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# The influence of the microcapsule wall on the assay of indomethacin microcapsules in the presence of antacids—implications for product stability

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## Summary

The analysis of indomethacin microcapsules prepared by a gelatin–acacia complex coacervation technique involved extraction with 70% aqueous methanol and subsequent UV absorption of the filtered solution at 320 nm. In the presence of antacid, hydrotalcite, a recovery of approximately 50% of the indomethacin from the microcapsules was observed. Paradoxically, complete recovery of unencapsulated indomethacin in the presence of antacid was found when subjected to the same analysis technique. The breakdown products were identified as *p*-chlorobenzoic acid (PCB) and 5-methoxy-2-methylindole-3-acetic acid (MMIAA) which were identical to those following the hydrolysis of indomethacin in aqueous sodium hydroxide, together with a third product, methyl-*p*-chlorobenzoate (MCB). The capsule wall thus had a catalytic effect in causing the decomposition of the core in the assay procedure. An alternative assay method was developed and the implications for product stability are discussed.

## Introduction

Gastrointestinal (G.I.) and CNS side-effects associated with indomethacin and other non-steroidal anti-inflammatory compounds have been previously reported (Wanka and Dixon, 1964; Katz et al., 1965; Boardman and Hart, 1967). The mechanism of these side-effects is still uncertain and it has been shown that the

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dosage form plays an important role on the incidence and severity of these side-effects (Ballabio and Caruso, 1964; Michotte and Wauters, 1964; Thompson, 1964; Lövgren and Allender, 1965; Smyth, 1965). Recently, Aylward (1979) has shown that a microcapsulated formulation of indomethacin significantly reduced the incidence and severity of both CNS and G.I. side-effects compared to a conventional capsule formulation. These results were reported by Rowe (1980). Using the Critical Flicker Fusion Frequency test (CFF) Carless and Rowe (1981) have shown differences in CNS activity between these two formulations when given in equivalent dosage. Although there is no conclusive evidence that indomethacin augments gastric acidity, or that an antacid decreases the rate of ulcer formation in patients treated with both drugs, the frequent use of the combination is based on the general rule 'no acid—no benign ulcer' (Galeazzi, 1977). It would thus seem feasible to formulate the microencapsulated indomethacin with a suitable antacid to achieve a further reduction in gastrointestinal side-effects. The problems associated with such a formulation were thought to be the inherent instability of indomethacin in the presence of alkali as reported by Hajratwala and Dawson (1977). This problem might be overcome by the physical separation of the indomethacin from the antacid by means of the microcapsule wall which may act as a protective barrier. The antacid chosen was hydrotalcite because of its quick onset of action and prolonged buffering action in the optimum pH range (Playle et al., 1974). The influence of the microcapsule wall on the assay of indomethacin microcapsules in the presence of hydrotalcite and the implications for product stability are now reported.

## Materials and methods

*Indomethacin*

The indomethacin core used in the preparation of the microcapsules was described previously (Rowe and Carless, 1981). Hydrotalcite (Altacite) was supplied by Roussel Laboratories, Wembley, U.K.

*Microencapsulated indomethacin*

Indomethacin microcapsules were prepared using a gelatin–acacia complex coacervation procedure essentially as described by Nixon and Nouh (1978). The ratio of drug core to colloid coat was 1 : 5. The microcapsules were assayed by refluxing with methanol and the indomethacin content determined by comparing the UV absorbance of the filtered solution at 320 nm to the standard curve of indomethacin in methanol (Carless and Rowe, 1981).

Analytical studies to determine the indomethacin content of microcapsules in the presence of antacid were performed after mixing an equal amount of microcapsules and antacid on a Luckham rotary mixer for 30 min. The proposed degradation products in the presence of alkali and methanol, i.e. *p*-chloromethyl benzoate and methyl(5-methoxy-2 methylindole-3-acetic acid), were synthesized and authenticated as described by Rowe (1980).

*HPLC studies*

These were carried out using a system consisting of a model 40 reciprocating pump (HS Chromatography Packings, Bucks, U.K.) fitted with a 10 $\mu$l injection valve, a Cecil Instruments UV variable wavelength detector, Model CE2012 connected to a Servoscribe pen recorder. The column used was a Partisil PXS 10/25 ODS (Whatman, U.K.). The mobile phase, which consisted of acetonitrile–0.1 M acetic acid (40 : 60), was pumped at the rate of 2.5 ml · min$^{-1}$ at a pressure of 1500 psi and the wavelength of analysis was 254 nm.

