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Research Papers

Interaction of NSA with cyclodextrins and hydroxypropyl cyclodextrin derivatives

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Summary

The effects of hydroxyalkylated cyclodextrins (CD) on the solubility and stability of the nonsteroidal antirheumatics (NSA) diclofenac, piroxicam and indomethacin were investigated. The stability constants of the indomethacin complexes calculated from the slope and the intercept of the phase solubility diagram are larger in the non-ionized form whereas the number of mol indomethacin per mol CD is much more pronounced in basic media. The pH profile of indomethacin at 21 and 41 °C shows four straight lines indicating no change in the degradation reaction on addition of CD. At both temperatures, hydroxypropyl-β-cyclodextrin (HP-β-CD) decreases the hydrolysis by one half. The influence of β-cyclodextrin (β-CD) and HP-β-CD on the stability of diclofenac solutions with and without oxygen at a stress temperature of 71 °C showed that the CD derivative has the most stabilizing effect. At room temperature the decrease was not significant, even when the solutions without CD were physically unstable due to recrystallization of the drug. In contrast to indomethacin and diclofenac, the CD have a destabilizing effect on the stability of piroxicam. Computer models of the complexes of indomethacin and diclofenac based on ^{1}H-NMR measurements are shown.

Introduction

The alkylated and hydroxyalkylated cyclodextrins (CD) appear to be more suitable for the formulation of solutions of poorly soluble drugs than the non-substituted parent CD, because of their increased aqueous solubility, lack of toxicity and ability to alter the phase solubility behaviour in favour of isotherms of the A-type (Müller and Brauns, 1985a,b; Pitha and Pitha, 1985; Pitha et al., 1986; Yoshida et al., 1988, 1989). Even in the field of stabilization of drugs, their improved aqueous solubility and capacity to form complexes, which are more stable than those of the parent CD, are of advantage (Hirayama et al., 1986, 1987; Backensfeld et al., 1990). The aim of the study reported here was to increase the aqueous solubility and stability of the NSA indomethacin, diclofenac and piroxicam with hy-

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droxyalkylated cyclodextrin derivatives. During this study attention was paid to the influence of the pH on both the solubility-increasing effect and the stabilizing influence of the CD.

Materials and Methods

Materials

The hydroxyalkylated cyclodextrin derivatives were kindly donated by Janssen (Beerse, Belgium) and were used as received. The determination of the molecular weight was calculated via the molar degree of substitution. α-CD was purchased from Lehmann and Voss (Hamburg, Germany), β-CD from Chinoin (Budapest, Hungary) and γ-CD from Nihon Shokukin Kako Co. Ltd (Tokyo, Japan). Indomethacin (Helm AG, Hamburg, Germany), diclofenac (Synopharm, Barsbüttel, Germany) and piroxicam (Schwarz, Monheim, Germany) were used in pharmaceutical grade without any further purification. All other reagents and solvents were of analytical grade and double distilled water was used throughout the study.

Apparatus

The high-pressure liquid chromatograph consisted of a Gynkotek 300B constant flow pump, a Gynkotek SP-4 variable-wavelength detector (Gynkotek, Munich, Germany) and a Shimadzu C-R18 integrator (Shimadzu, Kyoto, Japan). Injections were made with a Kontron MSI 660 autosampler (Kontron, Zurich, Switzerland) equipped with a 100 μl Rheodyne injection valve (Rheodyne, Cotati, U.S.A.). The pH of the solutions was measured with a pMX 2000 pH meter (WTW, Weilheim, Germany). The oxygen concentration in the atmosphere of the glove box was measured with a Toray type LF 700 oxygen analyzer (P. Lippke GmbH & Co. KG, Neuwied, Germany). An Oxi 530 oxygen analyzer with a Tri Ox EO 200 electrode (WTW, Weilheim, Germany) was used to detect oxygen in solution.

