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The use of dissolution rate data to account for differences in the absorption profiles of two controlled/modified-release capsule dosage forms of indomethacin in human volunteers

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Abstract

Reliance on in vitro-in vivo correlations using in vitro data obtained from a single dissolution test has frequently been shown to be misleading. The purpose of this study was to investigate the dissolution of indomethacin as a function of pH (pH 4.5, 5.0, 5.5, 6.0, 6.2 and 7.0). The official USP dissolution test (Apparatus 1 – rotating basket) for extended-release indomethacin dosage forms was used in all preformulation studies. Results from these studies indicated that indomethacin release from the test product was equivalent to that of Indocid®. A pilot scale ($n = 8$) comparative bioavailability study indicated that the two products were similar but not bioequivalent with respect to the extent of indomethacin absorption and quite different with respect to rate of absorption. Additional dissolution studies utilising the USP Apparatus 1 in buffered media over the pH range 4.5–7.0 were unable to predict these differences. Changing the dissolution apparatus to the USP Apparatus 2 (rotating paddle) over the same pH range revealed dramatic differences in the release of indomethacin from the two formulations. These differences were readily assessed with the use of topographical dissolution profiles. The relatively simple conversion to USP Apparatus 2, with pH profiling, provided a predictive test which may have forewarned of possible in vivo differences between the two formulations.

Key words: Dissolution rate; Extended-release indomethacin; In vitro-in vivo correlation; Bioavailability

1. Introduction

Indomethacin is a non-steroidal, anti-inflammatory drug with anti-pyretic and analgesic properties. It has been used effectively in the treatment of moderate to severe rheumatoid arthritis, ankylosing spondylitis, osteoarthritis, bursitis and in patent ductus arteriosus (Goodman and Gilman, 1980; Waller, 1983). Indocid® was first released in 1982 as an extended release preparation of indomethacin with the advantage of once or twice a day dosing (Yeh, 1985).

Dissolution testing was first introduced into

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some drug monographs in the USP in 1970. Initially, only six monographs included specifications for dissolution testing and this has steadily increased over the years to its present status whereby a substantial number of drug monographs include dissolution specifications. In 1977 a set of guidelines for implementation of dissolution specifications in the monographs was adopted. The USP stated that the dissolution behaviour of oral solid dosage forms had been shown to be a useful criterion for controlling the formulation and process variables which can influence the bioavailability of the drug in a particular dosage form. Although specific correlations could not be shown between the in vitro testing and the in vivo bioavailability results, dissolution testing was considered to be desirable in controlling the variables of the manufacturing process (USP XX, 1980).

In 1985 it was suggested that equivalence in dissolution behaviour was sought in light of both bioavailability and quality control. Furthermore, experience had shown that where a significant difference in bioavailability had occurred between two supposedly identical products, a dissolution test had been successful in discriminating between these (USP XXI, 1985).

Results of bioavailability studies often dictate formulation changes to achieve the desired product performance. Although dissolution rate testing has been primarily used as a method to assist in dosage form development or as a quality control procedure to assess batch uniformity, in vitro dissolution rate methods should also preferably have discriminating ability to obviate subsequent bioavailability problems.

At present the USP monograph for indomethacin extended release capsules requires the dissolution test to be carried out using the Apparatus 1 (rotating basket) at 75 rpm in a phosphate buffer medium of pH 6.2 (USP XXII, 1990).

It has been reported (Mojaverian et al., 1992) that the in vitro procedure should be compendially acceptable to regulatory agencies and possesses the ability to discriminate between products of varying bioavailability. Furthermore, unless adequate experimental data are available to demonstrate that the in vitro methods reflect the in vivo performance, release rate data have very little value in predicting overall bioavailability. It is now a well-established fact that the therapeutic efficacy of any dosage form is dependent on factors related to both the in vitro dissolution characteristics of the drug and its in vivo bioavailability. The development of more complex dosage forms has brought about the realisation that the standard methods of assessing products is no longer entirely adequate. The fact that controlled/modified-release dosage forms (CMRDs) are designed to release their drug content over extended periods of time implies that they will necessarily encounter a milieu of varying pH as they move through the gastrointestinal tract. These pH changes will therefore play a significant role in the dissolution of a drug from its dosage form and thus pH becomes an important variable that must be considered and evaluated during preformulation studies. This problem was exemplified by two quinidine gluconate formulations (Skelly et al., 1986a). This, together with the complexity of the many factors which are involved in in vitro dissolution rate testing, led to the development of a multidimensional topographical procedure as a tool for decision making by Skelly and co-workers (1986b). Hence, a dissolution test carried out at a single pH, therefore, appears inadequate to fully describe the in vivo performance of a CMRD.

