DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 19(8), 855-874 (1993)

DEVELOPMENT AND *IN-VITRO* EVALUATION OF A MULTIPARTICULATE SUSTAINED RELEASE THEOPHYLLINE FORMULATION

K. H. Yuen, A.A. Deshmukh and J.M. Newton

The School of Pharmacy, University of London, Brunswick Square, London, United Kingdom, present address at School of Pharmaceutical Sciences, University of Science, Penang, Malaysia

ABSTRACT

A multiparticulate sustained release formulation of theophylline was developed and evaluated *in-vitro*. The formulation comprised spherical pellets of high drug loading, coated with a rate controlling membrane. The pellets were prepared using an extrusion spheronisation method, whilst coating was performed with an aqueous dispersion of ethylcellulose using a fluidized bed coating technique. When ethylcellulose was used alone as the coating polymer, the drug release profile was unsatisfactory, but could be improved by incorporating a coating additive. Several additives were evaluated and methylcellulose of high viscosity grade was found most satisfactory. The *in-vitro* theophylline release was relatively linear and pH independent, and could be varied in a predictable manner by manipulating the coat thickness. In addition, when the coated pellets were subjected to additional thermal treatment, the drug release was stable after storage for one year.

INTRODUCTION

Oral sustained release dosage forms have gained increasing popularity in recent years. Their success is best exemplified with the drug theophylline (1). A variety of methods and approaches have been used in their formulation and are well reviewed (2), but they all basically work on the same principle of slowing the rate of dissolution or drug release from the dosage forms (3).

It has been asserted that products based on a multiunit system comprising many small pellets, offer some advantages over single unit preparations such as a matrix tablet. The gastric emptying of a multiunit dosage form occurs gradually in a more consistent manner with small individual variations(4). Individual pellets also have the potential to distribute widely over a large area in the stomach and small intestine, thus yielding a more predictable drug release profile by reducing local differences in the gastrointestinal environment (5,6). Local effects of an irritant drug could similarly be reduced (7). Moreover, since each dose consists of many subunits, there is better statistical assurance of drug release (8), and the risk of dose dumping is equally subdivided (9).

Coating of drug pellets with a non-soluble barrier membrane offers a reliable method of regulating the drug release (1). The coat can be varied in nature and thickness to give the desired release profile. In this regard, spherical pellets which have low surface area to volume ratio, possess the ideal shape for application of the coat. Drug release from the coated pellets occurs via diffusion of dissolved molecules through the continuous phase and plasticizer channels of the barrier membrane (10) and/ aqueous filled pores created by dissolution of soluble components incorporated into the coat (10,11). Osmotic pumping has also been suggested as an important mechanism for the drug release (10,12,13).

Theophylline has been shown to be well absorbed throughout the length of the gastrointestinal tract (14). This together with its narrow therapeutic index (15), make it suitable for sustained drug delivery. Peak trough fluctuations of steady state blood levels can reduced, thereby achieving better efficacy/toxicity

ratio with the drug (16,17). This paper describes the development and *in-vitro* evaluation of a multiparticulate sustained release preparation of theophylline. The spherical drug pellets were prepared using an extrusion spheronisation method and coated with an aqueous ethylcellulose based coating mixture to control the drug release.

MATERIALS AND METHODS

Pellet Preparation

Two pellet formulations of high drug loading were successfully prepared. The first formulation consisted of 25% microcrystalline cellulose (Avicel PH101, FMC Corporation) and 75% w/w anhydrous theophylline BP (BASF, UK., Ltd), whilst the second formulation consisted of 5% lactose (BP Fine grade, Dairy Crest), 15% microcrystalline cellulose (Avicel PH101) and 80% anhydrous theophylline. Both formulations were prepared by extrusion spheronisation. The dry powders were first blended in a Kenwood planetary mixer (Model A707A, Havant, Harts) for 5 minutes. Sufficient deionized water was then added and mixing continued for another 10 minutes to produce a wet mass.

The wet powder mass was extruded using a ram extruder (18) with a barrel of 2.54 cm internal diameter and 20.3 cm length, fitted with a die containing a single hole of 1 mm diameter and 4 mm length. Extrusion was carried out with the piston moving down at a constant displacement rate of 20-40 cm/min. The products of extrusion were collected and 200 - 300 G loaded into a 2.5 cm. spheroniser (G B Caleva, Ascot, Berks) with a radially grooved plate rotated at 1000 rpm for periods of 15 - 30 minutes. At the end of the spheronisation, the pellets were collected and dried in a fluidized bed drier (P R L Engineering, Flintshire), at 60 °C for 1 hour. The dried spheres were separated into size fractions and the most frequently occurring fraction, 1.18 - 1.4 mm, selected for further use.

Pellet Coating Procedure

The drug pellets were coated using an aqueous dispersion of ethylcellulose (Ethocel AQ, DOW Chemicals, USA). Coating was performed using an Aeromatic AG Strea 1 fluidized bed coater (ACM Machinery, Tadley) operated under the following conditions:

Atomizing air pressure	0.4 bar
Feed rate of coating dispersion	3G/min
Fluidization air (fan capacity)	18 units
Inlet temperature	60°C
Drying temperature	60°C
Drying time	1 hour.

The weight of pellets used was 50G in each coating process.