Solubility studies

Solubility measurements were carried out according to the methods of Higuchi and Connors (1965). Excess amounts of the drugs were added to solutions with different pH values: [(a) phosphate buffer pH 7.4 Ph. Eur.; (b) KH_2PO_4/Na_2HPO_4 buffer 133.4 mmol/l, with pH values varying from 4.9 to 7.8] containing various concentrations of CD and were shaken at 25 ± 0.5 °C in the dark. After equilibrium was attained, an aliquot was pipetted through a 0.45 μm membrane filter (Sartorius, Göttingen, Germany) and analyzed by HPLC. Apparent stability constants ($K_{1:1}$) were calculated from the slope and intercept of the straight portion of the phase solubility diagram according to the following equation (Higuchi and Connors, 1965): $K_{1:1} = \text{slope}/\text{intercept} \times (1-\text{slope})$.

HPLC

The assay for indomethacin in the preparations was carried out with the HPLC method reported previously (Backensfeld et al., 1990). For the determination of diclofenac the chromatograph was operated at a flow rate of 2.0 ml/min and the eluent was monitored spectrophotometrically at 276 nm. A column (5 mm i.d. $\times$ 25 cm) containing 5 μm Shandon ODS Hypersil RP 18 (Shandon, Runcorn, U.K.) was used for separation. The mobile phase consisted of acetonitrile/tetrahydrofuran/acetic acid/water (50:5:0.2:44.8). For the separation of piroxicam a column with Shandon SAS Hypersil RP-2,4,6 (5 μm in 5 mm $\times$ 25 cm, Shandon, Runcorn, U.K.) was used running with acetonitrile-water (28:72) adjusted to pH 2.7 with phosphoric acid as eluent. The chromatographic analyses were carried out at 20 °C. Peak areas of the undegraded drug were measured and compared with areas of known amounts of external standards.

Preparation of solutions for stability studies

To investigate the stability of indomethacin at different pH values with and without hydroxypropyl-β-CD (HP-β-CD) MS 0.39, 0.05 mg/ml indomethacin (1.4×10^{-4} M) dissolved in Sörensen buffer with pH values varying from 5.7 to 8.4 was mixed with a 10-fold excess of the CD (1.4×10^{-3} M). These solutions were filtered through a 0.22 μm membrane filter into presterilised 2 ml glass ampoules under aseptic conditions. The am-

poules were stored at 21 ± 1 °C and 41 ± 1 °C in the dark.

Diclofenac solutions with and without oxygen were prepared for the stability tests of diclofenac.

Diclofenac solutions without oxygen

All operational steps such as dissolving, filtering, filling and sealing were performed in a glove box filled with nitrogen and continuously rinsed, the residual oxygen values being ≤ 0.010% by vol. In order to eliminate oxygen from the solid starting materials (diclofenac sodium, β-CD and HP-β-CD), these were evacuated in a desiccator (0.9 bar) and cautiously flushed with nitrogen 4.6. As soon as the starting materials had been prepared, diclofenac sodium (6.3×10^{-3} M) was mixed with phosphate buffer, pH 7.4 Ph. Eur. and dissolved in double the quantity (12.6×10^{-3} M) of β-CD or HP-β-CD MS 0.39. The solutions without CD were prepared likewise. Each batch was filtered through a 0.22 μm membrane filter and filled into sterile 5 ml glass ampoules whilst flushing with nitrogen.

Diclofenac solutions with oxygen

These solutions were prepared in a similar manner to that of diclofenac solution without oxygen, however, no nitrogen was used in any operational step.

The solutions had oxygen contents determined with an oxygen electrode. The oxygen content varied from 0.01 to 0.03 ppm in the solutions without oxygen and from 4.0 to 5.2 ppm in those with oxygen. The ampoules were stored at 21 ± 1 °C and 71 ± 1 °C in the dark. Piroxicam solutions with 0.5 mg/ml drug content (1.51×10^{-3} M) and a 10-fold excess of CD (β-CD, HP-β-CD MS 0.39 and HP-γ-CD M.S. 0.4) were prepared in phosphate buffer pH 7.4 Ph. Eur. Similarly to the indomethacin solutions they were filtered through a 0.22 μm membrane filter into presterilized 2 ml glass ampoules under aseptic conditions. The solutions were stressed at temperatures from 21 ± 1 °C to 71 ± 1 °C.

Computer modeling

Computer modeling was carried out with the reported method (Backensfeld et al., 1990).

