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A comparison between the in vivo serum levels and in vitro dissolution of indomethacin–polymer dispersion systems

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Summary

It has previously been shown that there was a correlation between the in vivo serum levels and in vitro dissolution of powdered indomethacin : PVP dispersion systems in sodium cholate solution (Hilton and Summers, 1986b). However, the incorporation of indomethacin into dispersion systems containing other polymer agents does not necessarily show that the observed in vitro dissolution rates correspond with the observed in vivo results. This has been shown using indomethacin : PEG6000 and indomethacin : PVP90 : PVA coprecipitates.

Introduction

To confirm that the in vivo results obtained from indomethacin : PVP dispersion systems (Hilton and Summers, 1986b) could be explained by differences in the dissolution rate, further investigations were undertaken to modify the dissolution rate of indomethacin by its incorporation into dispersion systems containing other polymer agents.

Polyethylene glycol (PEG) was chosen as it has been shown to complex with indomethacin (Hilton and Summers, 1986a) and this should therefore enhance dissolution rate.

Polyvinyl alcohol (PVA) was chosen because it is poorly water-soluble and would form an impermeable layer about the dissolving drug particles. Polyvinyl alcohol was incorporated into the indomethacin : PVP90 dispersion system to see whether the dissolution rate of indomethacin could be lowered by its incorporation.

Materials and Methods

Materials

Indomethacin (Nicholas Labs, Slough, U.K.), polyvinylpyrrolidone (Kollidon-90, BASF, supplied by Blagden Campbell Chemicals, Surrey, U.K.), polyvinyl alcohol, Type III (Sigma Chemical Co, Poole, U.K.), polyethylene glycol 6000 (Koch-Light Labs, Bucks, U.K.), cholic acid, sodium salt (Sigma Chemical Co, Poole, U.K.)

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and absolute alcohol (James Burrough (F.A.D.), London, U.K.) were used as received.

Methods

Sample preparation. The indomethacin : PEG 6000 dispersion system was prepared by the solvent method of Chiou and Reigelman (1971) in a 80 : 20 drug : PEG ratio.

The indomethacin : PVP90 : PVA dispersion system was also prepared by the solvent method of Chiou and Riegelman (1971) in a 80 : 6 : 14 drug : PVP90 : PVA ratio.

Characterization of the systems. The polymorphic form of the drug present in each system was determined by differential scanning calorimetry and infrared spectra as described by Tuladhar et al. (1983).

Surface area determinations of the powdered systems were carried out as described previously (Hilton and Summers, 1986a).

Equilibrium solubility. The equilibrium solubility of indomethacin polymorphic form α was determined in 0–4% w/v aqueous PVA solutions (pH 6.0) and 0–10% w/v aqueous PEG6000 solutions (pH 4.7) as described previously (Hilton and Summers, 1986a).

Dissolution studies. Dissolution of the powdered systems was carried out in water and 40 mM sodium cholate solution as described previously (Hilton and Summers, 1986a).

Reverse phase HPLC methods. Aqueous drug samples were assayed for drug content using the reverse phase HPLC method 1 (Hilton and Summers, 1986a) and drug samples containing sodium cholate were assayed using method 2 (Hilton and Summers, 1986a).

Extracted serum samples were assayed for drug content using a third HPLC method (Hilton and Summers, 1986b).

In vivo methods. The dosing technique, extraction technique and methods for evaluation of intestinal ulceration are described by Hilton and Summers (1986b). Control groups of rats were administered PEG and PVA solutions since PEG has been shown to be ulcerogenic after administration of concentrated solutions (Wilson and Thomas, 1984).

Viscosity determination. Viscosity determination of solutions was carried out using an Epprecht Rheomat 30 (Contraves A.G., Zurich, Switzerland) at room temperature and at 37°C, and shear stress and rate of shear factors were provided by the manufacturers to allow conversion of the instrument readings to absolute quantities.

Results and Discussion

Polymorphic form

The polymorphic form of indomethacin in the indomethacin : PEG6000 and indomethacin : PVP90 : PVA coprecipitates was form α, which was expected since this form is obtained by recrystallization from an ethanolic solution.