Dissolution rate studies conducted on Indocid® and a test product, in accordance with the USP requirements, indicated that the dissolution profile for the test product closely followed that of Indocid®. Both products were found to comply with the USP specifications for indomethacin extended-release formulations (USP XXII, 1990). However, following a bioavailability study (BRI 14/89, 1989), it became evident that the test product exhibited a delayed absorption. This showed that dissolution testing in only one medium was not a reliable indicator of in vivo bioavailability for such modified-release products. The purpose of this study was to establish a dissolution rate test procedure which would be able to account for the in vivo differences found between the two products.

2. Materials and methods

2.1. Materials

Indocid® 75 mg capsules (Logos Pharmaceuticals, South Africa) were obtained commercially. The test product (a capsule containing extended-release pellets equivalent to 75 mg indomethacin) was supplied by South African Druggist, Port Elizabeth, South Africa. Drug standards were also supplied by South African Druggists. Orthophosphoric acid was purchased from Holpro Analytics, South Africa and sodium hydroxide pellets were obtained from Merck, South Africa.

2.2. Methods

2.2.1. Content uniformity assay

The formulations were tested for drug content uniformity in accordance with the procedures as described in the USP XXII.

2.2.2. Dissolution media

All dissolution studies were carried out in a phosphate buffer medium of 0.05 M and adjusted to the required pH using sodium hydroxide. Dissolution media were prepared in the pH range 4.5, 5.0, 5.5, 6.0, 6.2 and 7.0.

2.2.3. Dissolution studies

The dissolution studies were undertaken using either the rotating basket (USP Apparatus 1) or paddle apparatus (USP Apparatus 2) (Pharmatest PTW-S Dissolution Apparatus, Pharmatest, Germany). The temperature of the dissolution medium was maintained at 37 ± 0.5°C and the agitation rate was 75 and 50 rpm for the rotating basket and paddle apparatus, respectively. Dissolution rate determinations on each dosage form were carried out in accordance with the USP specifications. Samples of 3.0 ml were removed from the dissolution medium at 0.5-h intervals for the first 4 h and then at 1-h intervals to 8 h using Apparatus 1. Tests conducted with Apparatus 2 were monitored for 24 h. An equal volume of fresh dissolution medium was immediately replaced in order to maintain sink conditions. The absorbance of all samples was measured at 280 nm using a Beckman DU 68 spectrophotometer (Beckman Instruments, U.S.A.) and the concentration of indomethacin calculated by reference to a linear calibration line.

3. Results and discussion

3.1. Content uniformity assay

The drug content of the dosage forms were found to be within the limits set out in the USP XXII. The difference between the mean of each formulation and the theoretical content was less than 5%. All standard deviations were less than 5%.

Table 1
Dissolution rate data[a] for Indocid® using USP Apparatus 1 (% released)

Time (h)	pH					
	4.50	5.00	5.50	6.00	6.20	7.00
0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.50	1.89 ± 0.16	3.43 ± 0.47	6.78 ± 1.16	7.34 ± 0.67	10.57 ± 1.30	22.00 ± 2.34
1.00	2.98 ± 0.49	6.17 ± 1.39	13.07 ± 2.44	17.14 ± 1.31	25.11 ± 1.90	69.26 ± 1.15
1.50	3.44 ± 0.70	7.45 ± 1.74	15.33 ± 1.16	24.16 ± 1.40	36.72 ± 3.40	83.94 ± 0.74
2.00	3.94 ± 0.89	8.20 ± 1.51	18.08 ± 0.86	29.90 ± 1.66	43.96 ± 3.40	91.84 ± 0.96
2.50	4.19 ± 1.13	9.77 ± 2.32	20.84 ± 1.060	34.61 ± 1.31	50.41 ± 4.10	95.62 ± 1.05
3.00	4.52 ± 1.13	10.34 ± 2.6	22.96 ± 4.363	38.67 ± 1.05	56.01 ± 4.80	97.38 ± 1.25
4.00	4.91 ± 1.25	11.55 ± 2.8	26.13 ± 0.976	45.12 ± 1.22	63.30 ± 5.20	98.36 ± 1.24
6.00	5.45 ± 1.35	13.46 ± 3.4	31.27 ± 1.246	53.95 ± 1.28	78.55 ± 10.0	99.62 ± 1.57
8.00	6.75 ± 1.48	15.65 ± 5.1	35.55 ± 0.96	60.80 ± 1.04	94.69 ± 14.4	99.59 ± 1.154

[a] Mean (+S.D); $n = 6$.