Study Of Ethylcellulose Film And Effects Of Coating Additives

Ethylcellulose was initially evaluated as the sole film former for the coat.This was carried out by coating the theophylline pellets with the polymer and evaluating the drug release. A series of products with different film thicknesses were prepared by varying the amount of coating dispersion used. The film thickness was expressed as a percentage of ethylcellulose used, relative to the weight of the pellets. Seven film thicknesses were examined, corresponding to 1.9, 2.5, 3.8, 7.5, 10.0 and 12.5%. In each case, the amount of polymer dispersion required was measured and diluted in a ratio of 2:1 with deionised water before coating.

Several water soluble compounds were also examined for improving the permeability of the ethylcellulose coat. They included polyethylene glycol 400 (PEG 400, BDH Chemical Ltd., England), polyethylene glycol 4000 (PEG 4000, BDH Chemical Ltd., England), methylcellulose of viscosity grade 15cp (MC 15, Fluka Chemie AG, Switzerland) and viscosity grade 400 (MC 400, BDH Chemical Ltd.,England), acacia BP (MaCarthys Ltd., UK), and sodium chloride

(G.P.R, BDH Chemical Ltd., England). The coating additive to ethylcellulose ratio used was 0.8 for PEG 400 and PEG 4000, 0.4 for acacia and sodium chloride, 0.32 for MC 15 and 0.16 for MC 400. These values represent the amount of the individual compounds that could be incorporated without affecting the coating dispersion or coating process. Sodium chloride at a higher concentration, tend to cause precipitation of the polymer dispersion. PEG 400 and PEG 4000 on the other hand, have a tendency to increase the tackiness of the coating dispersion, while the others can cause an increase in its viscosity.

All the compounds were dissolved in an appropriate volume of deionised water prior to mixing with a measured volume of Ethocel AQ to yield a 1:2 dilution of the polymer dispersion before coating. The effects of adding the coating additives were studied using two coat thicknesses of 5.0 and 12.5%. In all the studies above, pellets of 75% theophylline content were used as the drug cores. Dissolution studies were carried to determine the drug release characteristics of the coated pellets.

Preparation Of Sustained Release Theophylline Pellets

From the results of the preceding studies, the combination of ethylcellulose and MC 400 was chosen as the barrier coat for preparing sustained release pellets with drug cores of 80% theophylline content. Several products of different coat thicknesses were prepared. The coat thicknesses used were 2.3%, 2.9%, 3.5%, 4.1%, 4.7% and 5.8%. After coating, the products were stored in a screw capped container at normal room conditions (10-25°C). However, half the amount of the products with film thicknesses of 2.3%, 2.9%, 4.1% and 4.7% was subjected to additional thermal treatment at 60.0°C for 24 hours in an oven before storage in the same conditions. Drug release studies were performed on all the products shortly after preparation and repeated 6 months later. For the portions that were subjected to additional thermal treatment, drug release studies were also performed shortly after preparation and repeated after 6 months and 12 months of storage under ambient conditions.

In-vitro Dissolution Studies

The *in-vitro* theophylline release of both coated and uncoated pellets was determined using the paddle unit (method 2) of the USP XXI dissolution test apparatus (model PTWS, Pharma Test Apparatebau, W Germany). All the tests were conducted in 900 ml of dissolution medium maintained at 37.0 $\pm$ 0.5 °C with a paddle rotation speed of 100 rpm. In each case, the weight of pellets used was 300 mg. Samples of 3 ml volume were withdrawn at various predetermined time intervals using an automated sampler (Pharma Test Apparatebau Type PTFC1, W Germany). The drug concentration of the samples was determined by direct measurement of the UV absorbance at 273nm using a Perkin-Elmer 554 spectrophotometer after appropriate dilution. Preliminary experiments have established a linear relationship between drug concentrations and absorbance values. Each test was run in sets of six and the average percentage released over time was then calculated. Distilled water was used as the dissolution medium. However, some studies were conducted in 0.1N hydrochloric acid, and phosphate buffer BP of pH 4 and pH 7 to determine the pH dependency of drug release.

RESULTS AND DISCUSSION

Drug Release From Uncoated Pellets

The dissolution results of uncoated theophylline pellets are shown in Figure 1. Drug release from both pellet formulations appears relatively unaffected by pH, and is fairly rapid with essentially complete dissolution within 4 hours. They are thus satisfactory for preparing sustained release pellets after application of a rate controlling polymer coat. Whilst it was reported that a combination of theophylline and Avicel can lead to instability of drug release on storage(19), this was not observed in the present study. Dissolution studies repeated 6 and 12 months after storage of the pellets, showed that the drug release was stable (Figure 2). Since the instability was attributed to the

