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Bi-exponential first-order release kinetics of indomethacin from tablets containing polysorbate 80

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Summary

In the study reported, indomethacin tablets were prepared by direct compression. Microcrystalline cellulose and polysorbate 80 were used as excipients. Drug release was studied using a beaker method. The results revealed that no commonly used kinetic model could explain the pattern of release. A bi-exponential, first-order kinetic model was therefore offered. On the basis of this model, there was good correspondence between calculated and observed values. As a rule, polysorbate 80 enhanced both the faster and the slower rate constants of the bi-exponential model. In addition, the percentage of indomethacin dissolved according to the faster process was increased.

Introduction

Indomethacin is an anti-inflammatory drug, very slightly soluble in water. Because of its poor compressibility during tableting, the commonest dosage form is hard gelatin capsules. During indomethacin therapy, gastric irritation and nausea can occur. These side-effects could perhaps be avoided if drug release were not as rapid as with conventional capsule formulations. Indomethacin, like many other non-steroidal anti-inflammatories has been reported to cause oesophageal ulceration

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(Merkus, 1980). Gelatin capsules are not recommended as a dosage form for this kind of drug substance. Tablet formulations have a lesser tendency to adhere to the oesophagus than capsules (Carlborg, 1978).

For the above-mentioned reasons it seemed reasonable to try to develop from indomethacin tablet formulations, too. We made a series of investigations and the aim of the present part was to study the effect of polysorbate 80 on the drug release from directly compressed indomethacin tablets. In addition to indomethacin and polysorbate 80, the formulations contained microcrystalline cellulose.

Materials and Methods

Solubility of indomethacin

The effect of polysorbate 80 on the water-solubility of indomethacin was investigated using a Souder-Ellenbogen apparatus (1958), at a temperature of 37°C, for 6 h. The stirring speed was adjusted to 60 min^{-1}. 100.0 ml of phosphate buffer solution, pH 7.2 (USP XX), containing different amounts of polysorbate 80 was placed in 200 ml flasks. Indomethacin in a quantity exceeding the limit of solubility was suspended in the medium. Portions of 1.0 ml of this suspension were filtered through a 0.45 μm Millipore filter, and were then diluted to 100.0 ml using the buffer solution. The absorption of the solution was determined at 320 nm (Perkin Elmer Model 139 Spectrophotometer). Six replicate determinations were performed for each polysorbate concentration.

Tablet formulations

The following materials were used for tablet preparation: indomethacin (supplied by Orion Pharmaceuticals), melting point 158°C, polysorbate 80 (Atlas Chemicals), microcrystalline cellulose (Avicel PH 102, FMC), ethanol (Oy Alko Ab).

The composition of tablet formulations studied were:

Ingredient	Formulation			
	I	II	III	IV
Indomethacin	25 mg	25 mg	25 mg	25 mg
Microcrystalline cellulose	125 mg	122 mg	119 mg	116 mg
Polysorbate 80	0 mg	3 mg	6 mg	9 mg

Preparation of tablets

On each occasion the ingredients were mixed in sufficient amounts to allow 500 tablets to be made. Polysorbate 80 was dissolved in 10 g of ethanol, and microcrystalline cellulose was moistened in a mortar, using the resulting solution. The ethanol

was evaporated off at 35°C. Indomethacin was added to the dried mixture, and mixed in Wab turbula mixer for 40 min. The tablets were compressed in a Korsch EK-0 single punch machine, using 8 mm flat-face punches, from 150 mg quantities, weighed in advance. The average compressional pressure was 10 $kN \cdot cm^{-2}$. The force was recorded at the upper punch according to the method described by Krogerus et al. (1969).

Tablet characteristics

Strength of the tablets was determined using a Schleuniger-2E Tablet Hardness Tester, on 10 tablets from each batch. Tablet porosity was measured according to Higuchi et al. (1953) by determining the true and apparent volumes of tablets. The true volumes were determined using a Beckman 930 air comparison pycnometer, with helium as inert gas, on the basis of 20 tablets of each formulation. Three determinations were carried out on each occasion. The apparent volumes were determined geometrically. Weight uniformity was established using 20 tablets. Content uniformity was evaluated by determining the indomethacin content of 10 tablets, as described under 'Solubility of indomethacin'. Disintegration time was measured according to the European Pharmacopoeia, using 900 ml of phosphate buffer solution (pH 7.2) as medium.

