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Use of extrusion-spheronization to develop an improved oral dosage form of indomethacin

P.B. Deasy *, M.F.L. Law

Department of Pharmaceutics, Trinity College, University of Dublin, Shrewsbury Road, Dublin 4, Ireland

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Abstract

Two new pelletized formulations of indomethacin were developed and compared against pellets from the proprietary product, Indocid-R. Extensive dissolution testing involving pH-shift and topographical profiling showed that the new product containing polyvinylpyrrolidone had slightly faster in vitro release than the commercial product, but surprisingly the other new product containing sodium lauryl sulphate had reduced drug release. The cause of the anomalous result was shown by solubility studies and scanning electron microscopy to be related to the ability of the wetting agent to promote fragmentation of the microcrystalline cellulose used as spheronization aid into small crystallites, retarding drug release. The two new products had improved sphericity compared to the proprietary product when examined by image analysis. However, on in vivo testing in dogs, the new product containing sodium lauryl sulphate had the highest bioavailability of the three preparations examined due to its effect as a penetration enhancer. © 1997 Elsevier Science B.V.

Keywords: Extrusion-spheronization; Indomethacin; Polyvinylpyrrolidone; Sodium lauryl sulphate; Dissolution testing; In vivo dog studies

1. Introduction

Indomethacin is defined as the crystalline Form I (thermodynamically stable γ-form), but has been reported to exist in a number of other polymorphic forms (Yamamoto, 1968) having lower melting point and stability, and higher solubility. It is a non-steroidal anti-inflammatory drug (NSAID) used in the treatment of rheumatoid arthritis, osteoarthritis, alkylosing spondylitis and other disorders. Its most common side-effects are cerebral and gastrointestinal disturbances, which are dose-dependent and related to the plasma spike produced particularly by its conventional oral dosage forms (Alvan et al., 1975). In an attempt to overcome the problem, reduce dosing frequency and aid compliance, a number of con-

* Corresponding author. Tel.: + 353 1 2693333; fax: + 353 1 2696457.

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trolled-release dosage forms have been introduced. The brand-leader product in Ireland is Indocid-R capsules containing 75 mg of indomethacin in retard-release pellet form and intended to be administered once or twice daily. Quinn et al. (1993) have shown that the plasma profile produced by this product in humans is far from ideal, still exhibiting a sizeable peak about 2–3 h after dosing.

As indomethacin is a poorly wettable and water soluble drug, approaches applicable to designing sustained-release dosage forms for more water soluble drugs are likely to result in products with poor bioavailability, when compared to the brand-leader as confirmed by Quinn et al. (1993). Chowdary and Babu (1994) have observed that the in vivo absorption of the drug is dissolution rate limited. Komiyama et al. (1982) have reported that several commercial controlled-release preparations of indomethacin are not of equal bioavailability. Aoyagi et al. (1985) noted also that subjects with reduced gastric acidity produced higher plasma levels of indomethacin, presumably due to the greater solubility of the drug at higher pH. The animal model used in the study reported in the present publication is the beagle dog, which is known to have a higher gastric and intestinal pH and longer gastric residence time than humans (Lui et al., 1986) with larger intra-subject variation in gastric acidity (Ogata et al., 1985), which considerations must be taken into account when intrepreting the results of the in vivo studies presented. The aim of this study was: (i) to assess the in vitro release profile of a number of indomethacin pellet formulations previously developed by us (Law and Deasy, 1996) using optimization experiments with canonical analysis; and (ii) to compare selected products in vivo against Indocid-R. The selection criteria for the chosen products were: (i) in vitro dissolution profile showing more than 90% drug release in 6 h, with drug release rate greater than or comparable to the brand-leader; (ii) high yield in the desired size range 850–1180 μm ($>80\%$); and (iii) acceptable sphericity (>0.80) to ensure free flow with uniform packing into hard gelatin capsule shells in order to obtain accurate dosing.