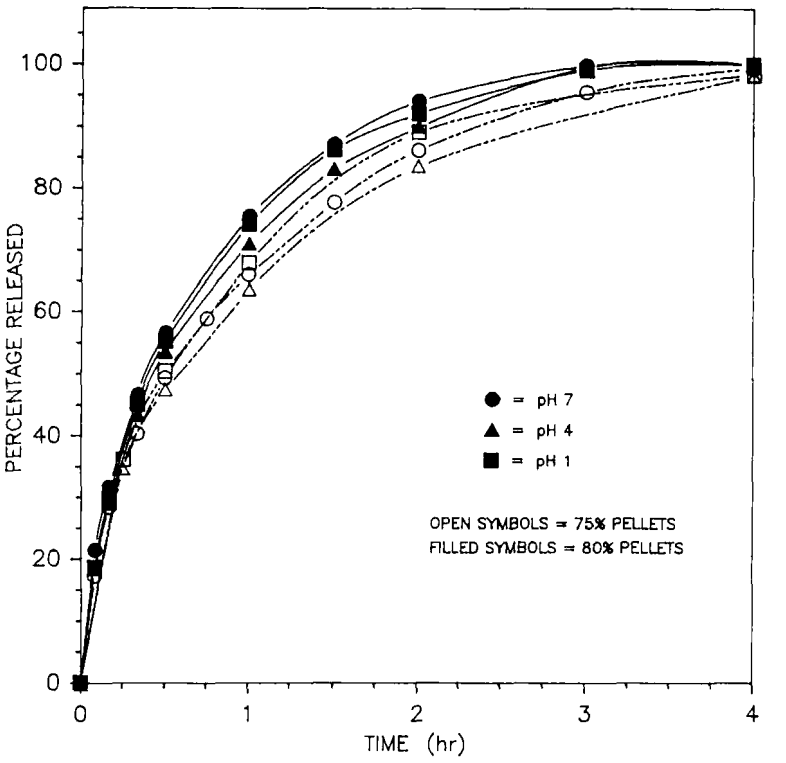

FIGURE 1

In-vitro theophylline release from uncoated pellets under different pH conditions.

presence of moisture(19), this contrast in observations could be due to the more efficient fluidized bed drying method employed in the present study.

Drug Release From Ethylcellulose Coated Pellets

The *in-vitro* theophylline release profiles of ethylcellulose coated pellets are as shown in Figures 3a and 3b. The rate of theophylline release was related inversely to the thickness of the coat, suggesting that the film was controlling the release process. This is consistent with the results of other studies (20,21). At a film thickness of 5.0% or greater, the ethylcellulose film appears to be

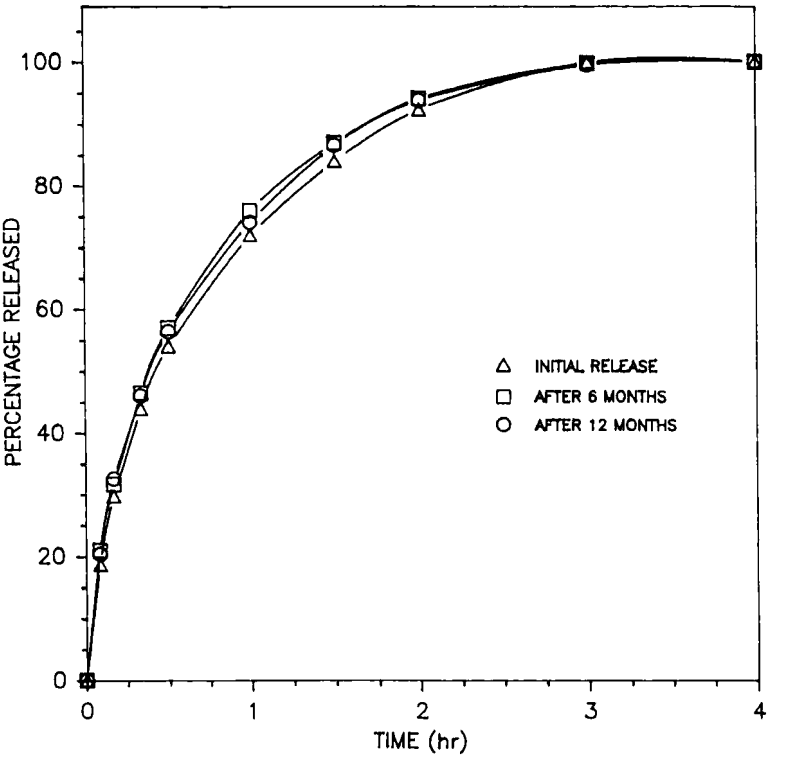

FIGURE 2
In-vitro theophylline release from uncoated pellets as a function of storage time.

poorly permeable to the drug. In all these cases, less than 5% of the dose was released in 12 hours.

In Figure 3b it is observed that when the amount of coating polymer was reduced to less than 5%, the rate of drug release was markedly increased. Almost complete dissolution was achieved at the film thickness of 1.9% after 12 hours. Whilst the rate of drug release could be increased by reducing the coat thickness, this was found to produce an unsatisfactory release profile. Both plots for the 1.9% and 2.5% film thicknesses show a fast release rate initially, but this diminishes rapidly after about two hours. A closer

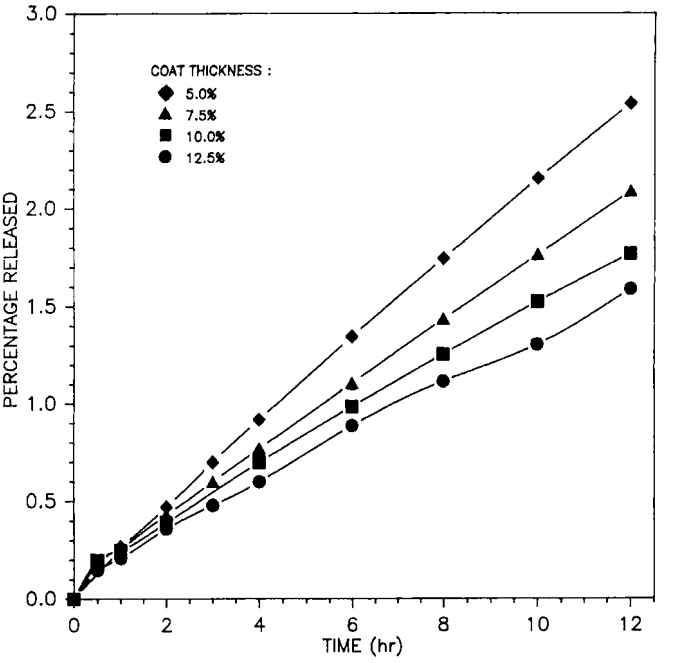

FIGURE 3a

In-vitro theophylline release from ethylcellulose coated pellets as a function of coat thickness.

