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# The behaviour of the sodium salt of indomethacin in the cores of film-coated granules containing various fillers

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## Summary

The aim of this study was to investigate the behaviour of sodium indomethacin trihydrate in granules made using various kinds of filler, and the effects of the fillers on the release rates of sodium indomethacin trihydrate, which is water-soluble, from uncoated and film-coated granules. The fillers used in the granules were lactose, glucose, microcrystalline cellulose, maize starch and calcium hydrogen phosphate dihydrate. The release rate from uncoated granules was very fast. Within 10 min all of the drug was released from nearly all of the granules. The effect of the porosity of the film in the coated granules was significant only when maize starch was used as filler in the cores. Release of the drug from granules containing microcrystalline cellulose, lactose or glucose as fillers was the same, regardless of the film used. Release was slightly slower from the granules containing maize starch than from the granules mentioned above. The release rate of sodium indomethacin trihydrate was markedly slower and the amounts of drug released were markedly less from granules containing calcium hydrogen phosphate dihydrate than from the other granules studied. A new component, the calcium salt of indomethacin, which is less water-soluble than the sodium salt, was probably formed in the core. Release from all of the granules studied corresponded fairly well first-order kinetics.

## Introduction

Previous studies have shown that physicochemical properties of the fillers used in the cores of film-coated granules affect the release of the slightly water-soluble drugs indomethacin and tolfenamic acid (Eerikäinen et al., 1989; Laakso and Eerikäinen, 1991). The most significant properties seem to be the swellability and solubility of the fillers. The results for indomethacin and the less water-soluble tolfenamic acid showed that the water solubility of the drug also had a marked effect on release behaviour. The effects of drugs of different solubilities on granule and tablet properties, and on drug release behaviour have been extensively examined (Donbrow and Friedman, 1975; Friedman et al., 1979; Chilamcurti et al., 1983). The results indicate that drug solubility can affect tablet properties such as disintegration time, hardness and friability. The results also indicate that drug solubility can affect drug release depending on the kinds of adjuvants used in the cores of coated granules or in tablets.

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It is well known that the sodium salts of weak acids usually dissolve in water more rapidly than the free acids (Nelson, 1958; Berge et al., 1977). In this study, sodium indomethacin trihydrate was therefore used as a model drug representing substances easily soluble in water. The aim of the study was to investigate the behaviours of various types of fillers in the cores of film-coated granules containing water-soluble sodium indomethacin trihydrate. The effects of various fillers on the release of sodium indomethacin trihydrate from film-coated granules were also studied.

## Materials and Methods

The sodium indomethacin trihydrate used was supplied by Merck Sharp & Dohme Research Laboratories. It is very soluble in water (201.2 mg/ml (Theeuwes et al., 1983)). Glucose monohydrate (Ph.Eur.), lactose monohydrate (Ph.Eur.), maize starch (Ph.Eur.), microcrystalline cellulose (Avicel PH 102, Serva, U.S.A.) and calcium hydrogen phosphate dihydrate (Emcompress, Ph. Eur.) were used as fillers in the granules.

*Preparation of granules*

Granules were prepared from 250.0 g of blended powders containing 20% of indomethacin sodium trihydrate and 80% of filler. The powder blends were mixed (Turbula Mixer, W.A. Bachofen, Switzerland) for 15 min. The blends were moistened with gelatin solution. The amount of gelatin (Ph.Eur.) added was 4.8% (calculated as dry powder) for each batch of granules. The moist mass was passed through the 2.0 mm sieve of an oscillator (Erweka GmbH, Germany). The granules were dried at 35°C and rescreened.

*Coating*

The granules were coated with ethyl cellulose (EC, N-10 Hercules Inc., U.S.A.) and the permeability of the film was modified by incorporation of varying amounts of hydroxypropylmethyl cellulose (HPMC, Methocel E 5, Methocel Dow Chemicals GmbH, U.S.A.). The total polymer concentration in the solution was 5%. The polymers were dissolved in ethanol (Oy Alko Ab, Finland)/dichloromethane (pro analysis, E. Merck) 1 : 2 containing glycerol as plasticizer (20% of the polymer weight). The EC/HPMC ratios used were 65 : 35, 70 : 30 and 75 : 25. The coating accounted for about 10% of the total weights of the granules.

The 710–1680 $\mu$m sieve fraction of the granules was coated using a fluidized bed coating technique (Aeromatic Strea 1, Aeromatic AG, Switzerland). The air flow rate was 100 $m^3\ h^{-1}$ and the drying temperature $32 \pm 1$°C. Coating solutions were pumped at a flow rate of 10 ml/min and the pneumatic spraying pressure was 1 bar. After coating, the granules were dried at 35°C and sieved. The sieve fraction 710–1680 $\mu$m was examined further.

*Granule characteristics*

Content uniformity was evaluated for 10 batches (20.0 mg of granules per batch). The indomethacin concentrations in the batches were measured spectrophotometrically at 320 nm (Perkin-Elmer UV-Vis Spectrophotometer, Japan).

*Dissolution test*

The release of sodium indomethacin trihydrate from 200.0 mg batches of uncoated and coated granules was determined using the USP XXI rotating basket method (Sotax AT 6, Switzerland). The dissolution medium was 750 ml of phosphate buffer solution (pH 7.2) and the temperature 37°C. The rotation speed was 60 $min^{-1}$. The nonlinear curves were fitted to the release data for the coated granules using the MathCAD programming package algorithm (Appendix 1).