Table 2
Dissolution rate data [a] for test product using USP Apparatus 1 (% released)

Time (h)	pH					
	4.50	5.00	5.50	6.00	6.20	7.00
0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.50	1.03 ± 0.06	2.09 ± 0.10	4.09 ± 0.15	5.05 ± 4.37	14.32 ± 0.51	40.87 ± 1.96
1.00	1.33 ± 0.20	3.54 ± 0.22	7.10 ± 1.58	14.76 ± 1.53	29.23 ± 1.06	85.06 ± 5.23
1.50	1.67 ± 0.43	4.95 ± 0.28	9.88 ± 2.28	20.64 ± 1.68	44.33 ± 2.63	104.89 ± 5.77
2.00	2.06 ± 0.45	6.71 ± 0.88	13.48 ± 3.77	26.10 ± 4.51	54.55 ± 2.43	112.90 ± 5.00
2.50	2.46 ± 0.40	7.86 ± 0.46	16.13 ± 4.05	32.0 ± 5.89	66.36 ± 2.87	113.76 ± 5.50
3.00	2.72 ± 0.60	9.17 ± 0.54	18.91 ± 4.91	37.40 ± 6.62	76.69 ± 2.61	114.66 ± 5.00
4.00	3.11 ± 0.72	11.68 ± 0.52	24.16 ± 6.23	47.07 ± 8.82	90.03 ± 1.45	115.20 ± 5.20
6.00	4.34 ± 1.03	16.60 ± 2.20	32.13 ± 8.17	62.90 ± 11.24	107.43 ± 1.60	116.11 ± 4.90
8.00	4.75 ± 1.13	19.14 ± 0.83	39.45 ± 10.26	75.84 ± 16.06	101.21 ± 15.2	116.26 ± 5.00

[a] Mean (±S.D); $n = 6$.

3.2. Dissolution rate studies

3.2.1. Apparatus 1

Visual inspection of the dissolution process revealed that the test product and Indocid® capsules burst after 2–5 min. The basket retained the pellets of the test product throughout the test, however, the granules of the reference formulation were only retained during the initial portion of the test upon which fine material sifted into the bulk of the dissolution medium, forming a small undisturbed mound at the base of the dissolution vessel. The percentages of indomethacin released from either formulation are summarised in Tables 1 and 2. The three-dimensional dissolution profiles are depicted in Fig. 1a and b. All dissolution rate profiles were evaluated using the procedure described by Leeson and co-workers (1985). This involved plotting the log % remaining to be released vs time and subsequent stripping of the curve using linear regression and the method of residuals to obtain the dissolution rate order and relevant rate constants (Table 3). Whereas a single rate constant (K_s) adequately described the release of indomethacin at most pH values for both products, at pH 6.2 two rate constants (K_s and K_f, slow and fast, respectively) were determined for the test product. When the test product was evaluated at pH 7.0, the dissolution process was complete within 1 h (Table 2) and thus insufficient data were available to determine any rate constants under these conditions. The release of indomethacin from both products was found to be relatively similar at pH values 4.5–6.0 (Table 3).

3.2.2. Apparatus 2

The dissolution rate studies were carried out under identical conditions to those employed with Apparatus 1. Visual inspection of the dissolution

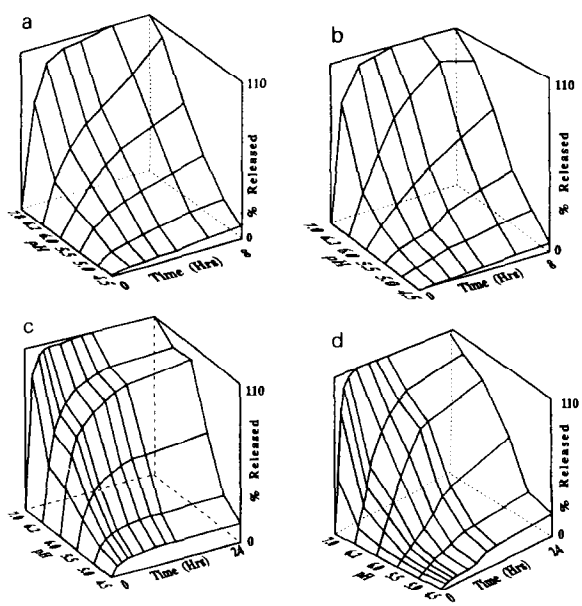

Fig. 1. Three-dimensional plot of % released vs time vs pH. (a) Indocid® – USP Basket Method (Apparatus 1); (b) test product – USP Basket Method (Apparatus 1); (c) Indocid® – USP Paddle Method (Apparatus 2); (d) test product – USP Paddle Method (Apparatus 2).