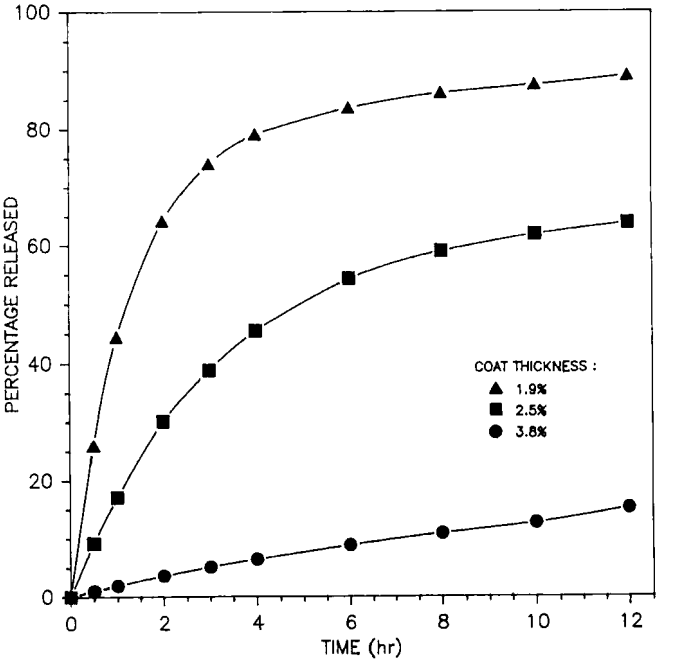

FIGURE 3b

In-vitro theophylline release from ethylcellulose coated pellets as a function of coat thickness.

examination of the plot for 1.9% film thickness reveals that more than 70% of the dose was released in the first 3 hours. However, only about 20% was released over the next 9 hours, and even after 12 hours dissolution was incomplete.

On the basis of these findings, it was concluded that ethylcellulose was unsatisfactory when used alone as the barrier membrane. Therefore it was necessary to incorporate a coating additive to improve the drug release characteristics. It is interesting to note that in a recent study, Li *et al* (22) also found ethylcellulose to be unsatisfactory as the sole coating material for preparing sustained release granules of theophylline. A coating additive was needed to produce the desired rate of drug release.

Effects of Coating Additives On Drug Release

The six coating additives examined in the present study have different solubility rates. Therefore it was interesting to examine how this could influence the permeability of the ethylcellulose film. Figures 4a and 4b show the theophylline release profiles of the pellets after incorporation of the additives. Although the additives appeared to be effective in increasing the rate of drug release, the rates of increase varied.

Of the additives used, PEG 4000 and MC 400 appear to be most effective and satisfactory in enhancing the film permeability. A linear release pattern was obtained with PEG 4000 (Figure 4a). Although a deviation from linearity was observed when the coat thickness was decreased (Figure 4b), there was a significant improvement in the overall release profile compared to the pure ethylcellulose film. The initial part of the plot in Figure 4b is linear for up to about 40% of the dose released and the subsequent decline in release rate is more gradual. The decline in the release rate could be attributed to a decrease in concentration gradient across the barrier membrane, consequent to the diminishing drug content where a constant concentration could no longer be maintained in the coated core.

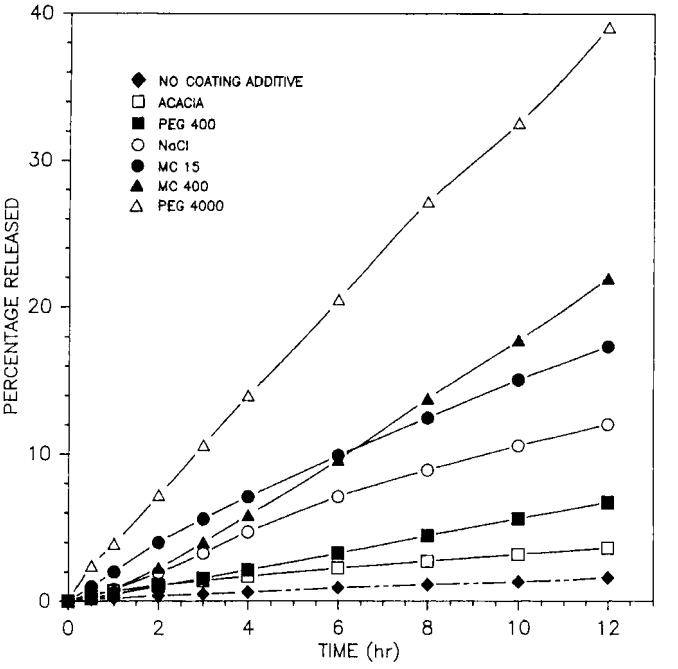

FIGURE 4a

In-vitro theophylline release from coated pellets with different coating additives (coat thickness = 12.5%).