*IR, NMR and MS studies*

IR spectra were performed in Nujol mulls using a Perkin-Elmer recording spectrophotometer. NMR studies were carried out using a Perkin-Elmer R12A 60 MHZ instrument using TMS as reference standard. Samples were dissolved in deuterated chloroform ($CDCl_3$) for analysis. Mass spectra were determined on a VG 12F mass spectrophotometer using both 18 and 70 EV ionizing potential. Samples were directly introduced into a relatively cool probe and minimum heat applied until vaporization occurred at which time the spectra were determined.

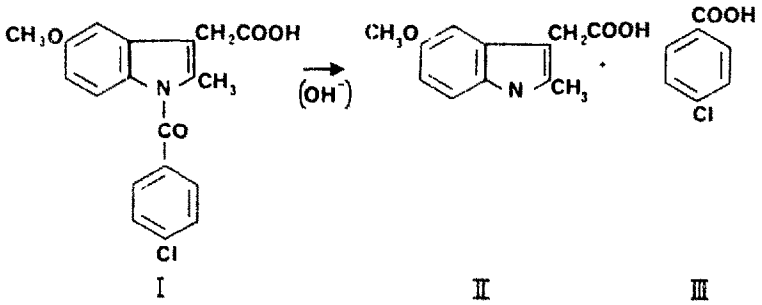
*TLC studies*

Thin-layer chromatography (TLC) studies were performed using silica gel G plates, of thickness 0.25 mm, developed with a mixture of acetic acid–chloroform (5 : 95). Preparative TLC studies were performed by streaking the TLC plate with the reaction product and the plate developed as before. The resulting bands were scraped off the plate and dissolved in a small quantity of methanol, filtered to remove the silical gel and the methanolic solution evaporated to dryness. The resultant products were recrystallized from 90% ethanol.

## Results

*Stability in the presence of aqueous sodium hydroxide*

Preliminary studies on the stability of indomethacin powder in the presence of aqueous NaOH confirmed the findings of Hajratwala and Dawson (1977) in that the rate of degradation was a function of the hydroxide ion concentration. Preparative TLC and spectral studies showed the degradation to occur as shown in Scheme I.




I II III

Scheme I. Hydrolysis of indomethacin powder in the presence of hydroxide ion. I = indomethacin; II = 5-methoxy-2-methylindole acetic acid (MMIAA); III = *p*-chlorobenzoic acid (PCB).

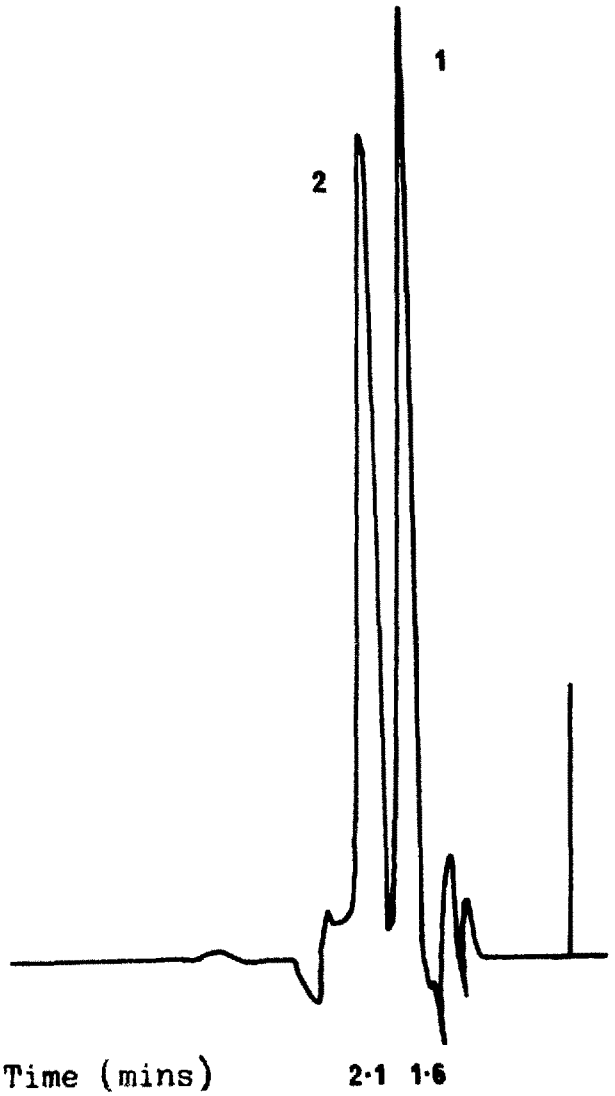



Fig. 1. HPLC analysis on the hydrolysis products of unencapsulated indomethacin in the presence of 0.1 N NaOH. (1) 5-methoxy-2-methylindole acetic acid (MMIAA); (2) *p*-chlorobenzoic acid (PCB).