## Results and Discussion

*Uncoated granules*

There were differences in the amounts of granulation solution added to the mass of 250.0 g, depending on the properties of the fillers. The water-soluble blends containing glucose or lactose needed 37 and 48 g of water, respectively, to allow granules of appropriate sizes for further examination (710–1680 $\mu$m) to be obtained. The degree of granulation was difficult to control because both

drug and fillers were water-soluble and their capacities for dissolving in the moisturizing solution made it difficult to predict exactly how much solution needed to be added. Granules containing calcium hydrogen phosphate dihydrate needed almost as much liquid as masses containing lactose as filler, namely some 49 g. The blends containing maize starch and microcrystalline cellulose differed in their needs for moisturizing liquid from other sodium indomethacin trihydrate-filler blends. The amounts needed were 117 g of water for maize starch granules and 181 g of water for granules containing microcrystalline cellulose as fillers, probably because of the capacity of these fillers for swelling by taking liquid inside and between the chains of the structure of both maize starch and microcrystalline cellulose, and inside the grains of maize starch (Nogami et al., 1969).

The release of indomethacin sodium trihydrate from uncoated granules was examined over periods of 10 min. As expected, the granules disintegrated most rapidly when water-soluble fillers were used (Fig. 1). When glucose or lactose were used as fillers in the cores release of the water-soluble drug took place completely within 3 min, no doubt because of the good water solubility of both the drug and the fillers. The filler dissolves around the drug particles and the granules disintegrate rapidly (Lapidus and Lordi, 1968). However, release from lactose granules was markedly slower than from glucose granules. Because of the different water solubilities of glucose and lactose there is a difference in release behaviour. In addition to the nature of the fillers used, the amount of moisturizing liquid can affect the properties of the granules because of water bridges formed inside the granules, when liquid is added. Formation of liquid bridges is very apparent when very water-soluble fillers like glucose and lactose are used (Jaiyeoba and Spring, 1980).

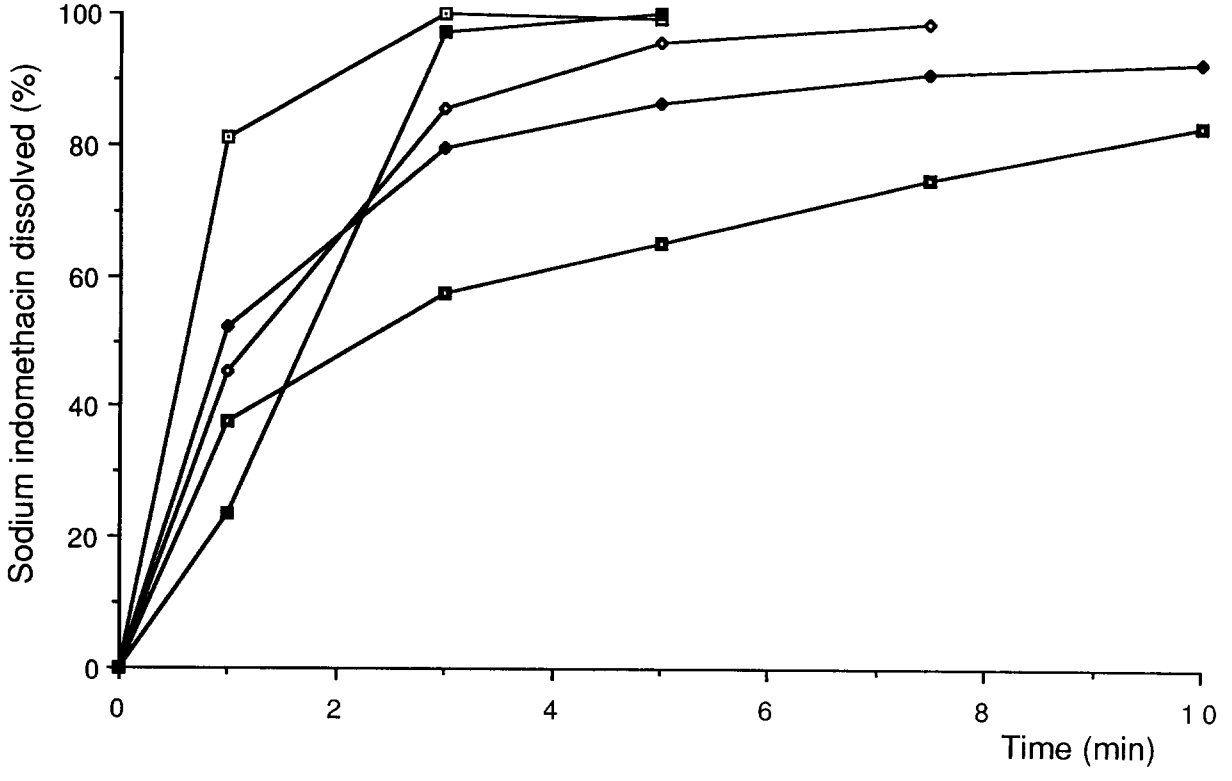


Fig. 1. Cumulative amounts (%) of sodium indomethacin released from uncoated granules ($n = 6$). (▣) Calcium hydrogen phosphate dihydrate, (■) glucose, (⊡) lactose, (◇) maize starch, (◆) microcrystalline cellulose.

Release of indomethacin sodium trihydrate over the first 5 min was slightly slower from granules containing maize starch as filler than from granules containing glucose or lactose as fillers. The maize starch particles probably form barriers, because maize starch swells and slows down diffusion of the dissolution medium into the granules. Because the water solubility of the drug was good, the swelling property of the excipient did not have a very marked effect on drug release. The swelling property can, however, hasten the drug release by causing the granules to disintegrate so that the drug particles dissolve faster through more dissolution medium being available in the inner parts of the granule.