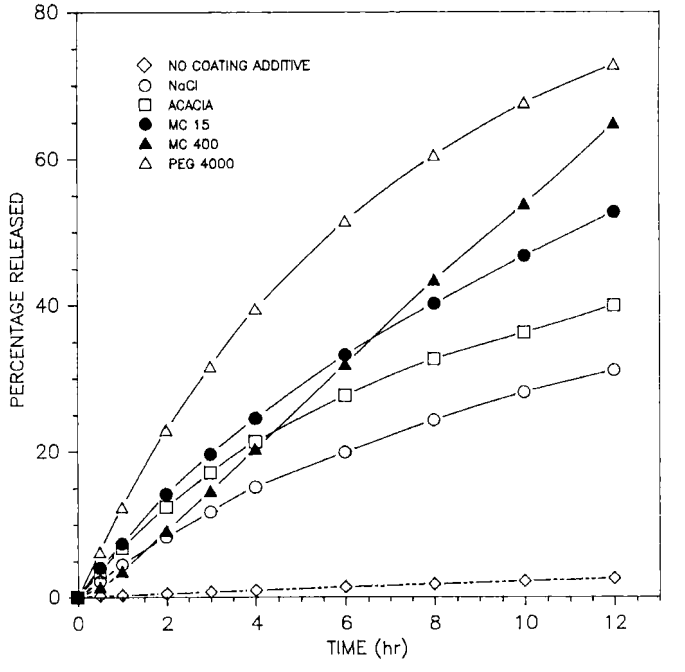

FIGURE 4b

In-vitro theophylline release from coated pellets with different coating additives (coat thickness = 5.0%).

It is interesting to note that when MC 400 was used, the release profile was different from that of the other coating additives. Referring to Figure 4a it can be seen that its release profile curves slightly upwards rather than downwards, with the release rate increasing with respect to time. This feature is again observed in the initial part of the plot for a thinner film in Figure 4b, with the subsequent part remaining linear. It may also be noted that this feature is characteristic only with MC 400, but not with MC 15, and nor was this observation made for the low viscosity grades methylcellulose studied by Li *et al* (22) and Coletta and Rubin (23). This unique pattern of release may be attributed to the MC 400 leaching from the coat at a much slower rate than the other additives, resulting in a slow and gradual increase in porosity of the membrane. Indeed, this may explain the relatively linear release profile achieved with MC 400. The gradual increase in porosity may counterbalance the declining concentration gradient in the barrier membrane when the drug content is diminishing, such that a relatively constant rate of release is attained, as observed in Figure 4b.

As promising release profiles were obtained with both PEG 4000 and MC 400, a further comparison was made between the two and the results are as shown in Figure 5. The film thickness was adjusted so that comparable rates of drug release were obtained for the two compounds. It may be seen in Figure 5 that MC 400 has a more uniform release at both sets of release profiles compared. Therefore, MC 400 was chosen for use in the final sustained release theophylline formulation.

Although PEG 4000 has been shown to be useful by Donbrow and Friedman (20,24), and Donbrow and Samuelov (25), their evaluations were mainly conducted using isolated films prepared by casting the polymer mixture onto a substrate such as glass or mercury. As a result, the films formed might be structurally quite different from those sprayed onto pellets or tablets and this could lead to differences in behaviour under test conditions (26).

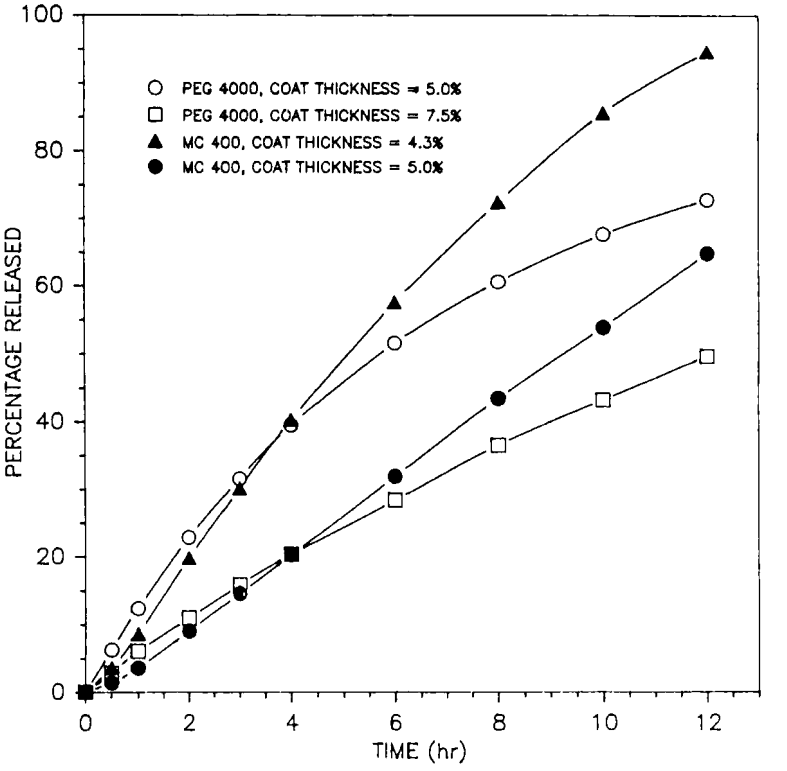

FIGURE 5
In-vitro theophylline release from coated pellets comparing the coating additives PEG 4000 and MC 400.

Moreover, their methodology would not immediately reveal the problems that could arise during the coating process used here. In the present study, the addition of PEG 4000 into the polymer dispersion yielded a tacky mixture which caused agglomeration of the pellets during coating. This may in part, be due to the low melting point of PEG 4000 (53°-56°C) which is less than the coating bed temperature used. Lowering of the bed temperature would be undesirable as this might prolong the film formation time (27). However, no such problem was encountered with MC 400, and it was easy to use. At the low concentration employed, the slight increase in viscosity of the coating mixture did not interfere with the coating process.