Dissolution test

Release of indomethacin from the tablets was determined using a modified beaker method (Levy and Hayes, 1960). The dissolution medium was 750 ml of phosphate buffer solution pH 7.2 at 37°C (USP XX). A propeller mixer (Nalgene 6160) was used and the speed of rotation was 60 min^{-1}. The height of the propeller above the bottom of the beaker was 3 cm. The tablet was placed in a wire basket (diameter 2 mm). Sampling was carried out at intervals, and drug concentrations were determined as described under 'Solubility of indomethacin'.

Kinetic models

The goodness of fit of the release data was initially tested with the following mathematical models: (1) zero-order kinetics (Eqn. 1); (2) first-order kinetics (Eqn. 2); (3) Hixson-Crowell's cube-root equation (Eqn. 3); and (4) square-root of time equation (Eqn. 4).

$$w = w_0 - k_0 t \tag{1}$$

$$\ln w = \ln w_0 - k_1 t \tag{2}$$

$$\sqrt[3]{w} = \sqrt[3]{w_0} - k_2 t \tag{3}$$

$$Q = K\sqrt{t} \tag{4}$$

Because the release data seemed to follow a biphasic profile, the goodness of fit of a bi-exponential, first-order kinetic model (Eqn. 5) was also tested.

$$w = A\,e^{-k_3 t} + B\,e^{-k_4 t} \quad (5)$$

Detailed calculations are demonstrated in Table 5. In the equations w = undissolved amount of the drug at time = t, w_0 = undissolved amount of the drug at t = 0, Q = amount of the drug dissolved at time = t, k_0, k_1, k_2, k_3, k_4, K = corresponding release rate constants. Lag-time was defined as the calculated value of t corresponding w = 100% (or Q = 0).

Statistical significance was assessed by means of Student's *t* = test.

Results and Discussion

The effect of polysorbate 80 on the solubility of indomethacin is shown in Table 1. If the polysorbate concentration was 0.2%, or above, the solubility of indomethacin increased. This finding is in agreement with that of Krasowska (1976). It has been reported that the critical micelle concentration of polysorbate 80 in water at 25°C is 0.0014% (Wan, 1974). It would therefore be expected that even polysorbate concentrations lower than 0.2% would increase the solubility of indomethacin. However, phosphate buffer may change the critical micelle concentration from that in pure water. The solubility of indomethacin in pure buffer solution at 37°C (0.95 mg · ml^{-1}) is clearly higher than its solubility in pure water at 25°C, which has been reported to be 0.014 mg · ml^{-1} (Krasowska, 1972).

TABLE 1

THE EFFECT OF POLYSORBATE 80 CONCENTRATIONS ON THE SOLUBILITY OF INDOMETHACIN IN PHOSPHATE BUFFER SOLUTION OF pH 7.2 (n = 6)

Polysorbate 80 concentration (%)	Solubility of indomethacin mean ± S.D. (mg · ml^{-1})	Student's *t*-test $P <$
0	0.95 ± 0.01	
0.001	0.95 ± 0.02	NS
0.002	0.95 ± 0.02	NS
0.02	0.95 ± 0.03	NS
0.1	0.98 ± 0.04	NS
0.2	1.07 ± 0.01	0.001
0.5	1.24 ± 0.01	0.001
0.8	1.42 ± 0.01	0.001
1.0	1.55 ± 0.03	0.001
2.0	2.02 ± 0.01	0.001
4.0	2.77 ± 0.02	0.001
6.0	3.54 ± 0.04	0.001

NS = not significant, $P > 0.05$.

TABLE 2

CHARACTERISTICS OF THE INDOMETHACIN TABLETS STUDIED

Formulation	Mean tablet weight ± S.D. (mg) n = 20	Mean indomethacin content ± S.D. (mg) n = 10	Mean tablet strength ± S.D. (N) n = 10	Mean tablet porosity (%) n = 3	Mean disintegration time (s) n = 6
I	146.3 ± 0.6	24.5 ± 0.3	79.9 ± 3.3	17.6	43
II	148.8 ± 0.6	24.6 ± 0.3	83.1 ± 6.3	17.1	26
III	147.4 ± 0.8	25.1 ± 0.6	55.0 ± 3.4	24.7	25
IV	150.2 ± 0.6	24.7 ± 0.3	55.9 ± 2.3	19.4	27

The characteristics of the indomethacin tablets studied are shown in Table 2. All formulations fulfilled the weight variation, the content uniformity and the disintegration tests of USP XX and Ph. Eur.

