J. Pharm. Pharmacol. 1981, 33: 561–564
Received March 2, 1981

0022–3573/81/090561–04 $02.50/0

Comparison of the in vitro dissolution behaviour of various indomethacin formulations with their in vivo bioavailability

J. S. ROWE* AND J. E. CARLESS

Department of Pharmaceutics, The School of Pharmacy, 29/39 Brunswick Square, London WC1N 1AX, U.K.

The effects of the core to colloid wall ratio and particle size of the core on the in vitro release of indomethacin microcapsules prepared by the gelatin-acacia complex coacervation process have been examined. All formulations showed a zero order release pattern after an initial burst phase. The release rate increased with increasing core to coat ratios and decreasing particle size of core material. In vivo plasma level studies showed no difference in bioavailability between different microcapsule formulations or a conventional indomethacin capsule. In vitro release studies on a commercially available sustained release formulation of indomethacin (Indocid R) were slower than any of the microcapsule formulations and exhibited a $\sqrt{t}$ dependence indicating a diffusion controlled process from a matrix formulation. In vivo studies show this formulation to have a longer, smoother plasma concentration than the microcapsule formulation, and to avoid high initial peak values of drug. Thus from the in vitro studies a sustained release effect was not unexpected but the in vitro differences between the microcapsule products were not paralleled by the in vivo behaviour. These results illustrate some of the problems in extrapolation of in vitro dissolution data to the in vivo situation.

The influence of dosage form on the incidence of side effects encountered with indomethacin has been well illustrated (c.f. Michotte & Wanters 1964; Wanka & Dixon 1964; Smyth 1965; Boardman & Hart 1967). Recently Rowe (1980) has reported that a microencapsulated formulation of indomethacin significantly reduced the incidence and severity of gastrointestinal side effects compared with a commercially available capsule (Indocid) when given in normal clinical doses. Carless & Rowe (1981) have also shown differences in central nervous activity utilizing Critical Flicker Fusion (CFF) tests between these two formulations when given in equivalent dosage. In an attempt to explain these gastrointestinal and c.n.s. effects, the in vitro dissolution behaviour of various microencapsulated formulations has been examined and compared with a commercially available sustained release formulation of indomethacin (Indocid R). In vivo studies were also conducted to compare the bioavailability parameters of two microencapsulated formulations, Indocid R, and a conventional indomethacin capsule (Indocid). These results are now reported.

MATERIALS AND METHODS

Indomethacin. The indomethacin raw material used in the preparation of the microcapsules was obtained from Merck Sharp & Dohme Ltd, Hoddesdon, Herts., U.K. The median particle size by weight was 6 μm as determined by Coulter Counter analysis. A range of particle sizes of indomethacin for microencapsulation was prepared, based on the crystallization technique described by Nyvlt (1973).

Indomethacin capsules. Indomethacin conventional capsules and sustained release capsules (Indocid 25 mg and Indocid R 75 mg, Merck Sharp & Dohme Ltd) were used as received.

Microencapsulated indomethacin. Indomethacin microcapsules of varying core-to-colloid coat ratios were prepared using a gelatin acacia complex coacervation procedure essentially as described by Nixon & Nouh (1978). The indomethacin content of the microcapsules was determined as described by Carless & Rowe (1981).

In vitro dissolution of indomethacin formulations. The method was based on the Beaker method of Levy & Hayes (1960) with a continuous flow system. The dosage form, either microcapsules or sustained release indomethacin (Indocid R) equivalent to 75 mg of indomethacin B.P. was placed in a dissolution flask containing 500 cm^3 of distilled water pH 5·6 at 37 °C ± 1 °C and stirred with a paddle at 100 rev min^{-1}. Sink conditions were maintained by constantly replacing the dissolution fluid with fresh distilled water at 37 °C at the rate of 2 cm^3 min^{-1}. The effluent was assayed for indomethacin content

* Correspondence to: Hibrow Pharmaceuticals, 135 Eign Street, Hereford, U.K.

by continuous u.v. monitoring at 320 nm. Dissolution studies on microcapsules with varying particle size cores were made using Sorensen's buffer pH 6·8 as it was anticipated that rates would be very slow in distilled water, pH 5·6.