HPLC analysis on the hydrolysis products of unencapsulated indomethacin in the presence of 0.1 N NaOH is shown in Fig. 1.

*Stability in the presence of hydrotalcite*

Analysis of indomethacin microcapsules in the presence of hydrotalcite by the technique described above resulted in a variable recovery in the order of 50% from the microcapsule due to degradation of the indomethacin core. Control experiments on unencapsulated indomethacin powder mixed with hydrotalcite resulted in complete recovery with no evidence of decomposition. HPLC analysis on the reflux mixture of unencapsulated indomethacin in the presence of hydrotalcite in 70% methanol is shown in Fig. 2.

*Development of alternative assay method*

In order to avoid decomposition arising in the microcapsules and hydrotalcite mixture, alternative methods of quantitatively extracting the core for assay were investigated. These included ultrasonification of the capsule wall in the presence of water and various solvents, physical grinding of the mixture in a mortar prior to extraction and refluxing with various solvents other than methanol. Poor recoveries resulted from all these techniques illustrating that breakdown of the indomethacin core had occurred, or that some form of physical or chemical binding of the drug to the microcapsule wall or one of its constituents had occurred which was only broken by heat treatment. The ultimate procedure chosen was to remove the antacid prior to assay by adding an excess of dilute hydrochloric acid. The mixture was then centrifuged at 2000 rpm for 5 min and the excess acid decanted. The capsules were then carefully washed with distilled water 3 times to remove any adsorbed acid and subsequently refluxed with methanol for the determination of indomethacin as


Fig. 2. HPLC analysis on the hydrolysis products of unencapsulated indomethacin in the presence of hydrotalcite in 70% MeOH. (3) Undegraded indomethacin.

previously described. Any traces of acid remaining were found to cause subsequent esterification of the indomethacin hydrolysis products during the extraction process. This was verified by comparison of spectral and HPLC studies on the authentic methyl esters of the hydrolysis products.

*Elucidation of breakdown products*

Samples of the supernatant liquid following the refluxing of the indomethacin microcapsules and hydrotalcite mixture were subjected to HPLC, and 4 peaks were observed, as shown in Fig. 3, with the retention time and peak identification based on retention times of authentic samples.

The occurrence of product 4, the methyl ester of *p*-chlorobenzoic acid was confirmed by preparative TLC and subjecting the product to IR, NMR and MS analysis. As a control experiment, empty capsules subjected to the same refluxing procedure produced no peaks on HPLC analysis. To determine whether the degradation pattern was a specific reaction of hydrotalcite with encapsulated drug on refluxing with methanol, other antacids were mixed with indomethacin microcapsules and refluxed with methanol as before, and the supernatant subjected to HPLC analysis. The antacids tested were sodium bicarbonate, aluminium hydroxide and magnesium trisilicate. Sodium bicarbonate produced similar results to the hydrotalcite but with aluminium hydroxide no decomposition was evident as only a single