2. Materials and methods

2.1. Materials

Ethylacetate-HPLC, *ortho*-phosphoric acid, sodium acid phosphate, sodium phosphate (Riedel de Haen), hydrochloric acid (BDH), Indocid-R capsules—batch no. 922476 (Thomas Morson), indomethacin (20 μm, Industrial Chimica Farmaceutica, Italy), lactose alpha monohydrate (Granulac 200 mesh, Meggle), mefenamic acid, sodium lauryl sulphate (SLS; Sigma), methanol-HPLC (Rathburn), microcrystalline cellulose (MCC; Avicel PH-101, FMC), polyvinylpyrrolidone (PVP; Povidone K24-26, GAF), and glass-distilled water were used. All reagents were GPR unless otherwise indicated.

2.2. Extrusion-spheronization process.

Powders were pre-blended for 10 min in a planetary mixer (Kenwood), wetted by gradual addition of the required volume of water and stored in a sealed container for at least 12 h to ensure uniform hydration of the mix, prior to extrusion through a 1-mm perforated screen using a gravity-fed cylinder extruder (Alexanderwerk GA 65). The extrudate was spheronized on a 120-mm diameter spheronizer (Caleva) using a cross-hatch friction plate.

2.3. Dissolution studies

Samples of pellets containing drug were agitated at 100 revs./min in 1 l pH 2.0 medium for 2 h followed by rapid change to pH 6.8 medium at 37°C for 4 h in an EP dissolution basket assembly (Erweka DT6), where adequate sink conditions existed during the pH-shift dissolution test. Pellets were subject also to similar testing for 6 h at pH 2.0, 3.2, 4.4, 5.6, 6.8 and 8.0 to provide data for the construction of topographical and other dissolution profiles. Five ml samples were withdrawn periodically with immediate replacement of the dissolution medium, and following filtration through a 0.45-mm filter (Gelman), were assayed by UV spectroscopy (Shimadzu UV-160) at 318 nm.

2.4. In vivo studies

A licence under the Cruelty to Animals Act was obtained as legally required in Ireland. A panel of six fasted beagle dogs (three male and three female) was used, whose plasma drug levels were compared in a single-dose randomized cross-over study following administration of two new pellet formulations and the pellets removed from Indocid-R capsules at idential assayed dosage of 2 mg/kg, filled into clear hard gelatin capsules (size four). The Indocid-R preparation contains both white and blue coloured pellets in the ratio of 85:15% by weight. The white pellets assayed with a drug content 64 times greater than the white pellets and the appropriate mix of both types was administered. A two-week washout period was allowed between consecutive treatments. To limit degradation, plasma samples were stored at −20°C prior to assay. Samples (20 ml) extracted with ethylacetate from acidified plasma, containing drug and mefenamic acid as internal standard, were injected onto the main column (25 × 0.46 cm) protected by a guard column (1 × 0.3 cm), both packed with Ultratechsphere C18, 5 μm (HPLC Technology). The filtered and degassed mobile phase consisting of di-sodium hydrogen phosphate dodecahydrate 0.1% in water/methanol 35:65, adjusted to pH 7 with aqueous *ortho*-phosphoric acid 5%, was pumped at a flow rate of 1.0 ml/min. A Waters liquid chromatograph equipped with a Waters 484 tunable absorbance detector set at 254 nm was used. Output from the detector was plotted and analysed for peak area using a Waters data module M730 integrator. The retention times of indomethacin and mefenamic acid were 6.45 and 7.80 min, respectively. The assay was validated for precision, linearity, recovery and specificity. Each sample was injected in duplicate and the entire extraction and analysis was repeated once.

2.5. Solubility studies

The solubility of indomethacin was determined in various aqueous solvent systems by placing an excess of drug (0.2 g) into 10 ml, sealed into glass ampoules with or without the inclusion of microcrystalline cellulose, and shaking in a water bath (Gallenkamp) at 37°C. Samples were removed at 24 and 48 h, filtered through a 0.2-μm membrane filter (Gelman) and diluted prior to drug assay by UV spectroscopy (Shimadzu UV-160). Studies were performed in triplicate and the mean result presented.

2.6. Scanning electron microscopy

Samples from batches of pellets were mounted on aluminium stubs using double-sided sticky tape, vacuum coated with gold film (Polaron SC 500 sputter coater) and examined using a scanning electron microscope (Leo Stereoscan S-360).