When indomethacin, which is only slightly water-soluble, was used in the core instead of indomethacin sodium trihydrate (Laakso and Eerikäinen, 1991) and when the almost water-insoluble tolfenamic acid was in the core (Eerikäinen et al., 1989) release was much more affected by the swelling properties of fillers. However, drug solubility seems to be the most important factor affecting release.

Release of indomethacin sodium trihydrate was slow from granules containing microcrystalline cellulose as filler and very slow when granules were made from indomethacin sodium trihydrate-calcium hydrogen phosphate dihydrate blends. The swellable, hydrophilic microcrystalline cellulose behaves like maize starch in the granules but its swelling properties are less effective and the forces developed as a result of swelling are less strong than those produced by maize starch (Caramella et al., 1984).

The slow release rate from uncoated calcium hydrogen phosphate dihydrate granules was probably a consequence of a reaction between sodium indomethacin trihydrate and calcium hydrogen phosphate dihydrate. A calcium salt of indomethacin is obviously formed in the core during dissolution. It is only slightly water-soluble and is released more slowly than sodium indomethacin from granules. Formation of a calcium salt of indomethacin was indicated by the reaction observed when a solution of sodium indomethacin

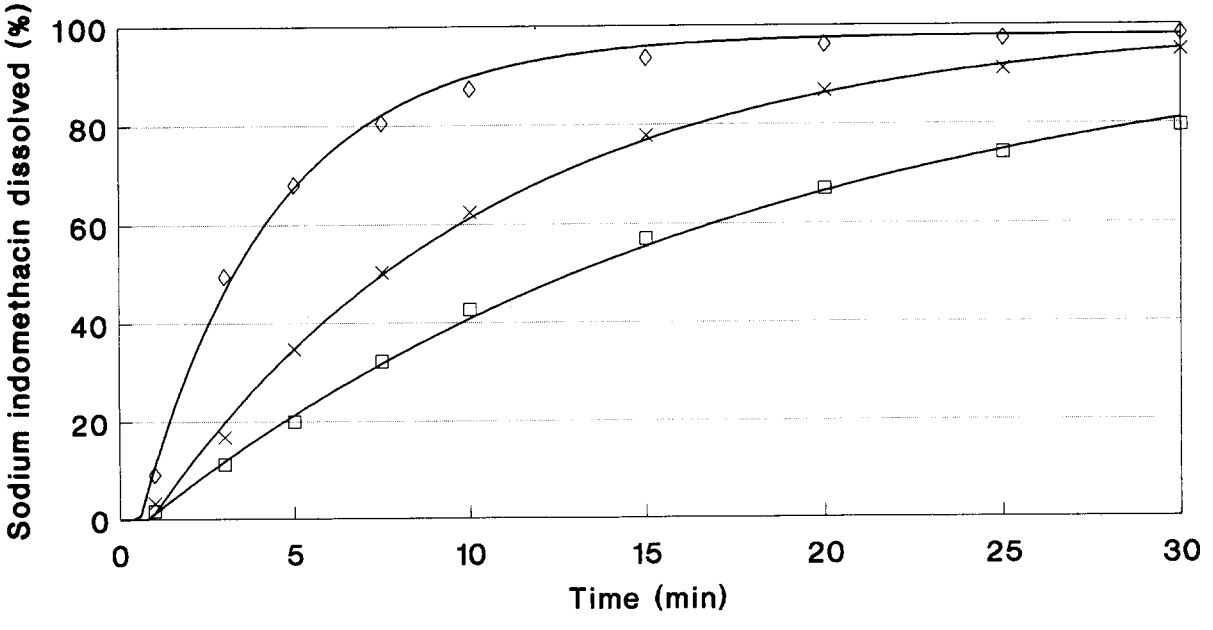


Fig. 2. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-coated granules containing maize starch as filler ($n = 6$). The fitted curves were calculated using Eqn 1. (◇) 65 : 35, (×) 70 : 30, (□) 75 : 25.

trihydrate and a saturated solution of calcium phosphate dihydrate were mixed — a sediment formed.

*Coated granules*

The amounts of sodium indomethacin trihydrate in the coated granules varied from 32.9 mg to 36.3 mg (the total amount of granules per batch was 200.0 mg). The theoretical amount of sodium indomethacin trihydrate in the granules was 34.4 mg. The porosities and permeabilities of the films were changed by varying the amounts of hydroxypropylmethyl cellulose in the ethyl cellulose film. The curves in Figs 2–6 were calculated using Eqn 1 (Appendix 1). The effect of permeability was most apparent when maize starch was used in the cores as filler (Fig. 2). In such granules it would seem possible to modify sodium indomethacin trihydrate release from the core fairly easily by changing the permeability of the film. However, release of the drug was fairly fast: 80% was released in 30 min when the EC/HPMC ratio was 75 : 25. This film had fewest pores of all those studied. The effect of film permeability on drug release had been expected on the basis of results of earlier investigations (Kannikoski, 1984; Kannikoski et al., 1984). The effect of the porosity of the film was less marked when other fillers were used in the core. The release of sodium indomethacin trihydrate from granules containing lactose (water-soluble) is shown in Fig. 3, that from granules containing glucose in Fig. 4, and that from granules containing microcrystalline cellulose in Fig. 5. When there are components in the core which moisten easily, the numbers of pores forming in the film because of hydroxypropylmethyl cellulose dissolution seem to be adequate for the liquid to penetrate and for the dissolved drug to be leached out from the core in a fairly short time. The dissolution of hydroxypropylmethyl cellulose and the higher porosity reduces the effective path length of permeation and thus increases the drug-release rate when there is a water-soluble component in the coat (Friedman et al., 1979). The release rate of sodium indomethacin was markedly slower and the amount released was less over 30 min from the granules containing calcium hydrogen phosphate dihydrate as filler than from the other granules studied (Fig. 6).