Table 3
Summary of dissolution rate constants using the USP Apparatus 1

Dissolution pH	Product	
	Test product	Indocid®
4.5	$K_s = 0.0052\ h^{-1}$	$K_s = 0.0052\ h^{-1}$
5.0	$K_s = 0.0258\ h^{-1}$	$K_s = 0.0168\ h^{-1}$
5.5	$K_s = 0.0615\ h^{-1}$	$K_s = 0.0405\ h^{-1}$
6.0	$K_s = 0.1790\ h^{-1}$	$K_s = 0.0995\ h^{-1}$
6.2	$K_s = 0.4260\ h^{-1}$ $K_f = 0.7680\ h^{-1}$	$K_s = 0.2360\ h^{-1}$
7.0	–	$K_s = 1.248\ h^{-1}$

K_f, fast first-order rate constant; K_s, slow first-order rate constant.

process revealed that the capsule contents were dumped within 2–3 min after introduction into the dissolution medium. The mass of granules from Indocid® showed a high degree of dispersion in the bulk of the medium, whereas movement of the pellets within the dissolution medium was less pronounced. The percentages of indomethacin released from the products are summarised in Tables 4 and 5. The three-dimensional profiles are depicted in Fig. 1c and d. Table 6 depicts the dissolution rate constants obtained with Apparatus 2. At pH values of 4.5 and 5.0, the rate constants were found to be of similar magnitude between the two products. At pH 5.5, two rate constants were obtained for both products to adequately describe the dissolution process.. At pH values 6.0–7.0 the release of indomethacin from the test product could be adequately described by a single slow rate constant (K_s) whilst two rate constants were obtained to describe the dissolution behaviour of indomethacin from Indocid® at pH values 6.0 and 6.2. The release of indomethacin from Indocid®, however, was generally seen to be relatively more rapid than that from the test product from media of pH 5.5–7.0. This is in contrast to the findings when data obtained with Apparatus 1 are considered.

Dissolution data obtained using the official USP dissolution testing specifications (Apparatus 1, pH 6.2) indicated that in vitro release of indomethacin from both the test product and Indocid® was similar (Table 3). Mean drug serum-concentration profiles obtained following a comparative bioavailability study (Study No. BRI 14/89), however, revealed the obverse (Fig. 2). From these plots it is evident that the test product had a longer lag time and T_{max} and a lower C_{max}, indicating a decreased rate of absorption. A summary of the pharmacokinetic parameters obtained is depicted in Table 7. Analysis of variance was performed using a statistical package, (Biopak, Microcomputer programme, Clin Trials Inc.,

Table 4
Dissolution rate data[a] for Indocid® using USP Apparatus 2 (% released)