2.7. Pellet shape analysis

The sphericity of pellets was determined using an image analysis system (Quantimet 520, version 4.0, Cambridge Instruments), which calculated derived parameters using the magnified image of pellets from a microscope (Ergolux). A random sample of 200 pellets approx from each batch of product was examined and a roundness function was calculated as follows:

$$\text{Roundness factor} = \frac{P_m^2}{4\pi A}$$

where P_m is the perimeter length and A is the projected area. A perfectly round pellet would have a value of 1.0 irrespective of size and the value would tend towards 10.0 for pellets that were progressively non-spherical. As such, a decrease in the roundness factor would imply an increase in pellet sphericity. However in order to facilitate a correlation between increasing sphericity value and increasing pellet roundness, the reciprocal of the roundness factor was calculated and termed the 'sphericity factor'.

3. Results and discussion

3.1. Dissolution studies

Dissolution studies were carried out on a range of formulations hydrated with 25% water as

shown in Table 1, which in previous studies (Law and Deasy, 1996) were all shown to give high yield of spherical pellets. The results are shown in Fig. 1 compared to Indocid-R. IND 1 displayed the fastest release of indomethacin, with increasing PVP content being associated with increasing rate of drug dissolution. This is in agreement with the findings of others (Corrigan et al., 1985; Najib and Suleiman, 1985), who have shown that PVP retards the conversion of indomethacin into the crystalline form, favouring the formation of an amorphous form having enhanced dissolution. The presence of PVP in the dissolution medium also increases the solubility of both the crystalline and amorphous forms of indomethacin due to the formation of a soluble complex between the two materials. A slight discolourization of pellets containing PVP was observed, which was associated with the formation of other polymorphic forms of indomethacin that are known to be coloured yellow and of higher solubility. However, surprisingly an increase in SLS content was associated with an unexpected reduction in the dissolution rate, when normally it would be expected to increase drug dissolution by aiding wetting, deflocculation and micellar solubilization (Shah et al., 1989), and this anomalous finding is investigated in the next section of this paper.

As IND 1, IND 2, IND 4, IND 5 and IND 7 had faster release profiles than Indocid-R in the preliminary study, these products were selected for more extensive dissolution testing over a wider pH range relevant to GIT conditions, compared to the brand-leader. Indomethacin in a weak acid (pK 4.5, O'Brien et al., 1984) and consequently at low pH it is less ionized and soluble. This trend is

Table 1
Composition (%) of various formulations, hydrated with 25% added water, used in dissolution studies

Key	Indomethacin	PVP	SLS	MCC	Lactose
IND 1	30	1.0	0	19.0	50.0
IND 2	30	1.0	1.25	19.0	48.75
IND 3	30	1.0	2.50	19.0	47.50
IND 4	30	0.5	0	19.5	50.0
IND 5	30	0.5	1.25	19.5	48.75
IND 6	30	0.5	2.50	19.5	47.5
IND 7	30	0	0	20.0	50.0
IND 8	30	0	1.25	20.0	48.75
IND 9	30	0	2.5	20.0	47.5

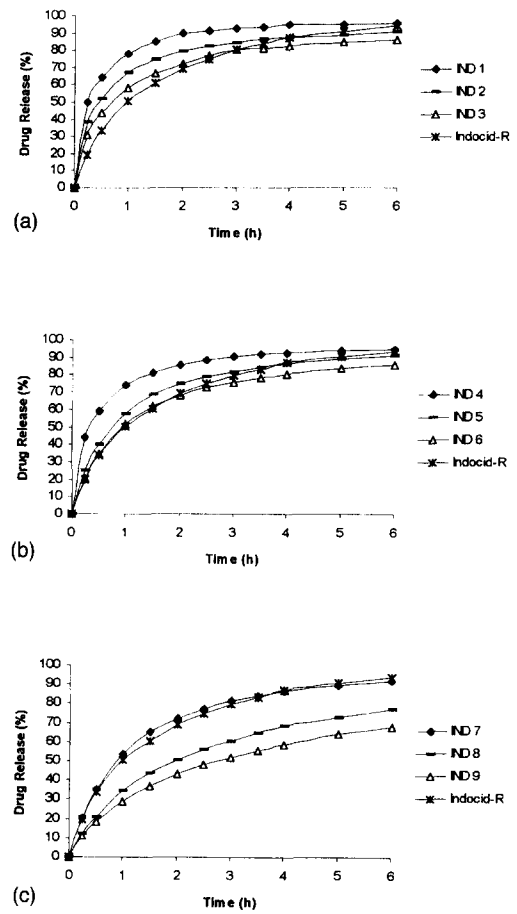

Fig. 1. Dissolution of indomethacin from pellets in pH 6.8 for 6 h at 37°C.