The results of our earlier studies let us suppose

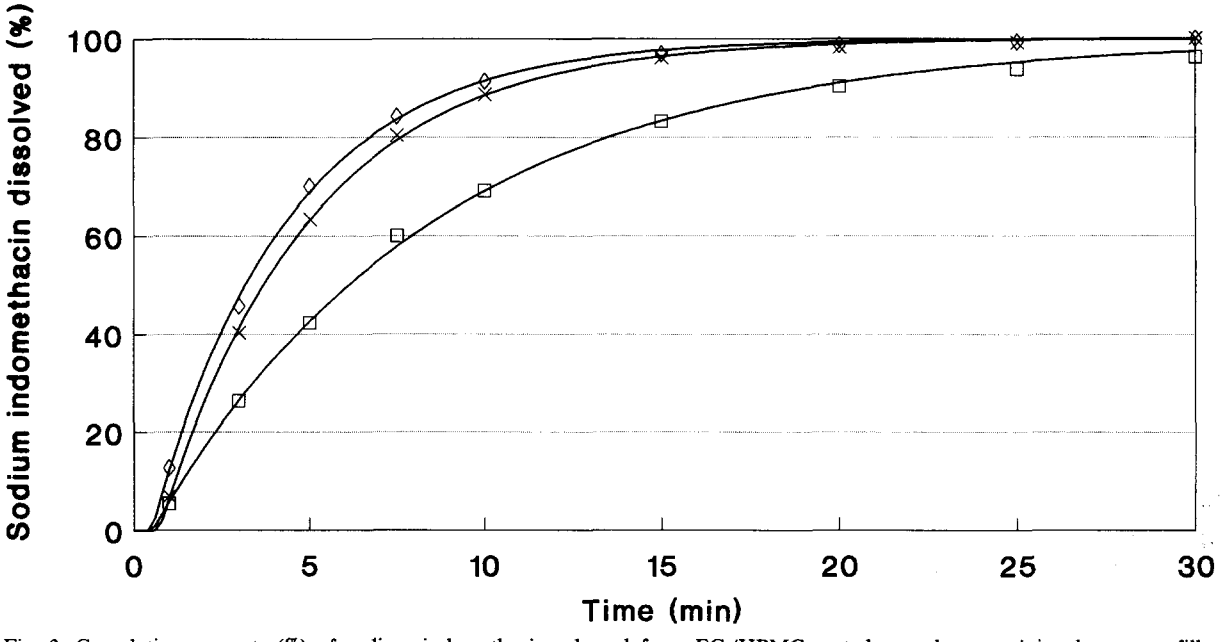


Fig. 3. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-coated granules containing lactose as filler ($n = 6$). The fitted curves were calculated using Eqn 1. Symbols as in Fig. 2.

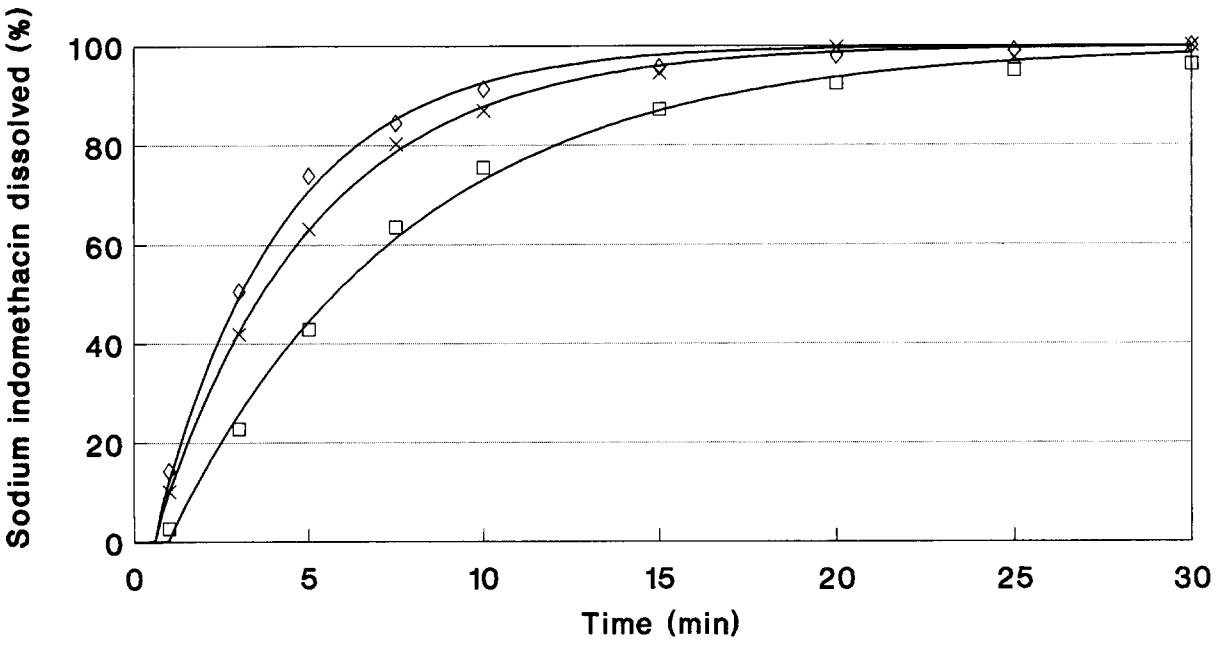


Fig. 4. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-coated granules containing glucose as filler ($n = 6$). The fitted curves were calculated using Eqn 1. Symbols as in Fig. 2.