Results and Discussion

Solubility studies

Fig. 1 shows the phase solubility diagrams obtained for indomethacin and piroxicam with HP-β-CD MS 0.39 and HP-γ-CD MS 0.4, and Fig. 2 shows the diagrams for diclofenac. Regarding diclofenac, HP-γ-CD shows a solubility curve with a larger slope than the slope of the solubility curve obtained with HP-β-CD, in the case of indomethacin and piroxicam; HP-β-CD compared to HP-γ-CD has a greater complexing ability. All solubility curves can be classified as those of type A_N. We have previously reported on the typical A_N-type behaviour of indomethacin with various cyclodextrin derivatives (Müller and Brauns, 1985a). However, the question remains as to whether the capacity of the buffer used is sufficient for the relatively high indomethacin concentration of 0.02 M. When measuring the pH of the solutions it was found that, e.g., the pH of the indomethacin solutions decreases from pH 7.4 without HP-β-CD to pH 6.9 at 0.077 M HP-β-CD. A pH decrease is observed for all six solubility curves demonstrated here due to the low buffering capacity and the resulting concentration of drug. The indomethacin concentration noted on the ordinate is the sum of the saturation solubility and that part which is complexed by the

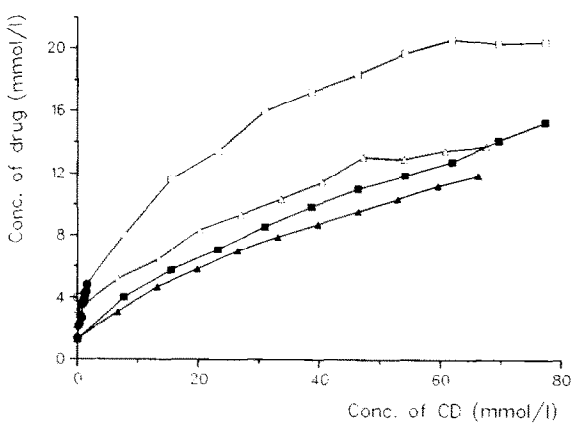


Fig. 1. Phase solubility diagram of indomethacin and piroxicam in phosphate buffer pH 7.4 at 25 °C. (□) Indomethacin + HP-β-CD MS 0.39; (△) indomethacin + HP-γ-CD MS 0.4; (■) piroxicam + HP-β-CD MS 0.39; (▲) piroxicam + HP-γ-CD MS 0.4; (●) piroxicam + β-CD.

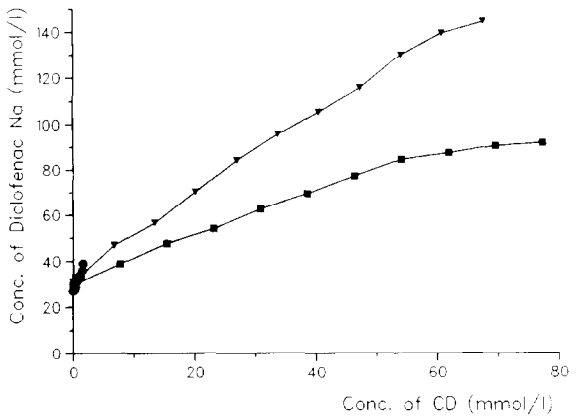


Fig. 2. Phase solubility diagram of diclofenac Na in phosphate buffer pH 7.4 at 25°C. (■) Diclofenac Na + HP-β-CD MS 0.39; (▼) diclofenac Na + HP-γ-CD MS 0.4; (●) diclofenac Na + β-CD.

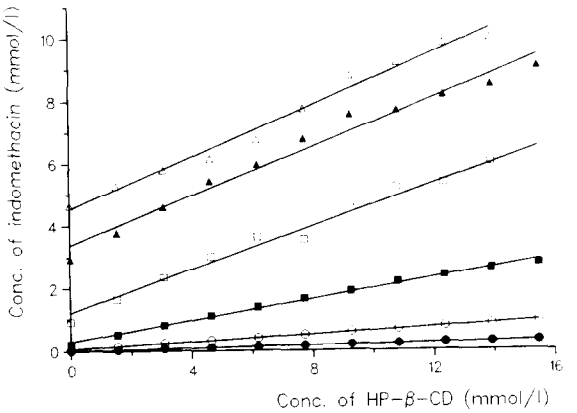
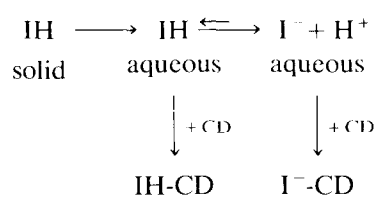


Fig. 3. Phase solubility diagram of indomethacin at 25°C at different pH values. (●) pH 4.9, (○) pH 5.5, (■) pH 6.1, (□) pH 6.7, (▲) pH 7.3, (△) pH 7.8.