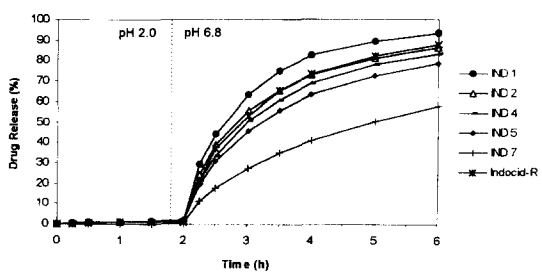

Fig. 2. pH-Shift dissolution of indomethacin from pellets in pH 2.0 for 2 h followed by pH 6.8 for 4 h at 37°C.

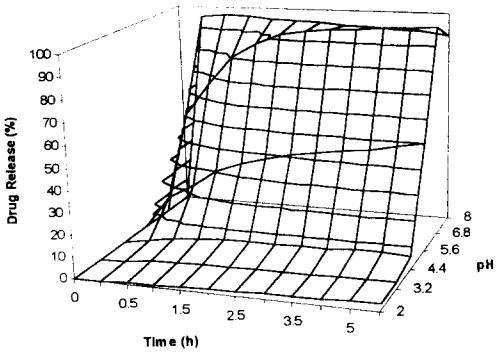

Fig. 3. Topographical dissolution profile over the pH range 2.0–8.0 for IND 1.

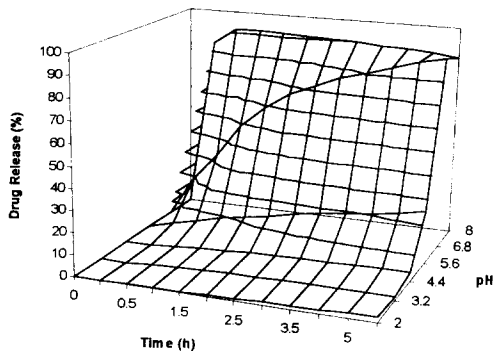

Fig. 5. Topographical dissolution profile over the pH range 2.0–8.0 for Indocid-R.

apparent in Fig. 2 which shows the results of a pH-shift dissolution study for the various formulations. The dissolution of indomethacin from IND 1 was found to be the highest, with more than 90% drug released in 6 h. IND 2 had a dissolution profile similar to that for Indocid-R with 85% drug released in 6 h. IND 4, IND 5 and IND 7 had an increasingly lower percentage drug released with time compared to the proprietary product.

The results of more extensive dissolution testing on the selected formulations, IND 1, IND 2 and Indocid-R are shown in the topographical plots shown in Figs. 3–5, respectively. The release of indomethacin from IND 1 is enhanced at all pHs compared to Indocid-R, which shows a very similar complex release profile to IND 2. The plots also confirms that the inclusion of 1.25% SLS in IND 2 compared to its absence in IND 1 caused an overall reduction in drug release. However, IND 2 containing SLS had enhanced dissolution at low pHs up to 4.4, presumably due to the excipient raising the pH of the micro-environment. These three formulations were chosen for in vivo studies in dogs because of similarity in release profile to the commercial product and in order to investigate if the unexpected in vitro retardant effect of SLS would be reproduced in vivo. Products IND 4, 5 and 7 in particular were not subject to in vivo testing as we had previously shown (Quinn et al., 1993) that product with significant retard effect on dissolution testing compared to Indocid-R, had poor comparative bioavailability when tested in humans.