that the properties of the fillers used in the cores could affect the release of sodium indomethacin trihydrate, which is water-soluble (Eerikäinen et al., 1989; Laakso and Eerikäinen, 1991). Fig. 7 shows how the release of sodium indomethacin trihydrate changes with the various fillers used in

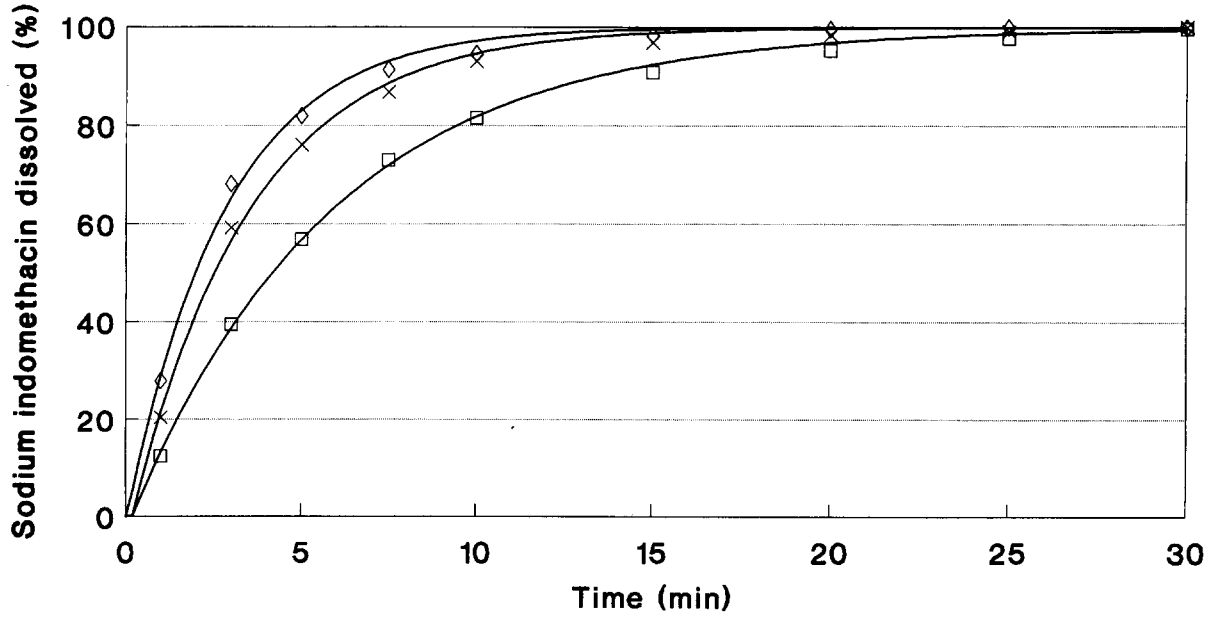


Fig. 5. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-coated granules containing microcrystalline cellulose as filler ($n = 6$). The fitted curves were calculated using Eqn 1. Symbols as in Fig. 2.

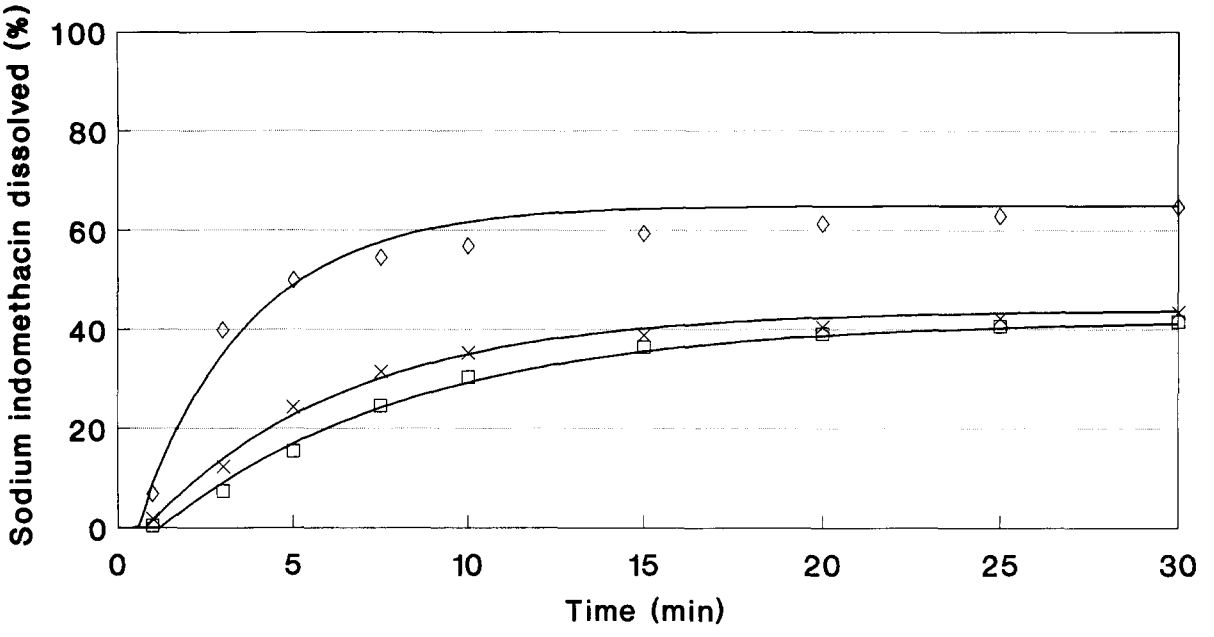


Fig. 6. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-coated granules containing calcium hydrogen phosphate dihydrate as filler ($n = 6$). The fitted curves were calculated using Eqn 1. Symbols as in Fig. 2.