Equilibrium solubility

Figs. 1 and 2 show the equilibrium solubility of indomethacin form α in PEG and PVA solutions. Indomethacin solubility increased with increasing

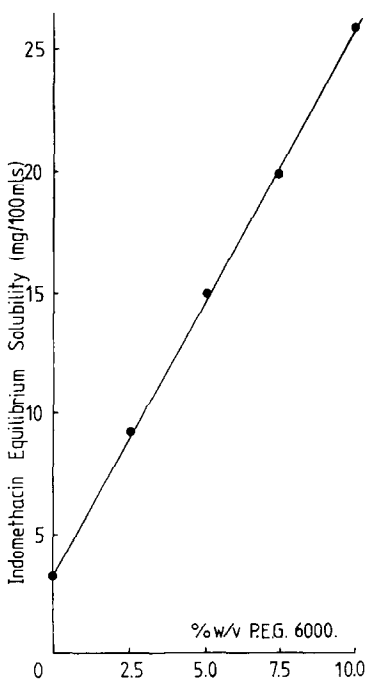

Fig. 1. Equilibrium solubility of indomethacin form α in PEG6000 aqueous solutions at pH 4.7, 37 ± 0.5°C. Correlation coefficient = 0.975.

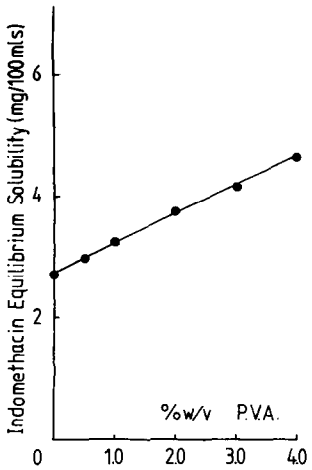

Fig. 2. Equilibrium solubility of indomethacin form α in 0–4% w/v PVA solutions after 48 h at pH 6.0, 37 ± 0.5°C. Correlation coefficient = 0.974.

polymer concentrations, the increase being more apparent in PEG solutions.

PEG probably interacts with indomethacin via hydrogen bonds between the hydroxyl groups of PEG and the carboxylic or amido groups of indomethacin. Likewise, PVA may interact with indomethacin by hydrogen bonding between the hydroxyl groups of PVA and the carboxylic or amido groups of indomethacin. However, the indomethacin solubility in PVA was not as great as in PVP solutions (Hilton and Summers, 1986a). Therefore, complex formation between PVA and indomethacin is less likely to occur in the diffusion layer of a dissolving indomethacin : PVP90 : PVA coprecipitate.

Dissolution studies

Figs. 3 and 4 show the dissolution profiles obtained from the powdered indomethacin : polymer systems and pure drug in water and 40 mM sodium cholate solution. The systems were well wetted in both dissolution media but the solubility of indomethacin in sodium cholate was greatly enhanced due to micellar solubilization, favourable pH conditions and a possible interaction between indomethacin and sodium cholate.

In both media, the powdered PEG coprecipitate exhibited a fast initial dissolution rate fol-

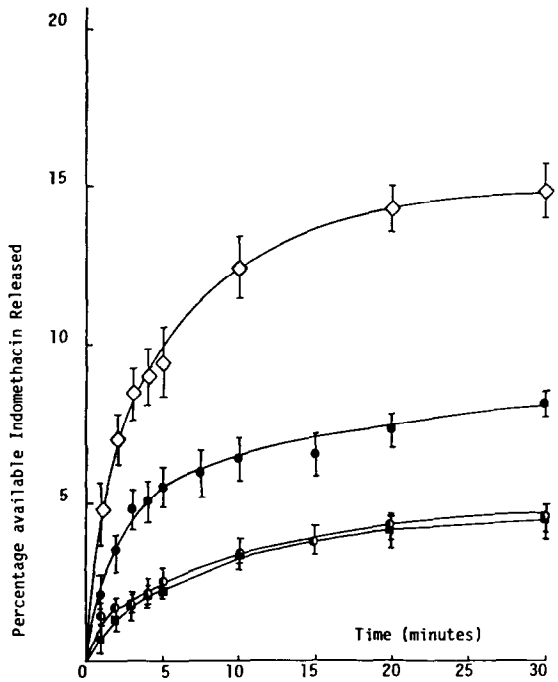

Fig. 3. Dissolution of powdered indomethacin : polymer coprecipitates in water at 37 ± 0.5°C (pH 5.6). Key: ◐, indomethacin (form α); ◇, 80 : 20 indomethacin : PEG6000; ●, 80 : 20 indomethacin : PVP90; ■, 80 : 6 : 14 indomethacin : PVP90 : PVA.

lowed by a slower limiting dissolution rate. The initial rate was due to increased drug solubility by the formation of drug : PEG complexes in the diffusion layer surrounding the dissolving drug particles. The slower limiting dissolution rate was probably due to the depletion of PEG and as a result, changed the initial dissolution rate order, which was identical to that obtained in water, from indomethacin : PEG coprecipitate > indomethacin : PVP90 coprecipitate > pure drug, to pure drug > indomethacin : PVP90 coprecipitate > indomethacin : PEG coprecipitate.