In the dissolution studies described here, sink conditions existed. The highest theoretical indomethacin concentration was less than 4% of the saturation concentration. The results of the dissolution tests are recorded in Table 3. As a rule, the higher the polysorbate concentration in the formulation, the more rapid the release of indomethacin. The differences in cumulative amounts released were statistically highly significant ($P < 0.001$) after 90 min in the case of the lowest polysorbate concentration. Statistically differences were highly significant ($P < 0.001$) after 5 min using polysorbate concentrations of 4% and 6%.

The goodness of fit of the release data was tested according to the 4 different kinetic models mentioned above.

Considering all points between 0 and 300 min, the best linear correlation coefficients were obtained for the first-order equation. Results of the first-order

TABLE 3

CUMULATIVE AMOUNTS (%) OF INDOMETHACIN RELEASED FROM DIFFERENT FORMULATIONS (n = 12)

Time (min)	Formulations							
	I		II		III		IV	
	mean ± S.D.		mean ± S.D.		mean ± S.D.		mean ± S.D.	
5	4.5	1.7	5.1	1.4	7.5	2.9	13.4	5.6
10	8.5	1.9	10.1	3.5	19.4	7.2	28.1	13.8
20	15.8	3.2	19.1	5.4	36.8	13.9	43.4	17.8
30	21.5	3.8	27.7	7.8	47.2	16.7	56.5	19.4
60	37.2	6.1	48.2	11.6	66.0	16.2	76.0	16.8
90	46.9	7.5	61.5	13.2	73.5	14.8	85.5	14.5
120	54.9	8.5	71.6	12.4	78.6	12.8	89.3	13.3
150	61.3	8.3	78.5	11.5	82.2	11.7	90.0	13.3
180	65.9	8.6	84.8	9.0	85.9	9.0	94.1	9.5
240	74.8	8.9	89.7	7.5	89.5	7.4	97.6	6.6
300	79.9	7.4	94.6	5.9	91.8	5.4	98.1	6.6

TABLE 4

PARAMETERS FOR THE RELEASE OF INDOMETHACIN ON THE BASIS OF FIRST-ORDER KINETICS AND HIXSON-CROWELL'S CUBE-ROOT EQUATION

Formulation	First-order			Cube-root		
	Rate constant (min^{-1})	Correlation coeff. (r)	Lag-time (min)	Rate constant (min^{-1})	Correlation coeff. (r)	Lag-time (min)
I	0.00543	0.994	−13.8	0.00657	0.984	−23.2
II	0.00972	0.998	−4.2	0.00995	0.985	−18.4
III	0.00843	0.966	−35.8	0.00872	0.933	−54.9
IV	0.0135	0.982	−25.1	0.0113	0.939	−54.5

equation and Hixson-Crowell's equation are shown in Table 4. Although all correlation coefficients are highly significant ($P < 0.001$), the lag-times are negative and in almost every case unreasonable. As Table 4 shows, first-order kinetics, however, always described the results better, even though it has been said that drug release from tablets prepared by direct compression should obey the cube-root law (McGinity et al., 1981).

However, even first-order kinetics did not describe the whole dissolution profile of indomethacin in the present study well. This is evident from Fig. 1, relating to the

Fig. 1.

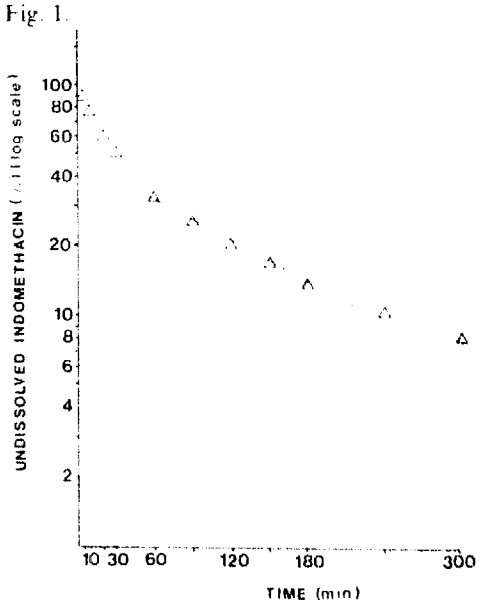

Fig. 2.