the cores. The EC/HPMC ratio of the film was 65 : 35. Almost all of the sodium indomethacin trihydrate was released within 30 min, regardless of the filler used, except in the case of the granules containing calcium hydrogen phosphate dihydrate as filler. A calcium salt of indomethacin probably

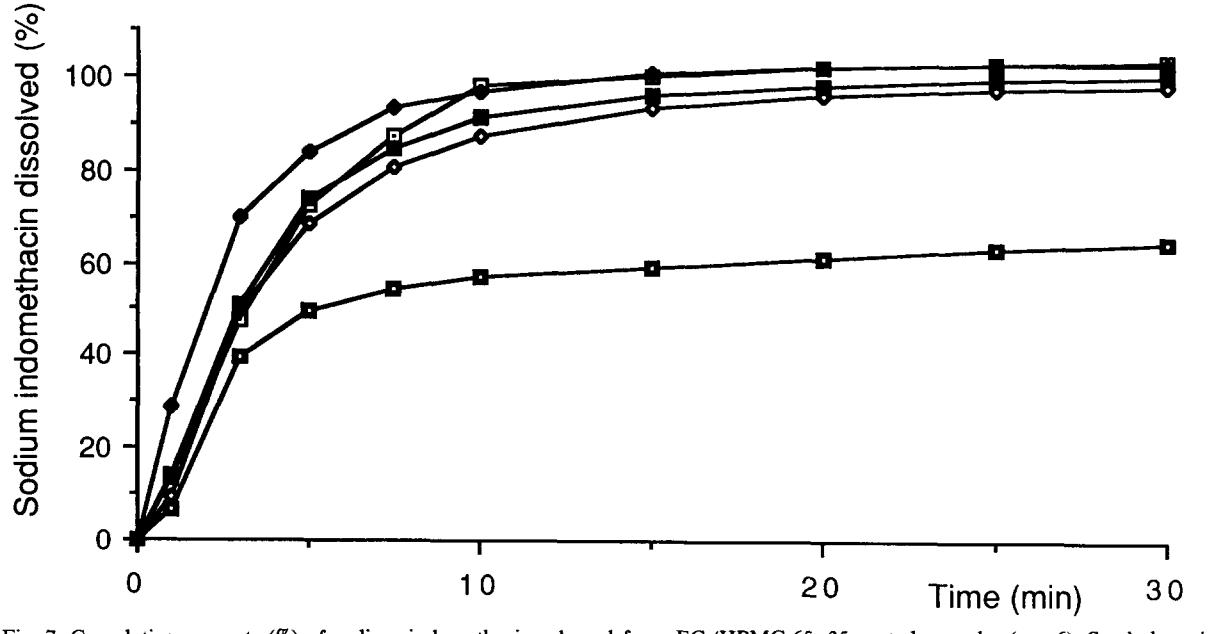


Fig. 7. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-65 : 35-coated granules ($n = 6$). Symbols as in Fig. 1.

replaced the sodium salt. Calcium salts are usually less water-soluble than sodium salts, leading to the drug release from the granules containing calcium hydrogen phosphate dihydrate as filler being slower than from the other granules.

The granules containing microcrystalline cellulose, lactose, glucose and maize starch as fillers released sodium indomethacin at the same rate. The water-soluble fillers glucose and lactose, surprisingly, slow down the release rate initially. This may be because of the rapid dissolution of these fillers. Following rapid dissolution, a liquid of high viscosity occupies the area just under the film; this behaves like a barrier to the drug release over the initial minutes (Lerk et al., 1979). Dissolution of both drug and filler is, however, still so fast that the barrier has only a small effect on drug release. Only within the first 10 min is there a marked difference in release rates from granules containing lactose or glucose as compared with release rate from granules containing microcrystalline cellulose. The difference is also evident in the lag times (Table 1). In addition, the microcrystalline cellulose, a hydrophilic substance, helps the drug to dissolve by accelerating penetration of the liquid into the core through the film. As the liquid dissolves the water-soluble sodium indomethacin trihydrate, the latter leaches rapidly from the core, through pores. The slight swelling of microcrystalline cellulose does not seem to affect drug penetration markedly (Khan et al., 1981). The swelling property of maize starch also had a less marked effect on the release behaviour of the water-soluble drug than it had when the slightly water-soluble substances indomethacin and tolfenamic acid were investigated (Eerikäinen et al., 1989; Laakso and Eerikäinen, 1991). The investigations reported here really indicate that when a drug is readily water-soluble, the properties of the fillers used do not have very marked effects on the release behaviour of the drug.

When the EC/HPMC ratio in the film was changed to 75 : 25 (Fig. 8), decreasing its porosity, the release was influenced by the properties of the diluents more than when the EC/HPMC ratios were 65 : 35 or 70 : 30. However, release was as fast from granules containing microcrystalline cellulose, lactose and glucose as fillers. Release of sodium indomethacin was slowest from the granules containing calcium hydrogen phosphate dihydrate. It was also noticeable that the amount of sodium indomethacin released within 30 min was low, only 40%, when the EC/HPMC ratio in the film was 75 : 25. Variations in porosity of the film affected maize starch granules more than granules made with other fillers. The decreased penetration of liquid into the core makes maize starch particles near the pores swell, with the result that a barrier of maize starch gel prevents dissolution of the drug and retards movement of dissolved drug from the core. Over a 30 min period this had a fairly marked effect on the release behaviour of sodium indomethacin.