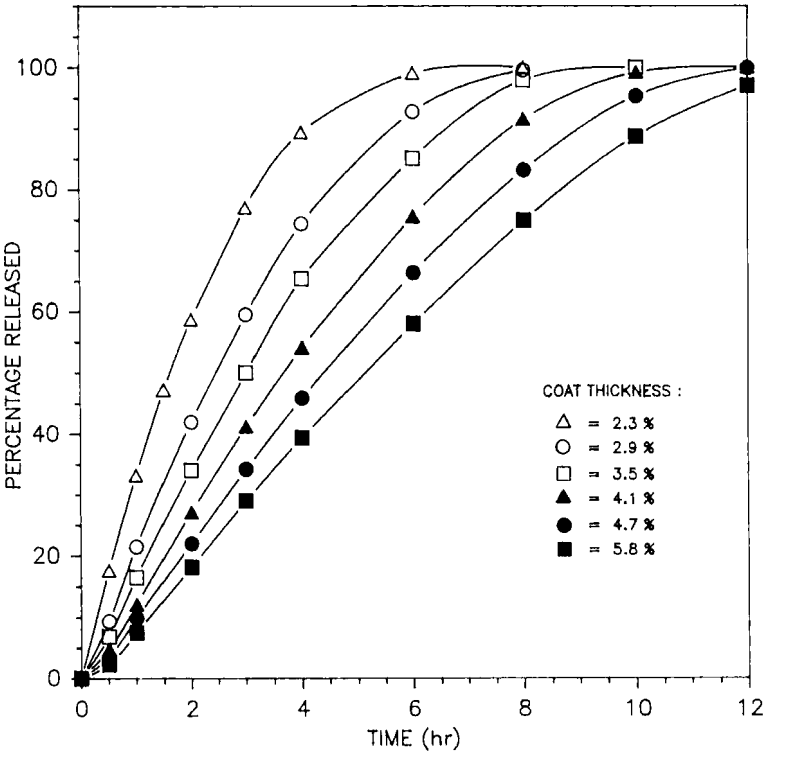

FIGURE 6
In-vitro theophylline release from mixed ethylcellulose-MC 400 coated pellets as a function of coat thickness.

With regard to the other compounds studied, MC 15 produced an increase in film permeability that was comparable to MC 400. However its release profile was not linear at either of the film thicknesses examined. Acacia, sodium chloride and PEG 400 also exhibited nonlinear release profiles, and their ability to increase the permeability of the ethylcellulose film was considerably less than PEG 4000 or MC 400. It is also apparent from the plots that, the deviation from linearity observed with these compounds, occurred even at low percentages of drug released. Therefore, the nonlinearity may not be solely related to a diminishing drug content, but may also be associated with

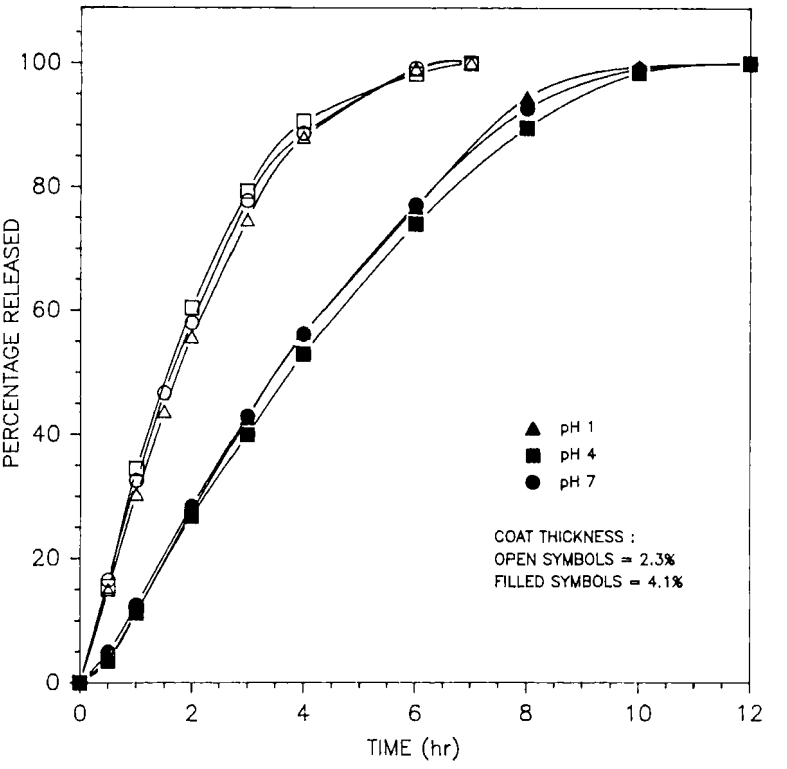

FIGURE 7
In-vitro theophylline release from mixed ethylcellulose-MC 400 coated pellets under different pH conditions.

changes in permeability of the film coat, such as due to swelling of the polymer membrane. A further disadvantage of PEG 400 was its tendency to cause agglomeration of the pellets, whilst sodium chloride on the other hand, tended to induce precipitation of the polymer dispersion, especially when a higher concentration was added. The latter may be more useful if the coating is applied using an organic based system such as when lactose was used by Benedikt *et al* (21).