Time (h)	pH					
	4.50	5.00	5.50	6.00	6.20	7.00
0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.50	4.91 ± 0.53	6.01 ± 1.27	11.53 ± 2.44	14.40 ± 2.06	18.20 ± 1.62	49.61 ± 4.73
1.00	6.91 ± 1.14	10.50 ± 0.54	20.68 ± 0.75	32.60 ± 1.88	38.89 ± 2.88	95.21 ± 3.61
1.50	8.00 ± 0.65	12.96 ± 0.43	26.70 ± 2.19	45.21 ± 2.29	51.11 ± 2.32	104.50 ± 3.73
2.00	9.01 ± 0.41	14.72 ± 0.62	31.00 ± 2.15	55.09 ± 2.81	61.24 ± 2.45	108.60 ± 3.63
2.50	9.81 ± 0.65	16.20 ± 1.33	35.60 ± 3.65	61.61 ± 4.39	68.21 ± 2.56	110.51 ± 4.01
3.00	10.24 ± 0.45	17.44 ± 1.30	38.51 ± 3.92	67.08 ± 2.49	73.11 ± 2.84	109.81 ± 3.38
4.00	10.81 ± 0.42	19.30 ± 1.26	42.83 ± 4.48	73.74 ± 2.81	80.29 ± 3.23	111.20 ± 2.94
6.00	11.75 ± 0.68	21.70 ± 1.60	47.79 ± 4.89	82.73 ± 3.11	88.44 ± 4.17	112.51 ± 2.96
8.00	12.46 ± 0.36	22.71 ± 2.11	53.00 ± 5.22	88.24 ± 3.11	92.71 ± 4.34	112.81 ± 3.52
10.00	12.92 ± 0.34	23.40 ± 2.31	55.25 ± 5.64	91.21 ± 2.90	95.43 ± 4.77	111.50 ± 3.09
12.00	13.29 ± 0.13	23.50 ± 2.12	55.60 ± 5.45	95.10 ± 2.87	98.80 ± 4.16	112.00 ± 2.38
16.00	13.70 ± 0.48	24.60 ± 2.53	57.61 ± 4.34	100.70 ± 2.67	100.50 ± 4.29	112.00 ± 2.38
24.00	14.10 ± 0.45	24.90 ± 2.07	60.00 ± 4.95	100.71 ± 2.03	100.50 ± 5.78	107.81 ± 2.38

[a] Mean (±S.D.); $n = 6$.

Table 5
Dissolution rate data[a] for test product using USP Apparatus 2 (% released)

Time (h)	pH					
	4.50	5.00	5.50	6.00	6.20	7.00
0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00	0.00 ± 0.00
0.50	1.66 ± 0.23	2.40 ± 0.62	3.09 ± 0.63	4.21 ± 1.43	6.19 ± 0.40	20.81 ± 0.96
1.00	1.93 ± 0.66	2.50 ± 0.17	4.24 ± 0.79	7.90 ± 1.71	12.71 ± 1.88	48.21 ± 4.64
1.50	1.89 ± 0.39	3.10 ± 0.19	5.50 ± 0.59	12.30 ± 2.26	20.09 ± 3.37	67.61 ± 6.31
2.00	2.20 ± 0.46	3.70 ± 0.36	6.89 ± 0.80	17.10 ± 2.89	27.67 ± 0.68	84.41 ± 7.02
2.50	2.37 ± 0.18	4.20 ± 0.30	8.92 ± 1.06	21.89 ± 3.43	35.61 ± 6.17	94.10 ± 7.92
3.00	2.52 ± 0.26	4.64 ± 0.30	10.61 ± 1.41	26.61 ± 4.05	42.31 ± 7.18	97.71 ± 7.89
4.00	2.89 ± 0.23	5.82 ± 0.30	13.94 ± 1.97	34.62 ± 5.38	54.83 ± 8.55	104.51 ± 8.96
6.00	3.80 ± 0.34	8.02 ± 0.55	19.71 ± 2.83	49.59 ± 6.52	71.51 ± 9.73	107.91 ± 9.69
8.00	5.86 ± 0.51	10.70 ± 0.56	27.86 ± 3.95	61.68 ± 7.84	81.93 ± 10.81	109.00 ± 9.13
10.00	6.54 ± 0.62	12.70 ± 0.90	32.30 ± 4.44	74.51 ± 9.02	87.71 ± 11.02	109.50 ± 8.35
12.00	7.06 ± 0.34	13.89 ± 0.87	34.60 ± 4.97	76.41 ± 9.60	91.73 ± 10.65	109.50 ± 8.35
16.00	7.78 ± 0.33	16.00 ± 1.21	45.50 ± 5.66	84.63 ± 9.59	95.81 ± 10.21	109.50 ± 8.35
24.00	9.88 ± 0.74	19.27 ± 1.76	50.70 ± 5.62	86.10 ± 10.48	96.73 ± 9.31	107.90 ± 5.67

[a] Mean (±S.D.); $n = 6$.

Lexington, U.S.A.) and the error variance term used to construct classical and Westlake confidence intervals for AUC_{0-24} and C_{max} (Table 8). It is thus seen that the products do not meet the criteria to claim bioequivalence.