The results (Figs 2–6) show that the dissolution of sodium indomethacin was described well by first-order kinetics (Eqn 1). The curves in the

TABLE 1

*Values of dissolution parameters calculated on the basis of Eqn 1 ($k_1$ is the first-order releasing constant ($min^{-1}$), lag is the lag time (min) and SSE = sum of the squared errors)*

| Filler EC/HPMC ratio | $k_1$ | lag | SSE |
|---|---|---|---|
| Maize starch | | | |
| 75/25 | 0.057 | 0.80 | 1.58 |
| 70/30 | 0.104 | 0.89 | 2.31 |
| 65/35 | 0.263 | 0.57 | 4.28 (1) |
| Microcrystalline cellulose | | | |
| 75/25 | 0.174 | 0.19 | 1.20 |
| 70/30 | 0.297 | 0.19 | 3.00 |
| 65/35 | 0.358 | 0.05 | 3.24 |
| Calcium hydrogen phosphate | | | |
| 75/25 | 0.136 | 1.21 | 1.49 (2) |
| 70/30 | 0.173 | 0.81 | 2.11 (3) |
| 65/35 | 0.314 | 0.54 | 14.86 (4) |
| Lactose | | | |
| 75/25 | 0.124 | 0.53 | 1.27 |
| 70/30 | 0.233 | 0.72 | 0.48 |
| 65/35 | 0.259 | 0.50 | 1.08 |
| Glucose | | | |
| 75/25 | 0.145 | 0.94 | 5.31 |
| 70/30 | 0.222 | 0.53 | 1.53 |
| 65/35 | 0.275 | 0.43 | 2.78 |

The total drug amounts which would be released over infinite time are approx. (1) 98%, (2) 42%, (3) 44% and (4) 65%, respectively.

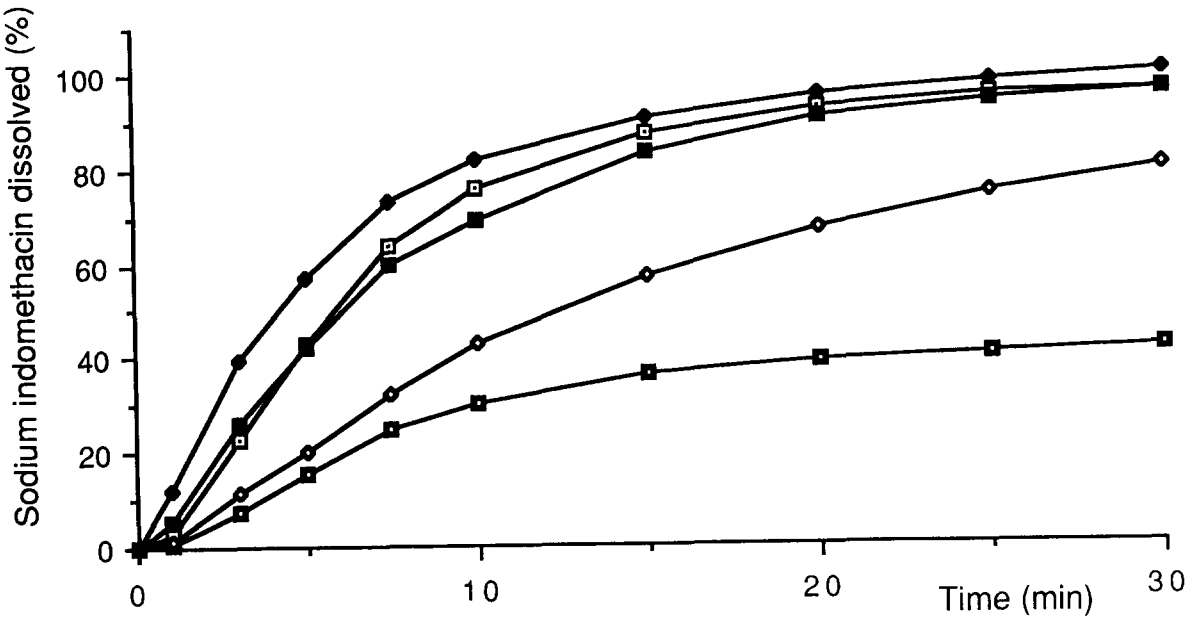


Fig. 8. Cumulative amounts (%) of sodium indomethacin released from EC/HPMC-75 : 25-coated granules ($n = 6$). Symbols as in Fig. 1.

figures were drawn using the values in Table 1. The values in the table were calculated using the short MatCAD algorithm explained in Appendix 1. The points in the figures represent averages of six parallel experiments.

Figs 2–6 show that indomethacin was released over 30 min almost completely from all of the granules except those containing calcium hydrogen phosphate dihydrate as filler. Fig. 6 shows that the total amount of indomethacin released over a 30 min period lay within the range 42–65%. The figure also shows that dissolution equilibrium was almost achieved within 30 min. Thus, it may be assumed that if longer dissolution times were used, the amount of the drug dissolved would remain markedly below 100%. A calcium salt of indomethacin might precipitate around the granules and prevent further dissolution. It is even possible that if longer dissolution periods (say 8 or 12 h) were studied the total amount of drug dissolved would decrease because of the incompatability between indomethacin ion and calcium ion. It would seem important to conduct such extended dissolution studies to achieve better and more detailed understanding of the unusual dissolution characteristics of sodium indomethacin in the presence of calcium hydrogen phosphate dihydrate.