The indomethacin dissolution rate from the PVA coprecipitate was slightly slower than the pure drug both in water and sodium cholate solution, although the difference between the dissolution rates was not significant. PVA is poorly water-soluble and therefore during dissolution it formed an impermeable barrier around the dissolving drug particles.

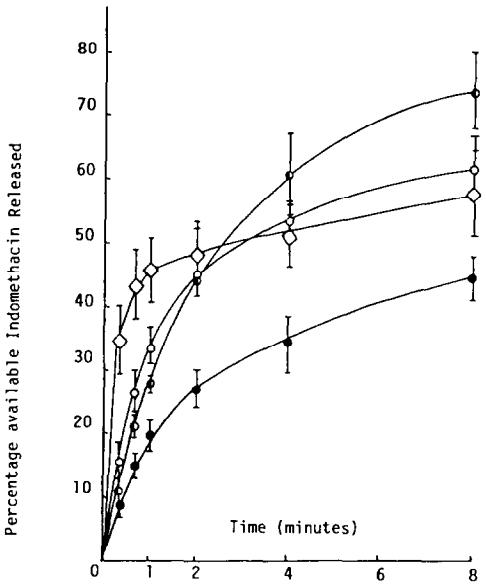

Fig. 4. Dissolution of powdered indomethacin : polymer coprecipitates in 40 mM sodium cholate solution at 37 ± 0.5 °C (pH 7.35). Key: ◐, indomethacin (form α); ◇, 80 : 20 indomethacin : PEG6000; ○, 80 : 20 indomethacin : PVP90; ●, 80 : 6 : 14. indomethacin : PVP90 : PVA.

Thus, the incorporation of indomethacin into dispersion systems of PEG and PVA had modified its dissolution rate into water. In PEG, the rate was greatly increased and in PVA, greatly retarded. Since the absorption of indomethacin and incidence of ulceration from PVP systems was dissolution rate limiting (Hilton and Summers, 1986b), when these systems are administered to rats, higher drug serum levels and a high incidence of ulceration should be obtained from the PEG coprecipitate and the opposite results obtained from the PVA coprecipitate if the previous results are valid for a range of solubilities.

In vivo studies

Fig. 5 shows the drug serum levels obtained after single oral doses of indomethacin : polymer dispersion systems and pure drug, form α. The indomethacin : PEG coprecipitate produced higher drug serum levels than the indomethacin : PVP90 coprecipitate, and the drug serum levels were significantly different from each other at each blood sampling time. However, the incidence of ulceration produced by the PEG coprecipitate was not significantly different from that produced by the PVP90 coprecipitate as shown in Table 1. This table also shows that ulceration was not produced by the control groups and therefore ulceration was caused by the presence of indomethacin in the systemic circulation.

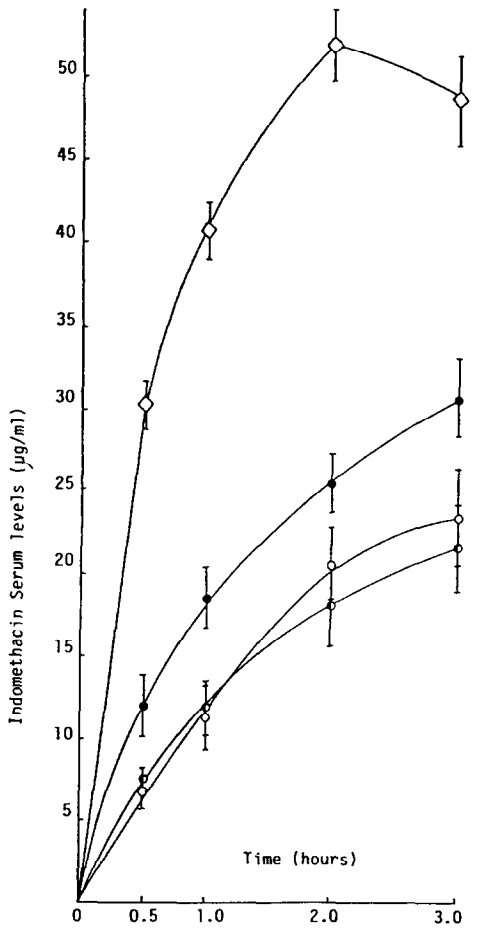

Fig. 5. Serum levels of indomethacin after oral administration of the indomethacin : polymer coprecipitates. Key: ◇, indomethacin (form α); ●, 80 : 20 indomethacin : PEG6000; ○, 80 : 20 indomethacin : PVP90; ◐, 80 : 6 : 14 indomethacin : PVP90 : PVA.