CD. If a decrease takes place in the pH of the solution with increasing CD concentration, there will be a lowering of the saturation concentration of the drug due to the opposing influence of the dissociation constant of the acid drug (Scheme 1). Hence, the total amount of indomethacin in solution cannot increase linearly. To establish that the A_N-type behaviour is the only one as conjectured, we investigated the solubility of indomethacin at CD concentrations up to 0.016 M HP-β-CD. The results are demonstrated in Fig. 3. At high pH values there is still a slight increase in the H^+ concentration but at lower values the initial pH remains unchanged, and the phase solubility behaviour changes to the A_L type. Additionally, the correlation coefficient of the solubility curves increases with decreasing pH change of the solutions (Table 1).

Regarding the influence of the pH on the solubility-increasing effect of the CD, it can be concluded that with increasing pH values an increase occurs in both the saturation solubility (*y*-cut) and the slope of the solubility curves. Similar results have been reported for the complexation of phenytoin with β-CD (Menard et al., 1988). The influence of pH on the stability constants and on the efficacy of the solubility-enhancing effect is shown in Fig. 4. The stability constants $K_{1:1}$ of the indomethacin complexes calculated from the slope and the intercept of the phase solubility diagram are larger in the less ionized form, whereas the number of mol indomethacin per mol CD is much more pronounced in basic media. Investigating the interaction of indomethacin with the parent β-CD, Szejtli (1982) pointed out the greater solubility-en-



Scheme 1. IH, undissociated indomethacin; I^-, dissociated indomethacin.

TABLE 1

Data of the phase solubility curves of indomethacin with HP-β-CD MS 0.39 at different pH values

pH	C_s [a] (mg/ml)	$K_{1:1}$ (1/M)	M [b]	r^2	ΔpH [c]
4.9	0.0044	1580	0.019	0.9998	0.01
5.5	0.021	820	0.056	0.9994	0.07
6.1	0.086	630	0.163	0.996	0.09
6.7	0.340	420	0.335	0.980	0.09
7.3	1.05	190	0.396	0.976	0.10
7.8	1.66	170	0.420	0.981	0.20

[a] Solubility of indomethacin.
[b] Number of mol indomethacin per mol CD.
[c] Decrease in pH.

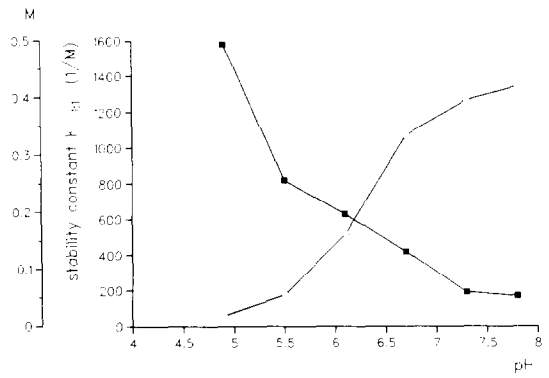


Fig. 4. (■) Stability constants $K_{1:1}$ of the indomethacin complexes vs pH. (○) Number of mol indomethacin per mol HP-β-CD MS 0.39 vs pH.

hancing effect with increasing pH. In a comparative study, Otagiri and co-workers (1984) observed a decrease in stability constants of inclusion complexes of flufenamic acid with β-CD and tri-*O*-methyl-β-cyclodextrin with rise in pH, whereas in a study of the system pirprofen/β-CD the stability constant changed with pH and a maximum value was found at pH 7.5 (Hibi et al., 1984).