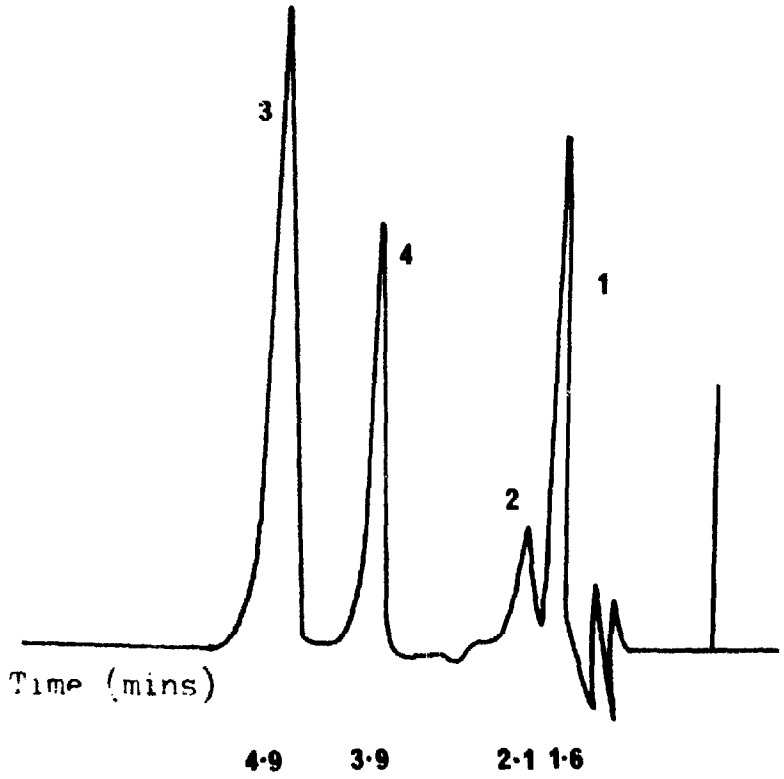



Fig. 3. HPLC on hydrolysis products of encapsulated indomethacin in methanol and hydrotalcite. (1) 5-methoxy-2-methylindole acetic acid (MMIAA); (2) *p*-chlorobenzoic acid (PCB); (3) indomethacin; (4) methyl-*p*-chlorobenzoate (MCB).

peak corresponding to indomethacin (4.9 min) was observed. The magnesium trisilicate resulted in a small amount of decomposition to PCB and MMIAA (in the order of 10%). No formation of the ester of *p*-chlorobenzoate was observed. On refluxing unencapsulated indomethacin with each of these antacids in methanol for 30 min, no decomposition of drug was observed in any case.

## Discussion

The degradation pattern of encapsulated indomethacin in the presence of hydrotalcite when refluxed with methanol is similar to that reported for the unencapsulated drug in sodium hydroxide in that the molecule is cleaved at the indole nitrogen to produce PCB and MMIAA. However, some of the PCB has been esterified to its methyl ester as illustrated in peak 4 in Fig. 3. All available spectroscopic evidence confirms peak 4 to be methyl-*p*-chlorobenzoate. Other evidence is that the retention time of the synthesized MCB corresponds to product 4, and the peak height ratio, MMIAA: PCB, increases as the product peak 4 increases. Thus the hydrolysis product, MMIAA, is not affected by the further formation of the subsequent degradation product, whereas the amount of the PCB detected decreases as the amount of its methyl ester increases.

Without the influence of the microcapsule wall, the ratio of the peak heights, MMIAA: PCB, is 1.3 following the hydrolysis of indomethacin in 0.1 N NaOH. This ratio increases to 4.3 after subjecting the microcapsule and hydrotalcite mixture to hydrolysis by refluxing with methanol. From the data it would seem that the hydrotalcite does not react directly with the indomethacin, but is a causative factor in its breakdown when the drug is encapsulated. The presence of the capsule wall does not by itself cause breakdown under the conditions of the extraction, but in the presence of hydrotalcite breakdown occurs. With other antacids, the extent of decomposition was directly related to the water-solubility of the antacid employed. It would seem that the presence of the antacid brings enough acid gelatin into solution, and vice versa, when the materials are refluxed with methanol. Some cleavage of the gelatin molecule is then thought to occur which creates an environment for some esterification to take place. This esterification (albeit a small side-reaction) occurs only on the PCB moiety following hydrolysis of the parent indomethacin, and no evidence was found for the formation of the methyl ester of MMIAA, the other product of the hydrolysis reaction. This is to be expected as esterification would preferentially occur on the PCB with its more ionizable acidic proton. It is also highly probable that the methyl group on the 2 position of the MMIAA exerts a considerable degree of steric hindrance to the esterification reaction and thus is not observed. This degradation process may be of predictive value in the overall stability of the product as paradoxically, instead of protecting the drug from the hydrotalcite which was thought to be a potential hydrolysing agent, the capsule wall may have a catalytic effect in causing decomposition of the drug in the presence of moisture. The resulting products of hydrolysis are PCB and MMIAA. It has also been shown that in the presence of methanol, the methyl ester

of PCB is also produced and hence in the assay procedure the antacid must firstly be removed by the addition of an appropriate amount of acid, followed by digestion of the capsule wall with the aid of heat to liberate the indomethacin core. The core is ultimately recovered by centrifugation and then redissolved in methanol for UV assay.

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