Bioavailability studies on the indomethacin formulations

The first phase of this study compared two microcapsule formulations with a drug core to colloid coat ratio of 1:5 and 1:20 designated NP1 and NP2 respectively. Healthy adult male subjects were randomly allocated single doses or one Indocid capsule 25 mg. NP1 or NP2 microcapsule formulation 25 mg. In the second phase the microcapsule formulation NP2 was compared with Indocid R. Each subject was randomly assigned single oral doses of three NP2 25 mg capsules or one capsule of Indocid R 75 mg. In both studies, a controlled, balanced and randomized crossover (within subject) design was adopted using six subjects in each phase of the study. The subjects remained fasted for at least 3 h after administration of the dose, but water was freely available. There was no restriction on food intake during the period after the 3 h fasting. Venous blood samples were taken immediately before the dose and at 0·5, 1·0, 1·5, 2·0. 4·0, 8·0, 12·0 and 24·0 h post dosing. Plasma concentrations of indomethacin were assayed using an h.p.l.c. technique based on the method of Skellern & Salole (1975). In each case the following pharmacokinetic characteristics were determined by the computer program of Saunders & Naturen (1973): The area under the plasma concentration time curve (AUC 0–24 h); time to reach peak plasma concentration (t_{max}); peak height (Cp_{max}) and elimination rate constant (k_{el}). Statistical analysis (Rowe 1980) utilized the *t*-test for dependent means (paired *t*-test) for analysis of AUC mean data, the Wilcoxon Rank—Sum test for t_{max} and the *t*-test for independent means for analysis of differences in Cp_{max}. A probability value (*P*) of 0·05 or less was considered significant.

RESULTS

In vitro dissolution studies

Dissolution studies on four batches of microcapsules with varying drug to colloid ratios prepared with finely powdered core material (mean particle size 6 μm) are shown in Fig. 1. The sustained release formulation (Indocid R) exhibited a release pattern with $\sqrt{t}$ dependence illustrating release from a typical matrix formulation as described by Higuchi (1963) giving a straight line.

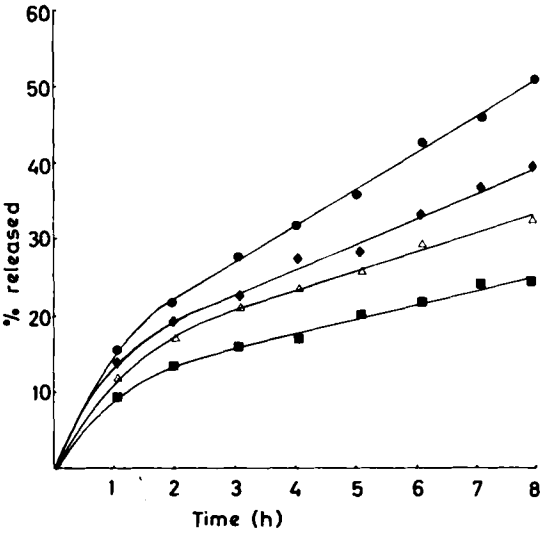

FIG. 1. Dissolution profile of indomethacin microcapsules. Drug: colloid ratio 1:2, ● 1:5 ◆ 1:10 △ 1:20 ■, Medium: Distilled water pH 5·6.

Dissolution results of microencapsulated formulations of varying indomethacin core sizes in Sorensen's buffer pH 6·8 are expressed as the time for 90% of the drug to be released (t_{90}) (Table 1).

Bioavailability studies

Mean plasma concentrations of indomethacin following the administration of the two microcapsule formulations are compared with a conventional non-sustained release indomethacin formulation (Indocid 25 mg) in Fig. 2.

A significant difference was not obtained between the three formulations in any of the three pharmacokinetic characteristics indicating they may be considered bioequivalent (Table 2). The plasma half lives of elimination of indomethacin have been calculated from the terminal post-absorptive phase of the plots of log plasma drug concentration against time. Mean plasma half lives for Indocid, NP1 and NP2 were 2·98, 2·64, 2·28 h^{-1} respectively and were not significantly different.

Table 1. Effect of core size on t90 of indomethacin microcapsules. Medium: Sorensen's buffer, pH 6·8.