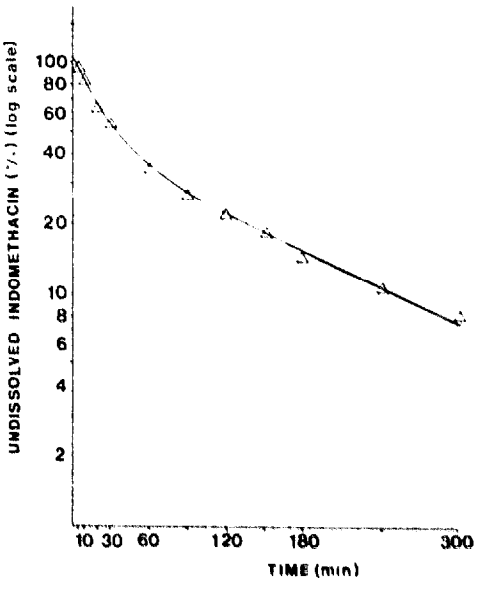

Fig. 1. Undissolved amounts of indomethacin from tablets of formulation III. The straight line relates to first-order kinetics.

Fig. 2. Undissolved amounts of indomethacin from tablets of formulation III. The curve relates to bi-exponential, first-order kinetics.

TABLE 5

MATHEMATICAL TREATMENT OF UNDISSOLVED AMOUNTS OF INDOMETHACIN FROM TABLETS OF FORMULATION III

(1) Time (t) (min)	(2) Amount undissolved (%)		(3) $y_1 = 44.7e^{-0.00593t}$	(4) = (2) − (3)		(5) $y_2 = 61.3e^{-0.04661t}$	(6) = (3)+(5)
0	100.0		44.7	(55.5)		61.3	106.0
5	92.5		43.4	49.1		48.6	92.0
10	80.6		42.1	38.5	(2)	38.5	80.6
20	63.2		39.7	23.5		24.1	63.8
30	52.8		37.4	15.4		15.2	52.6
60	34.0		31.3			3.7	35.0
90	26.5		26.2			0.9	27.1
120	21.4	(1)	22.0			0.2	22.2
150	17.8		18.4			0.1	18.5
180	14.1		15.4			0.0	15.4
240	10.5		10.8			0.0	10.8
300	8.2		7.6			0.0	7.6

tablets of formulation III. The release profile appears bi-phasic. We therefore investigated whether the results could be described on the basis of a bi-exponential, first-order model, analogous to that generally used to describe pharmacokinetics after rapid intravenous injection of a drug. The mathematical treatment in relation to tablets of formulation III is shown in Table 5. The values calculated on the basis of this kind of bi-exponential model correspond well with the observed values. The results relating to all dissolution tests on the basis of the above-mentioned model are recorded in Table 6. Linear correlation coefficients are very high, and the lag-times realistic. Small positive lag-times in dissolution can be explained on the basis of the disintegration time of the tablets.

It may therefore be concluded that the release of indomethacin in the present study was biphasic throughout. Some of the drug was released via a rapid process, the rest via a slower process. Both processes separately conformed to first-order

TABLE 6

BI-EXPONENTIAL FIRST-ORDER EQUATIONS FOR THE RELEASE OF INDOMETHACIN

Formulation	Equation	r Initial phase	r Terminal phase	Lag-time (min)
I	$y = 12.6e^{-0.0370t} + 87.4e^{-0.00513t}$	1.000	0.995	0
II	$y = 7.24e^{-0.02691t} + 92.8e^{-0.00954t}$	0.997	0.998	0
III	$y = 61.3e^{-0.04661t} + 44.7e^{-0.00593t}$	0.999	0.992	2.1
IV	$y = 50.9e^{-0.0538t} + 49.0e^{-0.0116t}$	0.996	0.986	0

kinetics. The intercept of the terminal phase indicates the percentage of the drug released via the slower process (e.g. for tablets of formulation III, 44.7%). On the basis of the rate constants it can be concluded what kind of effect any variable has separately had on the slower process and the faster process.

From the present results, it can be concluded that the faster initial phase is mainly due to the disintegration of the tablets resulting in fast enhancement in the dissolution area. The terminal phase mainly describes the dissolution of the sparingly water-soluble indomethacin from the aggregates after disintegration. Adding of polysorbate 80, in amounts high enough (4 or 6%), enhanced the percentage of the initial phase to 50–60% compared to 12.6% in formulation I containing no polysorbate (Table 6). This may be explained by better wettability caused by polysorbate 80. The faster disintegration of the tablets can also be seen in Table 2. Adding of polysorbate 80 to the formulations (4 or 6%) also increased the dissolution rate constants of both the terminal and the initial phases (Table 6). This can be explained by the fact that according to Noyes and Whitney's equation the dissolution rate is proportional to the solubility of the drug. The increase in the solubility of indomethacin, caused by polysorbate 80, is seen in Table 1.

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