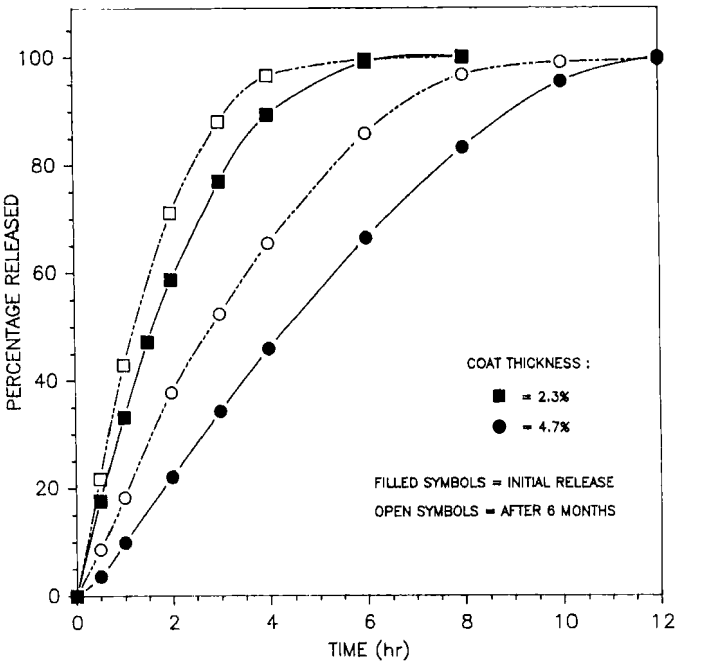

FIGURE 8a

In-vitro theophylline release from coated pellets with no additional thermal treatment as a function of storage time.

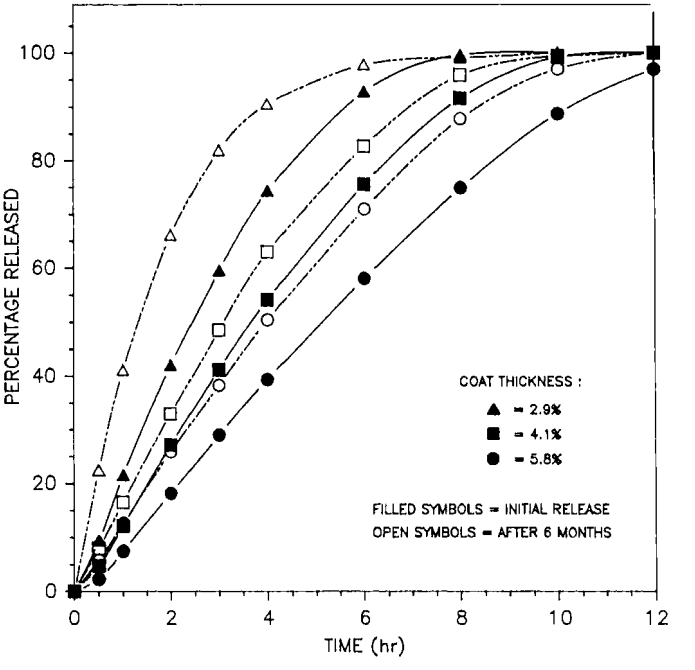

FIGURE 8b

In-vitro theophylline release from coated pellets with no additional thermal treatment as a function of storage time.

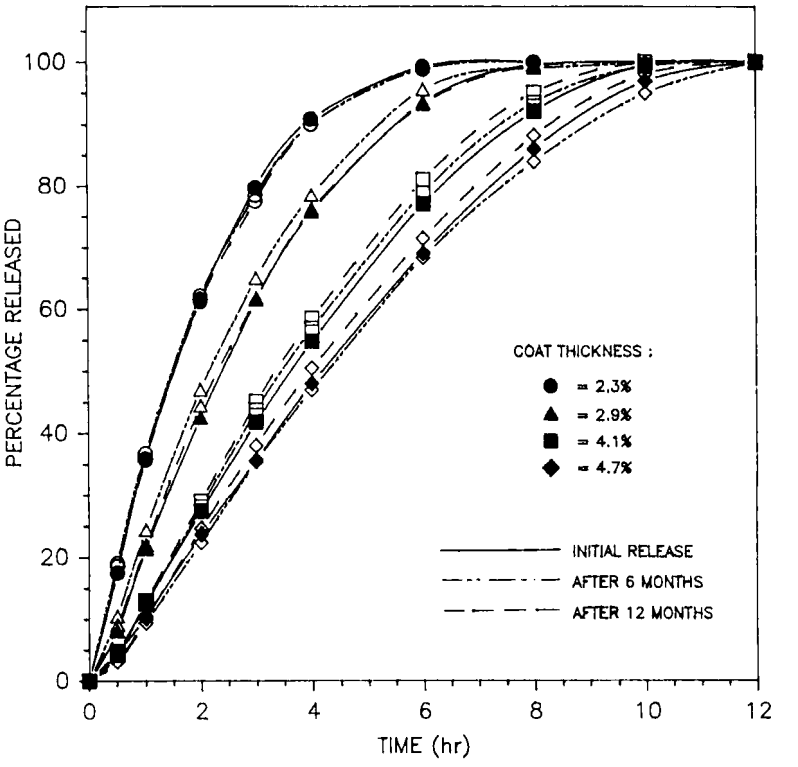

FIGURE 9

In-vitro theophylline release from coated pellets after additional thermal treatment as a function of storage time.