Mean particle size of core (μm)	Time for 90% release (t90) h
58	2·0
69	2·2
82·5	2·32
115	2·42
137·5	2·6

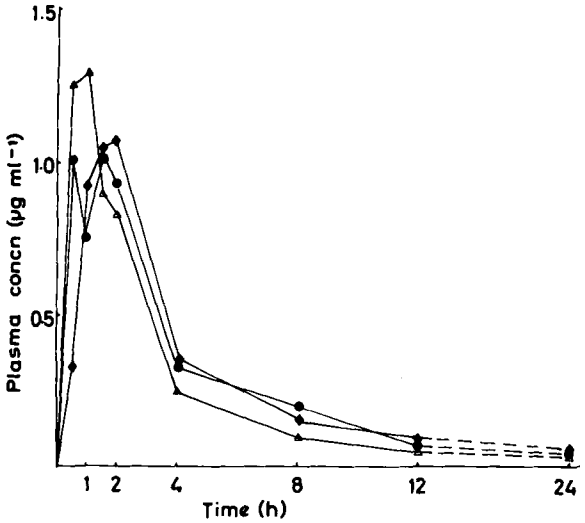

FIG. 2. Mean plasma concentrations in 6 adult male subjects after single oral dosing with 3 formulations of indomethacin. △ NP1 capsule 25 mg. ● Indocid capsule 25 mg. ◆ NP2 capsule 25 mg.

In the second phase of the study, the bioavailability characteristics of sustained release indomethacin (Indocid R) were compared with those of an equivalent dose of the NP2 microcapsule formulation (75 mg). Mean plasma concentrations of the two formulations are shown in Fig. 3 and the pharmacokinetic parameters of the two formulations determined as described previously, are in Table 3.

Statistical analysis showed no difference between the AUC values of the two formulations. However, comparison of t_{max}, showed that the Indocid R had a significantly greater t_{max} than the NP2 formulation. A significant difference was also shown in the values for C_{max} and the half life of elimination, in that the peak values of NP2 were significantly higher than those of Indocid R, and the half life of Indocid R was significantly longer than the NP2 formulation.

DISCUSSION

The release of indomethacin from microcapsules shows a typical zero order pattern after an initial burst phase which is probably due to a small percentage of malformed microcapsules or to drug trapped in the wall. This high initial rate of release is common to microcapsule formulations as illustrated by studies on steroid release from microcapsules (Gardner et al 1976) and the release of naltrexone from polylactic acid microcapsules (Thies 1976). The dissolution rate is related to the core to colloid coat

Table 2. Summary of pharmacokinetic data in 6 subjects after single dose oral administration of two indomethacin microcapsule formulations NP1 and NP2 and Indocid 25 mg.

	Indocid	σ	NP1	σ	NP2	σ
Peak height (Cp_{max}) μg ml^{-1}	1·81	0·80	1·61	0·60	1·46	0·26
Time to reach peak height(t max) h	1·0	0·80	1·10	0·85	1·60	1·0
Ratio of AUC's		σ				
Ind: NP1	1·15	0·26				
Ind: NP2	1·16	0·43				
NP1: NP2	1·01	0·30				

ratio (Fig. 1) and to the particle size of the core material itself (Table 1). It was observed that little encapsulation of core took place when the particle size exceeded 150 μm. In fact, the encapsulation process was very inefficient for all particle sizes except the microfined core material. The in vitro release pattern of the sustained release indomethacin (Indocid R) was much slower than any of the microcapsule formulations.

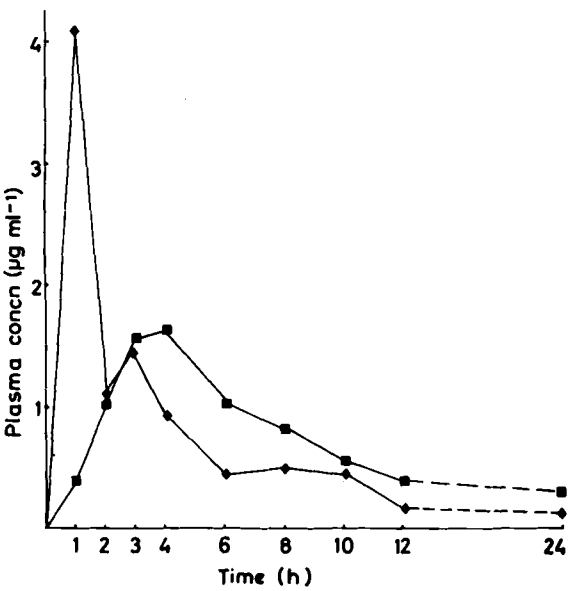

FIG. 3. Mean plasma concentrations in 6 adult male subjects following oral administration of microencapsulated indomethacin NP2, 75 mg ◆ and Indocid R 75 mg ■.