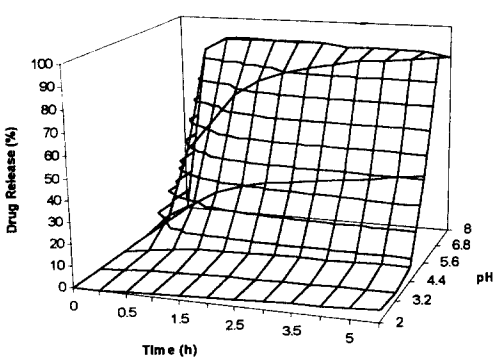

Fig. 4. Topographical dissolution profile over the pH range 2.0–8.0 for IND 2.

3.2. Effect of SLS on indomethacin release from pellets

In an attempt to investigate the unexpected apparent reduction in drug release caused by the inclusion of the surfactant SLS in the formulation, compared to the enhancing effect of PVP, solubility studies and scanning electron microscopy were performed on selected systems.

The solubility of indomethacin was determined at 37°C in pH 6.8 McIlvaine buffer, 1% PVP in the buffer, 1% SLS in the buffer and 1% PVP plus 1% SLS in the buffer, all with or without the presence of 19% MCC. Equilibrium saturated solubility (C_s) was achieved after 48 h (Table 2). The inclusion of 1% PVP was observed to increase the

Table 2
Saturated solubility (C_s) of indomethacin in pH 6.8 McIlvaine buffer at 37°C for 48 h in the presence of the stated concentration of additives

System	PVP (%)	SLS (%)	MCC (%)	C_s (mg/ml)	S.D. (mg/ml)
A	0	0	0	0.8002	0.0012
B	1	0	0	1.1257	0.0029
C	0	1	0	3.6324	0.0039
D	1	1	0	3.9108	0.0041
E	0	0	19	0.8008	0.0001
F	1	0	19	1.1236	0.0003
G	0	1	19	3.4098	0.0040
H	1	1	19	3.7800	0.0030

C_s of indomethacin from 0.80–1.25 mg/ml in the absence of MCC. Likewise 1% SLS inclusion increased C_s of indomethacin by 4.5 times to 3.63 mg/ml and there appeared to be an additive increase in solubility to 3.63 mg/ml when both PVP and SLS were used together, indicative of no interaction between the two additives. However, when 19% MCC was added, using the Student's t-test (assuming equal variance) and single-factor ANOVA at 0.05 level of significance, there was found to be a significant reduction in indomethacin solubility when SLS was present alone or in combination with PVP, but not with PVP alone or caused by the addition of MCC. It was also noted that when SLS was present with MCC, the reduction in indomethacin solubilty was progressive with time, C at 24 h for systems G and H being 3.6265 and 3.9016 mg/ml respectively.

In an attempt to explain the unusual solubility data, a model system involving treatment of MCC with aqueous 5% SLS solution for 24 h to simulate the duration of hydration prior to extrusion–spheronization was prepared, and after drying was examined by SEM as shown in Fig. 6. Porous aggregates of microcrystals are shown in the electron micrograph of previously hydrated MCC. However their treatment with SLS solution caused disintegration into much smaller needle-shaped particles and fragments thereof. Submicroscopic swelling of individual cellulose particles probably also occurred. These phenomena would contribute to the hindered release/solubility of indomethacin by SLS reported above, by forming a more effective retardant matrix and by providing a greater surface area of cellulosic material for drug binding.

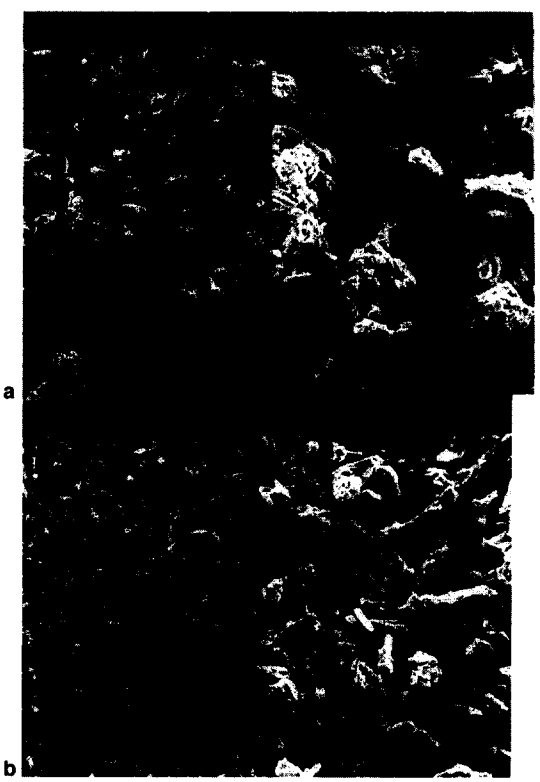

Fig. 6. Scanning electron micrographs of (a) MCC and (b) MCC treated with 5% SLS (magnification × 50, zoom × 4).