Stability studies

Fig. 5 shows the log k_{obs}-pH profiles for the hydrolysis of indomethacin in the absence and presence of HP-β-CD MS 0.39 at 21 and 41 °C. The four parallel straight lines indicate a linear

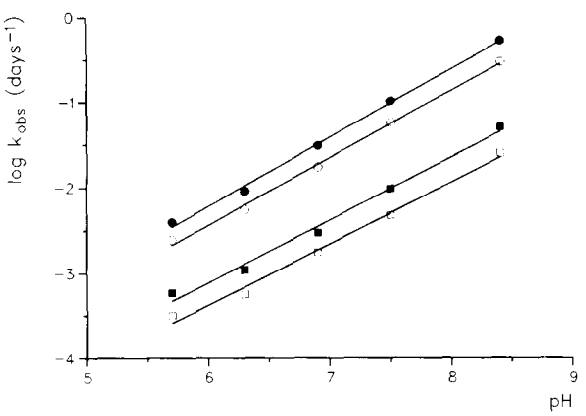


Fig. 5. Log *k*-pH profile of indomethacin hydrolysis in the absence and presence of HP-β-CD MS 0.39. 41 °C: (●) without CD, (○) with CD; 21 °C: (■) without CD, (□) with CD.

relationship between log k_{obs} and pH. With increasing H^+ concentration the observed pseudo-first order rate constant decreases and the system becomes more stable. The degradation of indomethacin to 5-methoxy-2,3-dimethylindole and *p*-chlorobenzoic acid is pH-dependent and shows a general catalytic effect at basic pH (Krasowska, 1974; Tomida et al., 1988). With a slope of −0.8 the investigations support this finding. In addition to the influence of the pH, e.g. buffer ions can act as a degrading agent (Stricker, 1987). The parallel course of the straight lines indicates that the stabilizing effect of the CD is independent of pH. Using the Sörensen buffer, HP-β-CD decelerates the hydrolysis of indomethacin by a factor of 2, whereas using the buffer of the Ph. Eur. the extent of retardation is a factor of 6 (Backensfeld et al., 1990). Obviously, the buffer ions of the salt 'Na_2HPO_4' additionally included in the Sörensen buffer have a negative effect on the CD stabilizing effect. Possibly, the buffer ions are also complexed and displace the drug molecule out of the CD-cavity.

Even when using very low pH values, it is not possible to obtain a stable aqueous indomethacin solution ($t_{90\%}$ = 3 years) with HP-β-CD as stabilizer. A more lipophilic CD derivative might be more suitable for stabilizing aqueous indomethacin solutions (Backensfeld et al., 1990). Therefore, it is advantageous to adjust the desired pH value with an acid or base and not with a buffer.

The parallel course in Fig. 5 is rather surprising in view of the increase occurring in the stability constants with decreasing pH values. A more stable solution at low pH values would be expected with addition of HP-β-CD. The intensity of the interaction forces appears to be of minor importance for a stabilizing effect at a 10-fold excess of the CD, since nearly every indomethacin molecule is included in the CD cavity. On the other hand, the spatial structure of the complexes seems to be the decisive factor.

The influence of β-CD and HP-β-CD on the stability of diclofenac solutions with and without oxygen was examined at 21 and 71 °C. No significant decrease in drug content could be observed at 21 °C during the storage time of 520 days. The

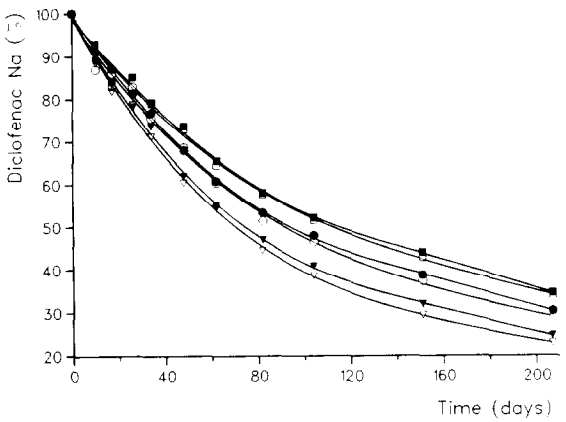


Fig. 6. Influence of CD on the stability of diclofenac Na in phosphate buffer pH 7.4 at 71°C. (▽) Only diclofenac Na with O_2; (○) diclofenac Na + β-CD with O_2; (□) diclofenac Na + HP-β-CD MS 0.39 with O_2; (▼) only diclofenac Na without O_2; (●) diclofenac Na + β-CD without O_2; (■) diclofenac Na + HP-β-CD MS 0.39 without O_2.

