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# THE EFFECT OF pH ON THE RELEASE CHARACTERISTICS OF THIABENDAZOLE MICROCAPSULES

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A standard gelatin-gum acacia complex coacervation technique has been used to prepare microcapsules contining thiabendazole. The effect of pH conditions on the release of the drug from these microcapsules has been studied and the results related to microcapsule size and the overall solubility of the drug. No long delay in the release was sought as a full dose response was required to occur by the time the dosage had reached the small intestine.

Microencapsulation, as a method of presenting small particles of solid or liquid drugs, makes use of gelatin-gum acacia coacervates as a wall material for water insoluble medicaments. Details of many of the techniques used may be found in the numerous papers of Luzzi & Nixon (1-3).



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An attempt has been made to reduce the incidence of toxic symptoms of thiabendazole such as dizziness, nausea, vomiting and hypersensitivity which are present in patients with hepatic disease, by microencapsulation. This improved the general tolerability of the above-mentioned patients to the drug and lowered the rate of absorption. The present investigation reports the in vitro pH-dissolution rate behaviour of microencapsulated thiobendazole of varying core:colloid ratios.

## EXPERIMENTAL

### Materials

Thiabendazole. Supplied by Merck Sharp & Dohme and characterised by its U.V. spectrum.

Colloidal Materials. The gelatin and gum acacia were from batches used in previous work at Chelsea College and the characteristics have been given in previous papers (3-5).

Buffer Systems. The details of buffer systems used are shown in TABLE 1.

### Methods

#### Preparation of Microcapsules

A suspension was prepared by adding thiabendazole powder to a 2% solution of gum acacia, which was stirred at 300 r.p.m. The same volume of a 2% gelatin solution was added slowly with continuous stirring and the coacervate mixture maintained at a temperature of $40^{\circ} \pm 0.5^{\circ}C$. The pH of the solution was adjusted to $4.0 \pm 0.2$ and formaldehyde solution added to cross link the gelatin in the microcapsule wall. After cooling the mixture free

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TABLE 1

Composition of Aqueous Buffer Systems

| pH | Composition |
|---|---|
| 2.0 | 119 ml M/5 HCl + 881 ml M/5 KCl diluted to 2 l |
| 2.2 | 75.2 ml M/5 HCl + 924.8 ml M/5 KCl diluted to 2 l |
| 7.0 | 500 ml M/5 $KH_2PO_4$ + 295.4 ml M/5 NaOH diluted to 2 l |
| 7.0 | 12.11 g Tris (hydroxymethyl) methylamine diluted to 1 l and adjusted to pH with HCl |
| 9.6 | 12.11 g Tris (hydroxymethyl) methylamine diluted to 1 l |
| 10.0 | 500 ml (M/5 $H_3B\ O_3$ + M/5 KCl) + 439 ml M/5 NaOH diluted to 2 l |
| 10.0 | 12.11 g Tris (hydroxymethyl) methylamine diluted to 1 l and adjusted to pH with $NH_4OH$ solution |

flowing microcapsules were obtained using three isopropanol washes followed by air drying. Care was taken to prevent depletion of the core due to its solubility in the alcohol. Unhardened microcapsules were prepared similarly but without the formalin treatment. Variations were used to give a core:colloid ratio of 1:4, 1:3 and 1:2 in which the core component was constant. Similar core:colloid ratios were prepared in which the colloid component was constant. A final variation involved adjusting to pH 9.2, as suggested by Luzzi and Gerraughty (1), in the later stages of preparation.

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Determination of Thiabendazole

Thiabendazole was assayed by means of the U.V. peak aborbence which occurred at 303 nm. The total amount of drug contained in the microcapsules was found by refluxing a known quantity of microcapsules for 15 minutes in a pH 2.2 buffer solution prior to U.V. assay.

Dissolution Studies

A flask and stirrer technique using 500 mg of microcapsules in 2 l of dissolution medium was used. This volume was sufficient to allow sink conditions to be maintained. The stirring speed was 100 rpm and the paddle was 2 cm above the bottom of the flask in order to maintain the microcapsules in suspension. The normal technique of volume replacement was followed and irrespective of the pH of the dissolution medium being used, the samples were adjusted to pH 2.2 prior to assay at 303 nm. The dissolution was followed over a period of 4 hours.