The expected serum level order, as obtained from the dissolution study in sodium cholate solution was pure drug > indomethacin : PVP90 coprecipitate > indomethacin : PEG coprecipitate. However, the serum level order corresponds with the

TABLE 1

EVALUATION OF ULCERATION IN THE RAT SMALL INTESTINE 72 h AFTER A SINGLE ORAL DOSE OF INDOMETHACIN : POLYMER COPRECIPITATES (15 mg INDOMETHACIN/kg)

System	Tensile strength after 72 h (mm Hg ± SEM)	Ulcer number	% weight loss
Control – PEG solution	198 ± 10.21	0	Weight gain
– PVA solution	219 ± 11.97	0	
Indomethacin (form α)	37.0 ± 8.80 [c]	many adhesions	−16.33%
80 : 20 indomethacin : PVP90 coprecipitate	53.4 ± 1.7 [c,d]	125 ± 5.0	−10.29%
80 : 20 indomethacin : PEG6000 coprecipitate	52.4 ± 3.4 [c,d]	120.6 ± 12.8	7.50%
80 : 6 : 14 indomethacin : PVP90 : PVA coprecipitate	54.0 ± 4.5 [c,d]	124.7 ± 1.2	−9.74%

[c,d] Significant difference ($P < 0.05$) from control and indomethacin (form α), respectively.

initial in vitro dissolution rate order, i.e. indomethacin : PEG coprecipitate > indomethacin : PVP90 coprecipitate, suggesting the in vivo absorption rate was reflected by the dissolution rate over the first 20–30% of drug released.

The PVP90 coprecipitate produced significantly lower serum levels than the pure drug due to an increase in viscosity of the gastrointestinal contents resulting in retardation of drug absorption. However, the administered suspension of the PEG coprecipitate was non-viscous (Table 2), suggesting that retardation of drug absorption was probably due to the formation of a PEG : indomethacin complex. This complex, although enhancing dissolution rate, could have been too large to cross the intestinal membrane which would mean that drug absorption depended upon the dissociation of the complex.

TABLE 2

VISCOSITY DETERMINATION OF ADMINISTERED SUSPENSIONS OF INDOMETHACIN : POLYMER COPRECIPITATES (WHICH IS EQUIVALENT TO 0.45 g OF POWDER IN 100 ml OF WATER)

Sample	Viscosity (cP) at a shear rate of 698 s^{-1}	
	22°C	37°C
Water	3.07	2.98
80 : 20 indomethacin : PVP90 coprecipitate	3.97	3.18
80 : 20 indomethacin : PEG6000 coprecipitate	3.04	2.89
80 : 6 : 14 indomethacin : PVP90 : PVA coprecipitate	3.77	3.12

The drug serum levels produced by the indomethacin : PVP90 : PVA coprecipitate were not significantly different from those produced by the indomethacin : PVP90 coprecipitate at each blood sampling time and consequently, the incidence of ulceration produced from both coprecipitates were not significantly different from one another (Table 1). Thus drug absorption was retarded equally for both coprecipitates. This would suggest that either:

(1) PVA may have altered in some manner in the gastrointestinal tract to increase drug absorption, either by enzymatic attack to release the enclosed drug particles, or it may have become more soluble in biological fluids. However, little work has been done on oral administration of PVA to be able to comment on possible gastrointestinal effects on the molecule. Or,

(2) the viscosity increase in the diffusion layer of the PVP90 coprecipitate may have retarded drug diffusion to the same extent as low PVA solubility retarded drug diffusion in the PVA coprecipitate.

Thus it is apparent that modification of indomethacin dissolution rate by incorporation into dispersion systems of different polymer agents, demonstrates that the in vivo results are not always comparable with the in vitro dissolution results. This is due to factors, such as formation of

drug complexes too large to cross the intestinal membrane, which cannot be foreseen in in vitro dissolution experiments.

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