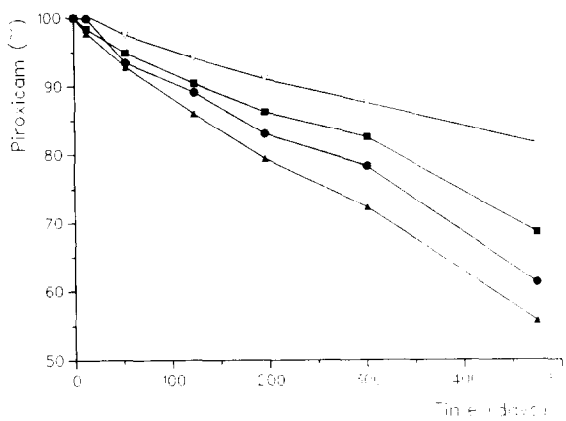


Fig. 7. Degradation of piroxicam in the presence of CD in phosphate buffer pH 7.4 at 61°C. (▽) Piroxicam alone; (●) piroxicam + β-CD; (■) piroxicam + HP-β-CD MS 0.39; (▲) piroxicam + HP-γ-CD MS 0.4.

analysis was carried out in triplicate; the coefficient of variation of the method was calculated as 1.2%, $p = 0.05$ (Grimm and Schepky, 1980). The solutions lacking additive, however, proved to be physically unstable due to the precipitation of some crystalline diclofenac observed during a short storage time. The results from investigation of the stress temperature are demonstrated in Fig. 6. The CD derivative has the strongest stabilizing effect on diclofenac decomposition. After 207 days, the amount of diclofenac remaining undegraded in a solution without oxygen and with HP-β-CD as stabilizer was found to be 34.6%. A solution with β-CD still contained 30.4% diclofenac and a nitrogen purged solution with diclofenac alone had a drug content of 24.7%. At the stress temperature of 71°C, the influence of oxygen on the stability was observed to be slight. However, in principle, the solutions without oxygen are more stable than those with oxygen. Because of the physical instability at room temperature, a diclofenac solution with CD addition would be preferred. The undesirable aspects of β-CD usage such as nephrosis or poor aqueous solubility can be avoided by using HP-β-CD as solubilizer to achieve the required dose of 75 mg/3 ml.

To examine the influence of β-CD, HP-β-CD and HP-γ-CD on the stability of piroxicam, solutions with a 10-fold excess of the respective CD were stored at 21°C up to 71°C. Table 2 summarizes the effects of the CD on the degradation of

TABLE 2

Piroxicam concentration in solutions at pH 7.4 stored at different temperatures

Temperature (°C)/ time (days)	Piroxicam without CD (%)	Piroxicam + β-CD (%)	Piroxicam + HP-β-CD (%)	Piroxicam + HP-γ-CD (%)
21/475	101.1	99.0	98.7	96.8
31/500	99.3	98.8	99.4	93.7
41/475	99.4	92.3	94.8	86.9
51/475	93.4	86.2	88.0	78.4
61/475	81.6	61.2	68.6	55.7
71/500	39.4	23.3	24.5	22.9

piroxicam. All CD studied accelerated the rate of decomposition. The destabilizing effect was in the order of HP-γ-CD > β-CD ≥ HP-β-CD. This is also demonstrated in Fig. 7. The decomposition reaction does not follow a simple kinetic law such as a first-order reaction. Thus, an evaluation using the Arrhenius equation is not possible. The decrease in drug content at room temperature after 475 days is only statistically significant with HP-γ-CD. The determination was carried out in triplicate; the coefficient of variation of the method was 0.9%, $p = 0.05$ (Grimm and Schepky, 1980). Therefore, it is possible that a piroxicam solution with less than 10-fold excess of the solubilizer HP-β-CD can lead to a stable aqueous piroxicam solution.