## RESULTS AND DISCUSSION

Thiabendazole is frequently considered to be an ideal anthelmintic because of its broad anthelmintic spectrum. Clinical trials (6-11) have proved its efficacy. Thiabendazole is particularly useful in tropical countries where multiple parasitic infection is the rule.

Many workers have demonstrated the efficacy of thiabendazole when compared with other anthelmintics. Salunkhe & Balwani (12) compared the anthelmintic activity of thiabendazole, thymolan and tetrachlorethylene on the basis of reduction in count of ova after

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therapy. With thymolan and thiabendazole a greater reduction in ova count was observed than with tetrachlorethylene. Abdul Quadir (13) showed that thiabendazole was more efficient than bephenium hydroxynaphthoate in reducing the egg counts of trichostrongylid type worms.

Microencapsulation would be expected to increase the tolerability of thiabendazole because it should allow the drug to be absorbed over the larger surface area available in the first part of the small intestine, rather than in the stomach, where the pH still remains on the acid side of neutrality.

The pH dependence of release from microcapsules has been shown by many workers for a variety of drug molecules (Nogami, Nagai & Suzuki (14); Mounajed (15); Agyilirah (16)). The effect of pH on the solubility of the drug is shown in TABLE 2. The maximum occurs at pH 2.2. Variations on this maximum solubility have been recorded, e.g: Robinson, Stoerk & Graessle (17) give 1.5% at pH 2.5, Merck Sharp & Dohme Ltd, 0.5% at pH 2, Merck Index (18) 3.84% at pH 2.2. With such wide variations it is important to determine the solubility of particular batches prior to dissolution studies.

TABLE 2

The Effect of pH on the Solubility of Thiabendazole

| pH | 1.5 | 2.0 | 2.2 | 2.6 | 3.6 | 4.6 | 7.0 | 10.0 |
|---|---|---|---|---|---|---|---|---|
| Solubility mg per 100 ml | 134 | 276 | 350 | 156 | 45 | 32 | 28 | 17 |

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Figure 1 illustrates the release pattern of thiabendazole from 1:4 core:colloid formalin hardened microcapsules. These microcapsules contained 93% of the theoretical quantity of thiabendazole originally included. The effect of varying the pH of the buffer solution is clearly observable. In the acid buffer of pH 2 the release was more than 90% over a period of 45 minutes. This is obviously a very rapid release when compared with that at pH 7 and 10 where there was 63% and 50% release respectively over the full four hours dissolution period. The shape of the curve