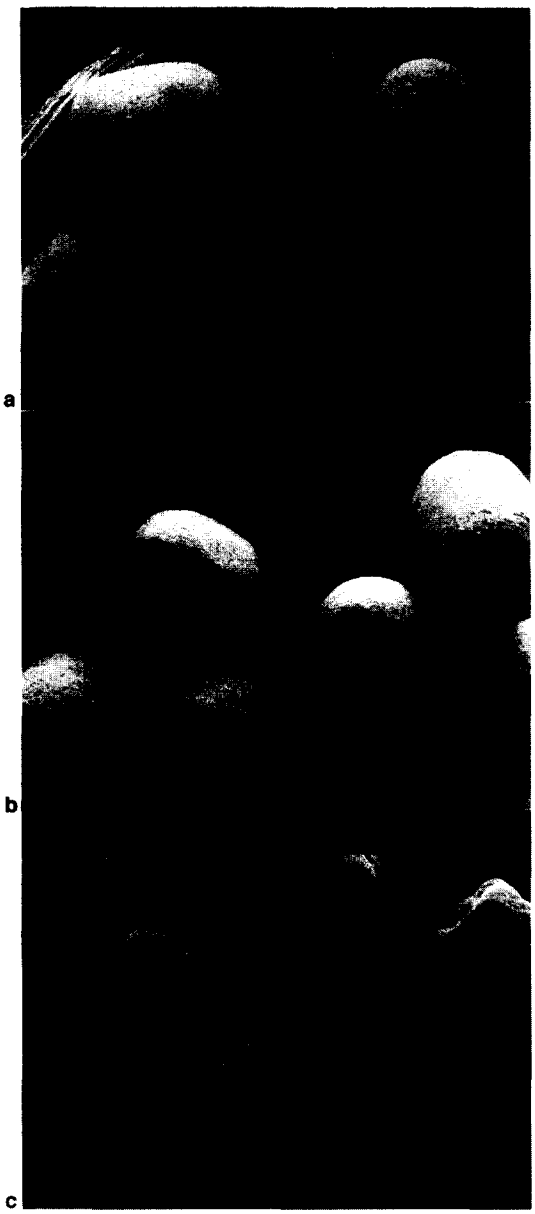

Fig. 7. Scanning electron microscopy of pellets from (a) IND 1, (b) IND 2, and (c) Indocid-R (magnification × 25).

3.3. Scanning electron microscopy and image analysis of pellets

Samples of pellets from typical formulations developed and Indocid-R are shown in Fig. 7. Whereas the new formulations were both reasonably well-rounded and smooth, the commercial product shows unevenness in shape and surface with an overall appearance of a poorly spheronized product. The inclusion of 1.25% SLS in IND 2 appeared to impart the extra plasticity required to produce an improvement in sphericity as is apparent in Fig. 7, compared to IND 1. The improved rounding of IND 2 compared to IND 1 was confirmed by image analysis studies, which gave sphericity factors of 0.87 and 0.85, respectively. The corresponding factor for Indocid R was 0.79 indicating poorer sphericity in the pellets of the proprietary product.