Computer modelling

For modelling of the inclusion complex between indomethacin/β-CD and diclofenac/β-

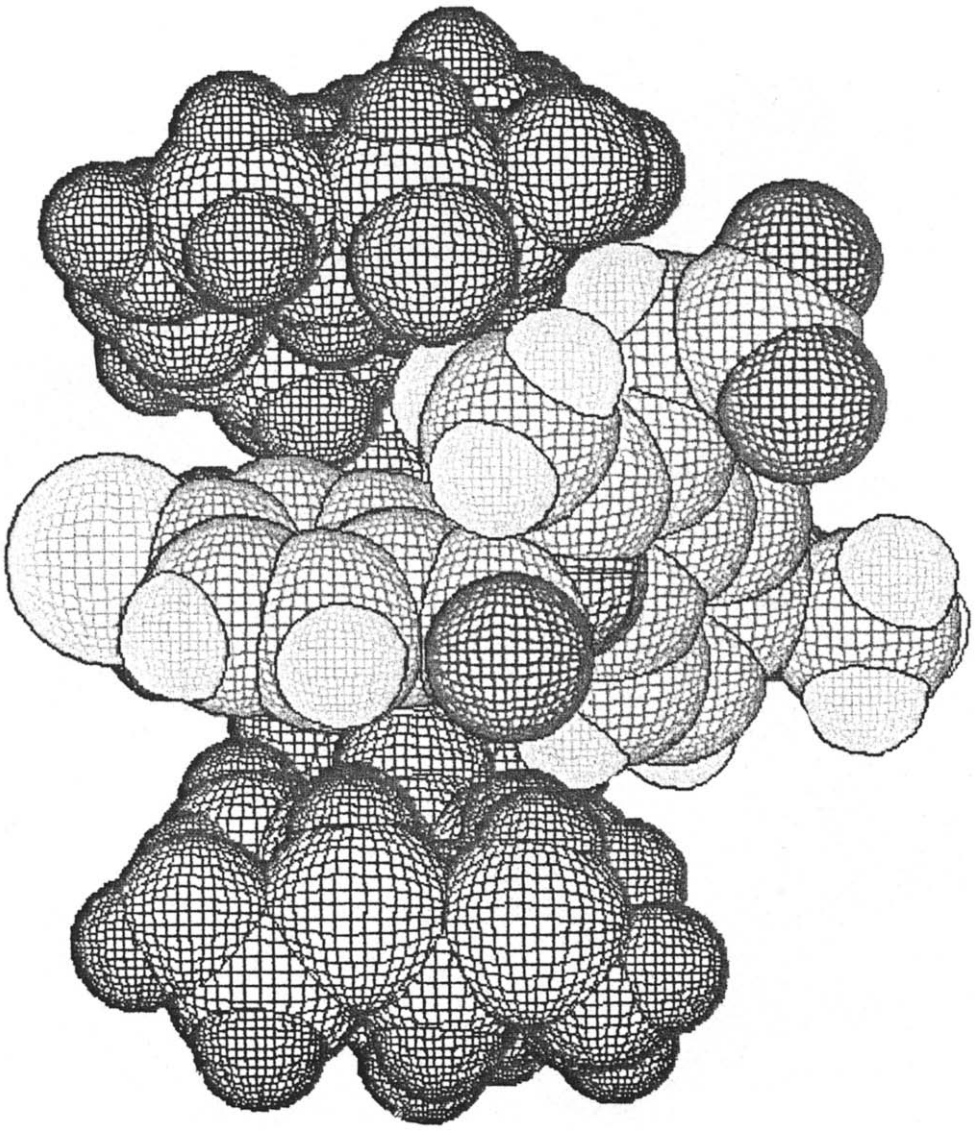


Fig. 8. Computer model of the inclusion complex between indomethacin and β-CD.

CD, the selected low-energy conformations were docked into the CD. The distances between the CD atoms and those parts of the drugs which were influenced by complexation were monitored. Those conformations which were in agreement with the NMR data showed no significant difference in the calculated binding energy. Fig. 8 shows the modelling of the indomethacin molecule docked into the polymer ring structure of β-CD. β-CD X-ray coordinates were selected for this modelling, since CD derivatives are amorphous and thus no crystal data are available. Fig. 8 demonstrates the inclusion of the *p*-chlorobenzoic part of the indomethacin molecule into the CD channel. The CD ring has been cut in order to provide a better illustration and shows the CD ring with the glucose molecules at the rear having a darker shading than the drug molecule.

Modelling of the diclofenac/β-CD complex under the conditions described is shown in Fig. 9.