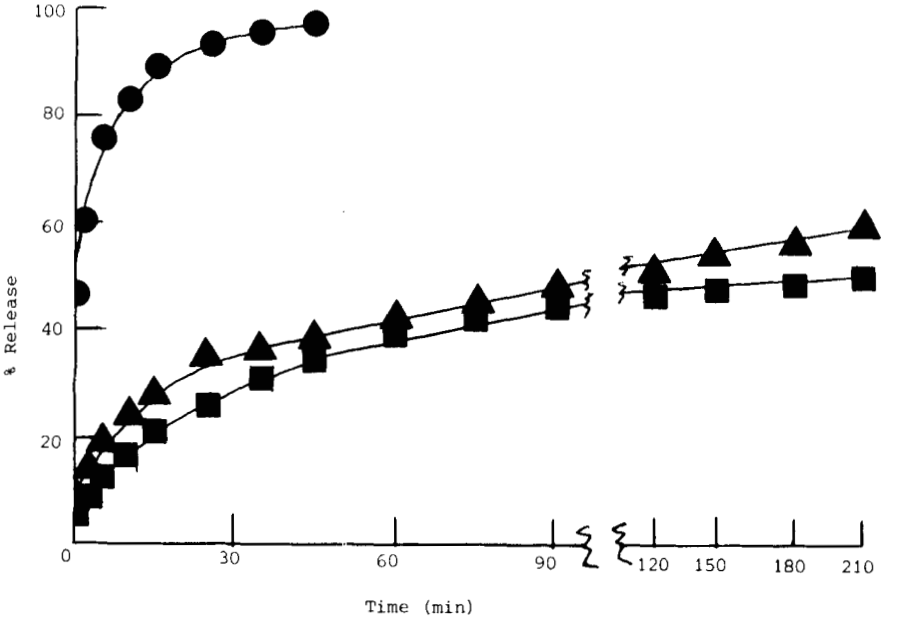


FIGURE 1

The Effect of Buffer pH on the Release of Thiabendazole from Microcapsules.
Core:colloid ratio, 1:4. Buffers, pH2 ● (N/5 KCl + N/5 HCl), pH 7.0 ▲ (N/5 $KH_2PO_4$ + N/5 NaOH), pH 10.0 ■(N/5 Boric Acid, KCl + N/5 NaOH). Temperature 37°.

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shows that even here the intial release was high and at the end of the first hour 40% approximately had been released.

More surprising was the observation that as the core:colloid ratio increased the precentage release at a given time was lower. It is possible that as the amount of core material increased within individual microcapsules larger particles or aggregates would occur and present a relatively smaller surface area for dissolution. This in turn would lead to slower release parameters. Alternatively if it is the surface of the hydrated microcapsule which is the controlling factor then with the higher concentration of thiabendazole the proportion diffusing through the total area in unit time will represent a smaller proportion of the whole and will show in plots as a smaller percentage release. Typical results are shown in Figure 2.

When a comparison is made between the release rate of the drug from hardened and unhardened microcapsules it was found that with the untreated material the rate of release was significantly faster (Figure 3). Only at pH 2 did the hardened microcapsules release their drug rapidly and completely although even here over one hour was required for complete release compared with 15 minutes for the non hardened microcapsules. With buffers of pH 7 63% was released in 4 hours and 40% within 1 hour from the hardened samples whilst with unhardened microcapsules 35 minutes was capable of releasing 88.5% of the drug. About the same difference was noticeable with the buffer solution of pH 10.0. This was 50% in 4 hours for the hardened microcapsules and 84% in

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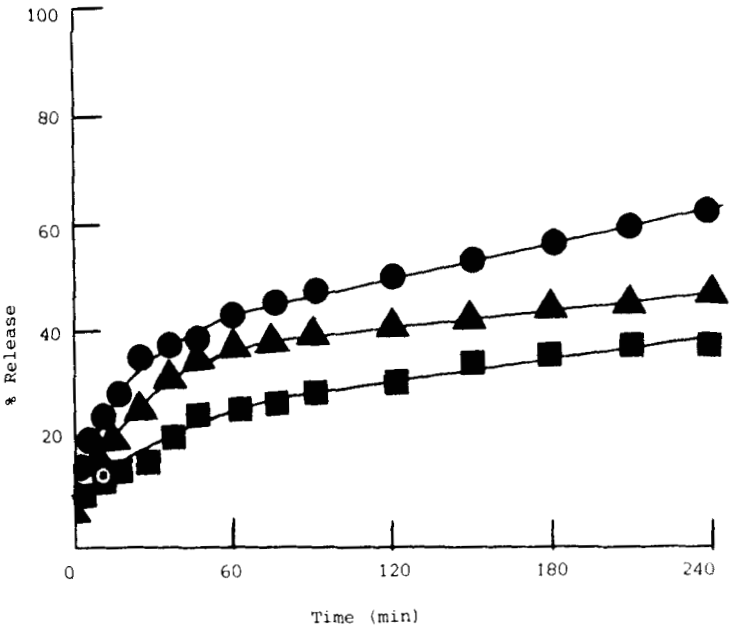


FIGURE 2

The Effect of Core to Colloid Ratio on the Release of Thiabendazole from Microcapsules.
Buffer, pH 7.0 (N/5 $KH_2PO_4$ + N/5 NaOH). Core:colloid ratio ● 1:4, ▲ 1:3, ■ 1:2. Temperature 37°.

35 minutes for unhardened microcapsules.