The dissolution topographs (Fig. 1a–d,) which illustrate the relevant pH profiles for each product using either Apparatus 1 or 2, allow for a more comprehensive assessment of dissolution behaviour. Both products exhibited similar dissolution characteristics at the lower pH values of 4.5, 5.0 and 5.5 using Apparatus 1 (Fig. 1a and b). Slight differences were, however, observed at higher pH values. Since the release of indomethacin from the test product under these conditions appears relatively faster than from Indocid®, these data are certainly misleading when considered in the light of in vivo behaviour. Simi-

Table 6
Summary of dissolution rate constants using USP Apparatus 2

Dissolution pH	Product	
	Test product	Indocid®
4.5	$K_s = 0.0043\ h^{-1}$	$K_s = 0.0037\ h^{-1}$
5.0	$K_s = 0.0089\ h^{-1}$	$K_s = 0.0063\ h^{-1}$
5.5	$K_s = 0.0034\ h^{-1}$	$K_s = 0.0092\ h^{-1}$
	$K_f = 0.0245\ h^{-1}$	$K_f = 0.0650\ h^{-1}$
6.0	$K_s = 0.1247\ h^{-1}$	$K_s = 0.3580\ h^{-1}$
		$K_f = 0.4870\ h^{-1}$
6.2	$K_s = 0.2090\ h^{-1}$	$K_s = 0.2420\ h^{-1}$
		$K_f = 1.21\ h^{-1}$
7.0	$K_s = 1.59\ h^{-1}$	$K_s = 3.04\ h^{-1}$

K_f, fast first-order rate constant; K_s, slow first-order rate constant.

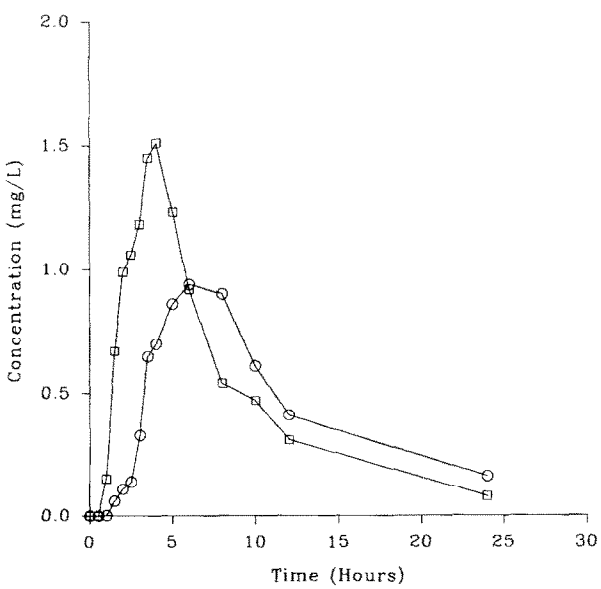

Fig. 2. Mean serum concentrations of indomethacin following the oral administration of Indocid® (□) and test product (○) capsules (75 mg) to eight healthy human volunteers. (Study No. BRI 14/89).

Table 7
Mean bioavailability parameters for test product and Indocid®

Parameter	Test product Mean ± S.D.	Indocid® Mean ± S.D.	Ratio
AUC_{0-24} (mg h l^{-1})	10.29 ± 4.07	11.11 ± 2.03	0.89
C_{max} (mg l^{-1})	1.5 ± 0.4	2.1 ± 0.6	0.69
T_{max} (h)	6.5 ± 2.8	3.6 ± 1.4	N/A

lar conclusions were drawn when data obtained according to the official dissolution specifications were compared. On the other hand, topographic data using Apparatus 2 (Fig. 1c and d) appear to be more relevant. Differences in dissolution behaviour are more apparent over the entire pH range studied and more accurately reflect the in vivo data. Inspection of Fig. 1c and d, particularly in the lower pH regions, indicates that the release of indomethacin from the test product is relatively slower when compared to Indocid®. This observation may be reconciled with the lag phase associated with the test product during the bioequivalence assessment resulting in an increase in T_{max}. It is thus clear that although both products complied with the USP dissolution specifications for extended-release indomethacin capsules, conversion to Apparatus 2 provided more realistic data which could be correlated with the actual in vivo performance of the products. The three-dimensional topographic plots appear to be more informative, since they more closely reflect the conditions which the product will encounter during transit through the gastrointestinal tract where it is exposed to a milieu of varying pH. The use of this type of approach to the dissolution testing of extended-release products therefore provides a valuable in vitro test that can be used to obtain useful information about the in vivo absorption behaviour of such formulations.

Table 8
Inferential statistics for Indocid® and Test product

Parameter	Ratio of means	Confidence limit	Classical	Westlake
AUC_{0-24}	0.93	95%	78–108	81–120
C_{max}	0.69	95%	42– 96	47–153

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