## Conclusions

The release of sodium indomethacin, which is readily water-soluble, was not affected markedly by the porosity of the ethyl cellulose/hydroxypropylmethyl cellulose film. The porosity of the film affected drug release most when swellable maize starch was used in the core. Nearly all of the drug was released within 30 min from granules containing water-soluble lactose and glucose or slightly swellable microcrystalline cellulose as filler. Only calcium hydrogen phosphate dihydrate had a marked retardant effect on the release rate of sodium indomethacin. The total amount of drug released was also markedly smaller than with the other fillers. It would seem that during the dissolution of sodium indomethacin and filler in the core a new compound, a calcium salt of indomethacin, was produced. This less water-soluble salt was not released easily from the core. The

release of sodium indomethacin trihydrate followed first-order kinetics, calculated using the MathCAD programming package algorithm, fairly well.

**Acknowledgement**

The authors would like to thank the Merck Sharp and Dohme Research Laboratories for their donation of the sodium salt of indomethacin.

## Appendix 1

*Use of the MathCAD programming package in nonlinear curve fitting*

Nonlinear curves were fitted using MathCAD programming package. A typical algorithm is shown in Fig. 9.

The MathCAD function Minerr was used to approximate the experimental points. First, a simple first-order fitting function $F$ is defined as follows

$$F(t,k_1,\text{lag}) := 100\%(1-\exp[-k_1(t-\text{lag})]) \quad (1)$$

where $k_1$ is the first-order release constant ($\text{min}^{-1}$), and lag is the lag time (min). The constant 100% is the total amount which would be released from the system over infinite time.

This function (Eqn 1) clearly fulfils natural boundary conditions. At time $t = 0$, the amount of drug released is zero. After infinite time all of the drug amount is released from the granules.

The sum of squares to be minimized is defined in MathCAD programming by the relationship

$$\text{SSE}(k_1,\text{lag}) := \sum_i [y_i - F[t_i,k_1,\text{lag}]]^2.$$

SSE, the sum of the squared errors, is the sum over the data points of the squared differences between actual $y$ values and the $y$ values predicted by the fitting function. SSE is written as a function of the parameters $k_1$ and lag.

The program also needs guessed parameters. Sometimes it is necessary to experiment guess parameters but in this kind of simple problem it is quite easy.

The MathCAD solve block needs a constraint $\text{SSE}(k_1,\text{lag}) = 0$. A solve block requires as many constraints as there are variables. In this case it is necessary to add a dummy constraint $1 = 1$, for there are two parameters to be fixed. The function Minerr is then used to find the numerical values of the parameters.

Finally, the values of the calculated parameters and the value of $\text{SSE}/(n-2)$ are calculated and the data points and the fitting function are plotted to ensure the goodness of the fit.

(1) MathCAD User's Guide, Mathsoft, Inc, One Kendall Square, Cambridge, MA 02139, 1989.
(2) Nonlinear Curve Fitting, MathSoft User's Journal, vol. 4, no. 1, p. 5, 1990.

*Example of curve fitting*

*Nonlinear curve fitting*

Origin ≡ 1

Read in data file INDO3 to matrix $M$:

$M$: = READPRN(indo3)

Length of vector $t$

$n$: = length($t$), $i$: = 1 ... $n$

Read columns 1 and 4 to time vector $t$ and concentration vector $y$[1]

$t$: = $M^{(1)}$ $\quad$ $y$: = $M^{(4)}$

$$t = \begin{bmatrix} 0 \\ 1 \\ 3 \\ 5 \\ 7.5 \\ 10 \\ 15 \\ 20 \\ 25 \\ 30 \end{bmatrix} \quad y = \begin{bmatrix} 0 \\ 20.274 \\ 59.06 \\ 76.004 \\ 86.68 \\ 92.85 \\ 96.67 \\ 98.335 \\ 99.021 \\ 100 \end{bmatrix}$$

Define the fitting function $F$:

$$F(t,k_1,\text{lag}) := 100 \cdot [1-\exp\{-k_1 \cdot (t-\text{lag})\}]$$

Sum of squares to be minimized:

$$\mathrm{SSE}(k_1,\mathrm{lag}) := \sum_i \left[ y_i - F\{t_i,k_1,\mathrm{lag}\} \right]^2$$

Initial guess for parameters:

$$k_1 := 0.1,\ \mathrm{lag} := 1.$$

*The solve block*

Given the constraints

$$\mathrm{SSE}(k_1,\mathrm{lag}) \approx 0 \quad 1 \approx 1$$

Function Minerr finds the numerical values of the parameters

$$\begin{bmatrix} k_1 \\ \mathrm{lag} \end{bmatrix} := \mathrm{Minerr}(k_1,\mathrm{lag})$$

Plot the fitting function $L(z)$ and the experimental data points $y_i$

$$L(z) := F(z,k_1,\mathrm{lag}) \quad z = 0, 1, \ldots t_n$$

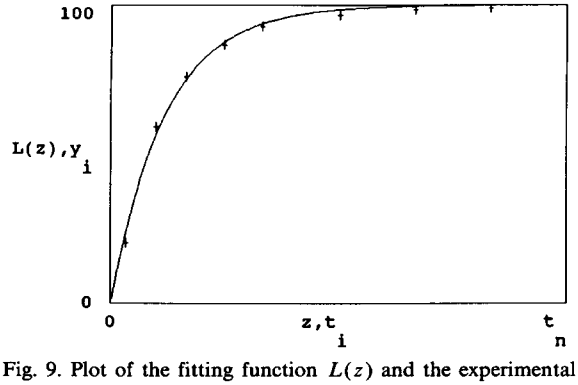


Fig. 9. Plot of the fitting function $L(z)$ and the experimental data points $y_i$. Parameters for best fit: $k_1 = 0.28$, lag = 0.043; mean square error: $\mathrm{SSE}(k_1,\mathrm{lag})/(n-2) = 3.502$.

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