Luzzi & Gerraughty (1) have suggested that the rate of release of pentobarbituric acid from complex gelatin-gum acacia coacervate walled microcapsules is variable and affected by the time of formalization of the walls. They suggested that high and low formaldehyde concentrations gave greater core release than with the unformalized material. They found that 8% and 10% formaldehyde showed a retarding effect on the release rate.

Changing the buffer formula, but retaining the same pH range gave the following release characteristics (TABLE 3).

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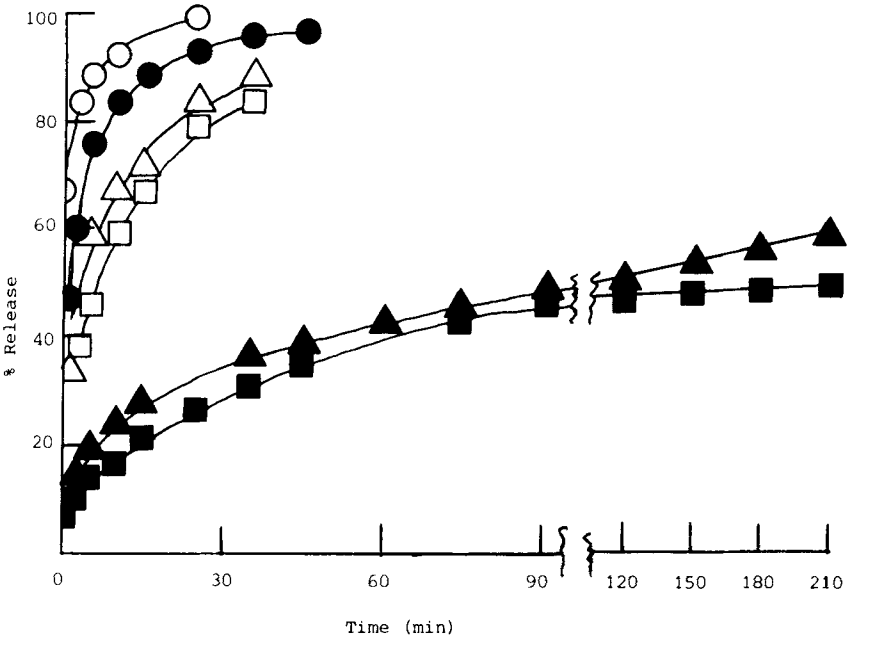


FIGURE 3

The Effect of Hardening the Microcapsule Wall on the Dissolution of Thiabendazole from Microcapsules.
Hardening agent, Formalin solution. Buffer pH2, O unhardened, ● hardened; pH 7, Δ unhardened, ▲ hardened; pH 10, □ unhardened, ■ hardened. Temperature 37°.

TABLE 3

Comparison of Release from 'Tris'

and other Buffers in a Four Hour Period

| pH | 7 | | 10 | |
|---|---|---|---|---|
| Buffer Composition | 'Tris' + dil. HCl | M/5 $KH_2PO_4$ + M/5 NaOH | 'Tris' + dil. $NH_4OH$ | M/5 Boric Acid-KCl + M/5 NaOH |
| Quantity released mg % | 66.6 | 63.1 | 54.7 | 50.0 |

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Some published procedures for the preparation of gelatin-gum acacia coacervate microcapsules have suggested hardening the walls by using sodium hydroxide to adjust the final pH to 9.2. However, Figure 4 indicates that if this hardening does take place than it has no effect on the release characteristics. A probable explanation of the phenomena found in other work is that incomplete coacervation was present and the pH adjustment resulted in the completion of precipitation of the gelatin. In the present study, where coacervation and wall deposition was complete this