Preparation Of Sustained Release Theophylline Pellets

From the results obtained above, MC 400 appears most satisfactory as the coating additive. Therefore, the combination of ethylcellulose and MC 400 was used to prepare the sustained release formulation with pellets of 80% theophylline content. A series of products with varying coat thicknesses were prepared and their drug release profiles are as shown in Figure 6. All the plots are essentially linear and it may also be observed that the release rate could be readily varied by altering the film thickness. The formulation was further evaluated under different pH conditions using two preparations of film

thickness 2.3% and 4.1%. The results in Figure 7 show that the drug release is unaffected by pH. This is in accord with the results of Benedikt *et al* (21) in which the theophylline pellets were coated with a mixture of ethylcellulose and lactose, but differed from the findings of Lippold *et al* (28), who reported changes in permeability of the polymer film at high pH (>6) due to the presence of a small amounts of carboxylic groups in the ethylcellulose used.

The drug release profiles as a function of storage time are shown in Figures 8a and 8b for the portions of pellets that were not given additional thermal treatment of the film coat. It can be seen that the release rates of all the preparations were increased after 6 months. In contrast, the release profiles of the fractions that were thermally treated for 24 hours remained stable even after 12 months of storage as seen in Figure 9. These results clearly indicate that additional thermal treatment is necessary for complete curing of the film coat so that the release will remain stable during storage. The increase in film permeability of the pellets that were not sufficiently cured may be attributed to formation of micro-cracks or fractures in the coat during storage, possibly due to the presence of some weak linkages between the ethylcellulose particles because of incomplete interdiffusion after coating (28).

CONCLUSION

In conclusion, a sustained release theophylline formulation with satisfactory *in-vitro* release characteristics was successfully prepared using the ethylcellulose-MC 400 coating mixture and theophylline pellets of 80% drug content. The rate of drug release is unaffected by pH and can be varied in a predictable manner by manipulating the film thickness. Stability of release during storage can be achieved by additional thermal treatment of the coat.

REFERENCES

1. R.F. Shangraw, Drug Dev. Ind. Pharm., 14, 319 (1988).

2. V.H.-L. Lee and J.R. Robinson, in "Sustained and Controlled Release Drug Delivery Systems," J.R. Robinson, eds., Marcel Dekker Inc., New York. 1978, p. 123.
3. J.E. Devereux, Ph.D. Thesis, London University, 1987.
4. H. Bechgaard, Acta Pharm. Technol., 28(2), 149 (1982)
5. K.S. Murthy, R.V. Jr. Nesbitt and M.R. Harris, Pharm. Eng., 3, 19-21, 28 (1983).
6. A.H. Beckett, Pharm. J., 233, 262, 509-510 (1984).
7. J.S. Rowe, Pharm. J., 231, 538 (1983).
8. N.G. Lordi, in "The Theory and Practice of Industrial Pharmacy", L. Lachman, H.A. Lierberman and J.L. Kanig, eds., Lea & Febiger, Philadelphia, 1986, p. 430.
9. A.H. Beckett, in "Proceedings of an international symposium on Recent Advances in The Design, Development and Assessment of Sustained Release Drug Delivery Systems", Liverpool, 1985.
10. A.G. Ozturk, S.S. Ozturk, B.O. Palsson, T. Wheatley and J.B. Dressman, in "Proceedings of 9th Pharmaceutical Technology Conference", Veldhoven, Holland, 1990, Vol. 1, p. 253.
11. B.C. Lippold and H. Forster, Acta Pharm. Tech., 27, 169 (1981).
12. G.M. Zentner, G.S. Rork and K.J. Himmelstein, J. Contr. Rel., 2, 217 (1985).
13. B. Lindstedt, M. Sjöberg and J. Hjärtstam, Int. J. Pharm., 67, 21 (1991).
14. A.H. Staib, D. Loew, S. Harder, E.H. Graul and R. Pfab, Eur. J. Clin. Pharmacol., 30, 691 (1986).
15. M. Weinberger and E. Bronsky, J. Paediatr., 84, 421 (1974).
16. F. Theeuwes, Curr. Med. Res. Opin., 8(suppl.2), 20 (1983).
17. J. Urquhart, Drugs, 23, 207 (1982).
18. P.J. Harrison, J.M. Newton and R.C. Rowe, J. Pharm. Pharmacol., 37, 686 (1985).

19. J. Hermen, N. Visararungrof and J.P. Remon, Int. J. Pharm., 55, 143 (1989).
20. M. Donbrow and M. Friedman, J. Pharm. Pharmacol., 26, 148 (1974).
21. G. Benedikt, V.W. Steinijans and R. Dietrich, Arzneim- Forsch./Drug Res., 38(II), 1203 (1988).
22. S.P. Li, G.N. Mehta, J.D Buehler, W.M. Grim and R.J. Harwood, Pharm. Technol. Int., 2(4), 48 (1990).
23. V. Coletta and H. Rubin, J. Pharm. Sci., 53, 953 (1964).
24. M. Donbrow and M. Friedman, J. Pharm. Pharmacol., 26, 148 (1974).
25. M. Donbrow and Y. Samuelov, J. Pharm. Pharmacol., 32, 463 (1980).
26. S.C. Porter, Int. J. Pharm. Tech. & Prod. Mfr., 3, 21 (1982).
27. C.R. Steuernagel, in "Aqueous Polymeric Coatings For Pharmaceutical Dosage Forms", J.W. McGinity, eds., Marcel Dekker Inc., New York, 1989, p. 1.
28. B.H. Lippold, B.K. Sutter and B.C. Lippold, Int. J. Pharm., 54, 15 (1989).