Despite differences in the in vitro dissolution rate, no differences were observed in vivo between the microcapsules or with a conventional indomethacin formulation (Indocid 25 mg). Comparison of a microcapsule formulation (NP2) with the commercially available sustained release indomethacin (Indocid R, 75 mg) showed the total amount of drug absorbed to be the same in each case. However, Indocid R has a longer, smoother plasma concentra-

Table 3. Summary of pharmacokinetic data in 6 subjects after single dose oral administration of Indocid R, 75 mg and indomethacin microcapsule formulation NP2, 75 mg.

	NP2		Indocid R	
	Mean	σ	Mean	σ
Peak height (Cp_{max}) μg ml^{-1}	4·88	1·57	1·88	0·51
Time to reach peak height(t_{max}) h	1·50	1·0	4·25	1·26
AUC(g ml^{-1} h)	13·03	1·91	13·0	1·71
$t_{1/2}$ (h)	4·10	1·99	7·39	2·45
k_{el}	0·20	0·08	0·10	0·04

tion than the NP2 formulation and high initial peak values of drug in plasma are avoided. Thus from the in vivo dissolution results a sustained release effect was predictable. The significance of the avoidance of high initial peak plasma values on the incidence of side effects or therapeutic efficacy has yet to be established. The reduction in observed side effects both gastrointestinal and central on administration of microencapsulated indomethacin compared with a conventional capsule thus could not be explained by in vivo plasma concentration profiles as might have been predicted from in vitro dissolution data. Microencapsulation may be a means of providing a method of administering indomethacin in a solid form and achieving a wide dispersion in the gastrointestinal tract by altering the surface characteristics of the hydrophobic drug. Any direct contact of solid drug with the mucosal wall would be avoided by inward diffusion through the capsule wall of the fluids of the g.i. tract, followed by drug dissolution and outward diffusion of drug in solution.

Acknowledgements

This work was supported in part by a grant from Nicholas Laboratories Ltd. Thanks are due to Dr Mansel Aylward, Simbec Research Ltd for providing facilities for this study, and to Professor L. Saunders for helpful discussions on computer programs.

REFERENCES

Boardman, P. L., Hart, D. F. (1967) Ann. Rheum. Dis. 26: 127–132

Carless, J. E., Rowe, J. S. (1981) J. Pharm. Pharmacol. in the press

Gardner, D. L., Fink, D. J., Patanus, A. J., Baytos, W. C., Hassler, C. (1976) in: Paul, D. R., Harris, F. W. (eds) Controlled release polymeric formulations. ACS Symposium 33, pp 171–181

Higuchi, T. (1963) J. Pharm. Sci. 52: 1145–1149

Levy, G., Hayes, B. A. (1960) New. Eng. J. Med. 21: 1053–1058

Michotte, L. J., Wanters, W. (1964) Acta Rheum. Scand. 10: 273–280

Nixon, J. R., Nouh, A. (1978) J. Pharm. Pharmacol. 30: 533–537

Nyvlt, J. (1973) in: Smith, A. L. (ed.) Particle growth in suspensions. Symposium on particle growth in suspensions, Society of Chemical Industry 1972 pp 131–141, Academic Press.

Rowe, J. S. (1980) Ph. D. thesis, University of London

Saunders, L., Naturen, T. (1973) J. Pharm. Pharmacol. 25: Suppl. 44P

Skellern, G. G., Salole, E. G. (1975) J. Chromatogr. 114: 483–485

Smyth, C. J. (1965) Arthritis Rheumatism 8: 921–942

Thies, C. (1976) in: Paul, D. R., Harris, F. W. (eds) Controlled release polymeric formulations ACS Symposium 33: pp 190–194

Wanka, J., Dixon, A. S. (1964) Ann. Rheum. Dis. 23: 288–294