3.4. In vivo studies

The objective of the in vivo studies in six dogs was to compare the bioavailability and other pharmacokinetic parameters of the two selected formulations, IND 1 and IND 2, with the brand-leader proprietary product, Indocid-R, following oral administration at equivalent dose in a random cross-over study. The in vitro release profile for IND 1 was slightly faster than IND 2 and the commercial product, both of which were similar. Fig. 8 shows that mean plasma profile obtained following acute dosing with the three products and relevant pharmacokinetic parameters calculated from the data are shown in Table 3. The three plots show evidence of enterohepatic circulation, which has been observed repeatedly in humans for the drug. Also the sharp peak at the beginning of the Indocid-R profile was similar to

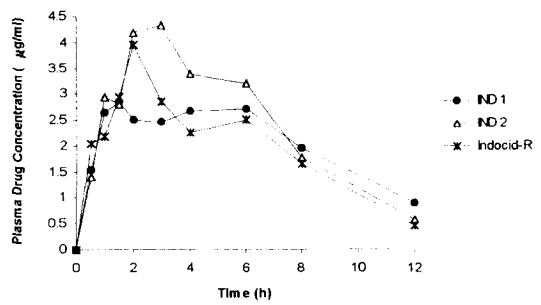

Fig. 8. Mean plasma profile of indomethacin in dogs ($n = 6$) following acute dosing with the formulations as indicated in the key.

Table 3
Mean pharmacokinetic parameters for the in vivo study

Parameter	IND 1	IND 2	Indocid-R
C_{max}	3.35	4.61	4.10
$AUC_{0\text{-}12\ h}$	24.9	29.0	23.6
F	1.06	1.24	—
t_{max}	3.0	3.0	2.2
$C_{max}/C_{12\ h}$	4.2	27.3	18.8

$AUC_{0\text{-}12\ h}$, area under the plasma concentration-time plot from 0–12 h in μg/ml·h calculated by the trapezoidal rule.
F, relative bioavailability compared to Indocid-R.
C_{max}, maximum plasma concentration in μg/ml.
t_{max}, time to maximum plasma concentration in h.
$C_{12\ h}$, plasma concentration at 12 h in μg/ml.

that reported in humans (Verbesselt et al., 1983; Quinn et al., 1993) The mean peak concentration for both IND 2 and Indocid-R were found to be significantly higher than for IND 1 ($P < 0.05$). Maximum mean plasma concentration and bioavailability ($AUC_{0\text{-}12\ h}$) were observed with IND 2, which preparation also had a significantly higher bioavailability (F) compared to Indocid-R or IND 1. Though the observed bioavailability of IND 1 was greater than Indocid-R, the difference was not significant. The higher bioavailabilty of IND 2 could be related to its enhanced dissolution rate under the low pH conditions of the stomach, as observed in dissolution studies reported above. Despite the greater in vitro retarded drug release from IND 2 compared to the other two preparations, the inclusion of SLS in its formulation has acted as a penetration enhancer in vivo, aiding drug absorption (Barry, 1987). Whereas the three products tested have sustained-release properties, the maximum effect as indicated by minimum peak to trough ratio (C_{max}/C_{12} h) is produced by administration of IND 1.

No evidence of adverse reactions during the study was observed in any of the dogs.

4. General discussion

The spherical pellets obtained in this project were easily produced in high yield by extrusion–spheronization once process variables had been optimized. In contrast, when Quinn et al. (1993) attempted to produce indomethacin loaded pellets by the time-consuming and highly-skilled process of drug loading non-pareil seeds using PVP in isopropanol as liquid adhesive (Deasy, 1984), cores with very irregular spiky appearance were obtained, precluding further coating or use. The phenomenon was attributed to partial dissolution of the drug in the organic solvent in which it is moderately soluble, followed by deposition on the forming cores as amorphous whiskers (spikes) with PVP as the solvent was evaporated, the drug partially recrystallizing from the glassy state to the γ-form. Attempts by these workers to produce drug-loaded cores of indomethacin using an aqueous solution of PVP proved unsuccessful as the liquid adhesive produced over-wetting and localized clumping of drug on the surface of inert seeds.

In general, there was a poor corelation between in vitro dissolution and in vivo bioavailability data. Factors contributing to this were: (i) the interaction between SLS and MCC resulting in a reduction in drug dissolution particularly at high pH; (ii) the inclusion of SLS in IND 2 resulting in an enhanced absorption of the drug due to its increased dissolution at low pH; and (iii) the in vivo penetration enhancing effect of SLS promoting good absorption of the drug. These products await further in vivo testing in humans involving both single and multiple dose studies.

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