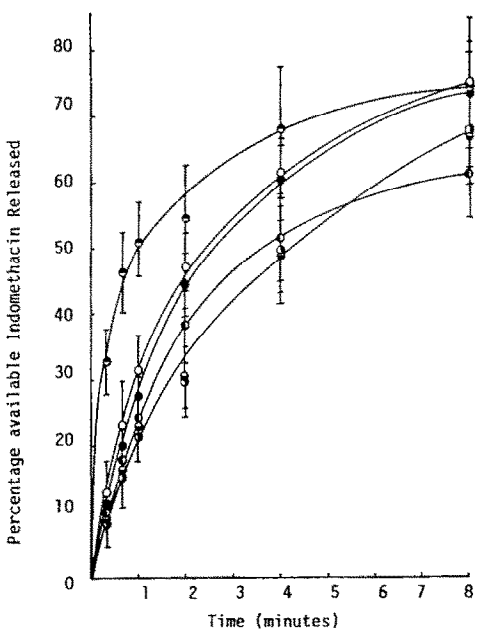

Fig. 5. Dissolution of indomethacin from powdered indomethacin:PVP 90 dispersion systems in 40 mM sodium cholate solution at 37 ± 0.5°C (pH 7.35).
Key:

Symbol	System	Polymorphic form present	Drug: PVP ratio
○	Co-precipitate	α	70:30
◒	Physical mixture	γ	70:30
◓	Physical mixture	α	70:30
◑	Spray dried product	γ	80:20
◐	Indomethacin	γ	–
●	Indomethacin	α	–

Figs. 4 and 5 show the dispersion systems exhibited similar dissolution rates which were not significantly different from each other or from the pure drug, with the exception of the PVP 17 co-precipitate which exhibited a significantly faster dissolution rate and the highest percentage drug released. These results suggest that the increase in drug solubility was such that PVP had a less significant effect on the drug dissolution rate. However, the PVP 90 systems exhibited slightly slower dissolution rates than the PVP 17 systems which could be the result of an increase in viscosity of the diffusion layer as the PVP dissolved, since PVP 90 solutions are more viscous than PVP 17 solutions (Lipman, 1982).

The faster dissolution rate from the PVP 17 co-precipitate could be due to the small particle size of the drug in the system and the presence of more soluble forms of indomethacin. However, the PVP 90 co-precipitate would be expected to have smaller drug particles because the viscosity of the solution during crystallization would produce finer crystallites. This system did not exhibit a faster dissolution rate than the PVP 17 co-precipitate, probably because the viscosity increase in the diffusion layer due to the PVP retarded drug diffusion.

These in vitro results indicate that the increase in dissolution rate often reported for solid dispersion systems will only be observed in a solvent in which the dissolution enhancing effects of small size, amorphous forms etc. usually associated with such systems is observed because the solubility of the preparation in that solvent is sufficiently low. Furthermore, wetting agents added to the system can affect the results if phenomena other than simple surface tension reduction takes place with these agents.

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