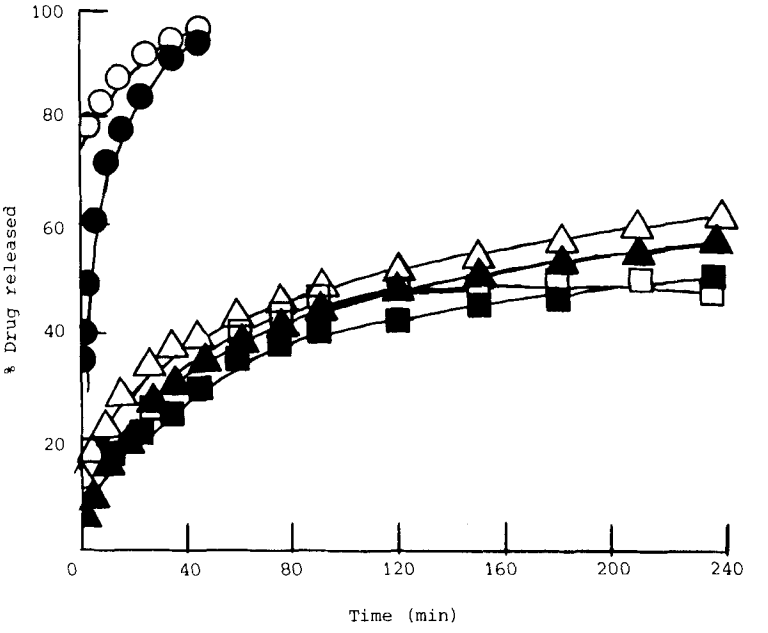


FIGURE 4

The Effect on Dissolution Behaviour of Adjustment to Alkaline pH during the Preparation of Thiabendazole Microcapsules. pH 2 O●, pH 7 Δ▲, pH 10□■; Non pH adjusted samples O△□, adjusted to pH 9.2 during preparation ●▲■; core:colloid ratio 1:2. Temperature 37°.

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final adustment to pH 9.2 was of no significance.

From the foregoing it is obvious that besides affecting the overall solubility of the drug that the pH of dissolution is an important factor in any in vitro dissolution study. However the results do indicate that release of the microencapsulated drug will take place in the stomach therefore rapidly reaching a therapeutic blood level and it is probable that improved tolerability will be due to the large area over which the individual microcapsules release the thiabendazole thus preventing local high concentrations.

## REFERENCES

(1) L. A. Luzzi and G. J. Gerraughty, J. Pharm. Sci., 56, 634 (1967)

(2) L. A. Luzzi, J. Pharm. Sci., 59, 1367 (1970)

(3) J. R. Nixon and B. R. Matthews, Microencapsulation, (Editor J. R. Nixon), Marcel Deckker Inc., New York and Basel (1976)

(4) B. R. Matthews, Ph.D. Thesis (Chelsea College, London) (1975)

(5) S. E. Walker, Ph.D. Thesis (Chelsea College, London) (1972)

(6) K. H. Franz, Am. J. Trop. Med. & Hyg., 12, 211 (1963)

(7) O. J. Stone and J. F. Mullins, Texas Rept. Biol. Med., 21, 422 (1963)

(8) T. Ishizaki and H. Kutsumi, Jap. J. Parasitol., 12, 182 (1963)

(9) W. H. Hvang and Brown, J. Parasitol., 49 (6), 1014 (1963)

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(10) K. S. Shah and S Zaman, Pakistan J. Med. Res., Lahore, No. 2, 69 (1964)

(11) T. Papasarathorn, V. Chulaserk and B. Tongkoom, Jap. J. M. Sc. and Biol., 17, 217 (1964)

(12) D. S. Salunke and J. M. Balwani, Indian Int. Med. Sci., 21 (2), 85 (1967)

(13) A. N. M. Abdul Quadir, Pak. J. Biol. Agr., 9 (2), 29 (1966)

(14) H. Nogami, T. Nagai and A. Suzuki, Chem. pharm. Bull., 14, 329, 1035 (1966)

(15) R. Mounajed, Associateship Thesis (Chelsea College) (1977)

(16) G. A. Agyilirah, M.Sc. Thesis (Chelsea College, London) (1978)

(17) H. J. Robinson, H. C. Stoerk and O. E. Graessle, Tox. and Appl. pharm., 7, 53 (1965)

(18) Merck Index (8th Ed.), Merck & Co. Inc., New Jersey, U.S.A. (1968)

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