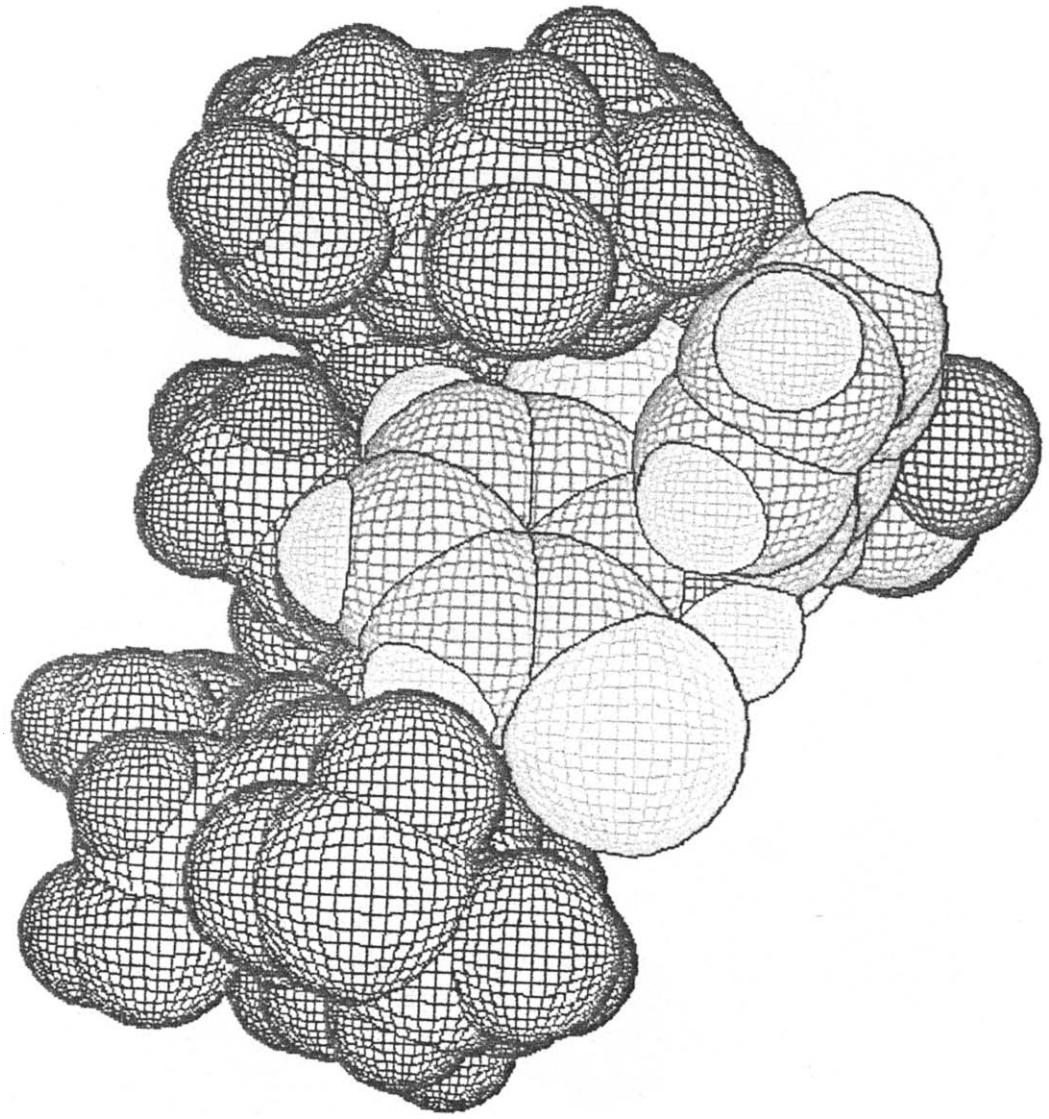


Fig. 9. Computer model of the inclusion complex between diclofenac Na and β-CD.

Because of the angled conformation of the two aromatic groups (Sallmann, 1976) with a torsional angle of 69°, the existence of a complex with the whole molecule in the CD cavity is impossible. The part with the two chlorine atoms penetrates into the cavity, whereas that with the polar carboxy group protrudes from the CD structure and abuts on the margin of the CD.

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