DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 21(13), 1545-1555 (1995)

COMMUNICATIONS

DEVELOPMENT AND IN VITRO EVALUATION OF A NOVEL MULTIPARTICULATE MATRIX CONTROLLED RELEASE FORMULATION OF THEOPHYLLINE

Kok-Khiang Peh and Kah-Hay Yuen
The School of Pharmaceutical Sciences, University of Science Malaysia, 11800, Penang, Malaysia.

ABSTRACT

A novel multiparticulate matrix controlled release preparation of theophylline was formulated and evaluated in-vitro. The preparation which consisted of spherical drug pellets in a size range of 1.18 - 1.70 mm diameter was produced using an extrusion-spheronisation technique. The drug was embedded in a mixture of nonsoluble matrix materials forming the pellets to control the drug release. For this purpose, microcrystalline cellulose (MCC) and its mixture with glyceryl monostearate (GMS) were evaluated. When microcrystalline cellulose was used alone, the drug release was not sufficiently sustained and was essentially complete within 6 hours. However, incorporation of glyceryl monostearate significantly retarded the rate of drug release. Moreover, the rate of drug release could be readily modified in a predictable manner by varying the amount of glyceryl monostearate. The rate of the drug release was relatively insensitive to changes in the drug to matrix ratio. Drying of the drug pellets at temperatures below the melting point of glyceryl monostearate (approximately 57°C) has no effect on the rate of drug release. In addition, the rate of drug release was found to be stable after storage for 6 months and was essentially independent of pH and agitation rate.

INTRODUCTION

Theophylline is at present still widely used in the management of asthma. However, it has a relatively narrow therapeutic index of between 5-20 μg/ml serum concentrations (1). Thus, sustained release formulations which can produce more uniform serum concentrations, with less fluctuations in peak-trough levels (2), are useful for the oral delivery of theophylline. Various methods and approaches have been utilized in the formulation of sustained release preparations

and are well reviewed and discussed in the literature (3). Basically, all these methods work on the same principle of slowing the rate of dissolution or release of the drug from the dosage form. For example, embedding the drug in an insoluble matrix provides a simple and reliable method of retarding the drug release.

In recent years, much interests have been focussed on multiparticulate dosage forms because they appear to have several advantages over the single unit system such as a tablet. Multiunit systems which typically comprised many small spherical pellets filled in a hard gelatin capsule, have the potential to distribute widely in the gastrointestinal tract, thus minimizing the local effects of irritant drugs (4). Other potential benefits include more consistent gastric emptying (5), reduced risk of dose dumping (6) and easy dose adjustments.

The present study was undertaken to formulate a multiparticulate matrix controlled release preparation of theophylline. The preparation which consisted of spherical drug pellets in the size range of 1.18 - 1.70 mm diameter was produced using an extrusion-spheronisation technique. Sustained drug release was achieved through embedding the drug in a non-soluble matrix forming the spherical pellets.

MATERIALS AND METHODS

Preparation of Pellets

Initially microcrystalline cellulose (Avicel PH 101, FMC Corporation) was used alone as the matrix forming material. Three formulations were prepared (as 200G batches) containing microcrystalline cellulose and anhydrous theophylline BP (Schweizerhall Pte Ltd, Singapore) in the ratio of 5:5, 6:4 and 7:3 respectively. In all three formulations, the microcrystalline cellulose and theophylline were first blended in a Kenwood planetary mixer for 5 minutes. Sufficient distilled water was then added and mixing continued for another 10 minutes. The resultant wet powder mass was extruded using a Ram Extruder (7) fitted with a single-holed die of hole size 1 mm diameter and 4 mm length. Extrusion was carried out at a constant displacement rate of 30.0 cm/min. The smooth extrudates obtained were loaded and processed using a 22.5 cm Spheronizer (G.B. Caleva Ltd, Ascot, Berks, UK), fitted with a cross-hatched plate rotated at 1000 rpm for 30 min. After spheronisation, the pellets were collected and dried in a fluid bed drier (PRL Engineering Ltd, Flintshine, UK) at 60°C for 30 min. The dried pellets were separated into different size fractions and the size fraction of 1.18 - 1.70 mm was selected for further studies.

Preparation of Pellets containing Glyceryl Monostearate

A series of formulations containing a constant proportion of theophylline but different proportions of microcrystalline cellulose and glyceryl monostearate (Euro Chemo-Pharma, Penang), were prepared and the manufacturing formulae are as shown below:

Theophylline	MCC	GMS
10	8	2
10	7	3
10	6	4
10	5	5
10	4	6

In the preparation of these pellets, the glyceryl monostearate was first dispersed in sufficient quantity of hot distilled water heated at approximately 80°C, followed by the addition of theophylline with constant stirring until a slurry was formed. The hot slurry was immediately mixed and blended with microcrystalline cellulose in the Kenwood planetary mixer for 10 min. The wet powder mass was then extruded and spheronized as described previously. However, for these preparations, the spheronisation was performed at 1000 rpm for only 10 min. The spherical pellets obtained were dried in a fluid bed drier at 40°C for 30 min. Again, the size fraction of 1.18 - 1.70 mm was selected for further use.

Another series of formulations comprising various proportions of drug to matrix materials were also prepared using the method described above. The matrix materials consisted of equal parts of microcrystalline cellulose and glyceryl monostearate, whilst the proportions of drug to matrix materials were 3:5, 4:5, 5:5, 6:5, 7:5 and 8:5 respectively.

Study of Drying Temperature, Duration of Drying and Storage Time

In view of the relatively low melting point of glyceryl monostearate (approximately 57°C), the influence of drying temperature and duration of drying on the rate of drug release from the pellets were also investigated. A 500 G batch of pellets containing theophylline, microcrystalline cellulose and glyceryl monostearate in a proportion of 10:5:5 was prepared. The pellets were then divided into four approximately equal portions and each portion dried at a different temperature, namely 30, 35, 40 and 60°C. In addition, the pellets dried at each temperature were further subdivided into two portions, each subjected to a different drying duration. The drying durations used were 30 and 60 min.

For the evaluation of storage time, only the pellets dried at 40°C for 30 and 60 min were used. Dissolution studies were repeated on these batches of pellets after storage for 6 months.

In-vitro Dissolution Studies

The in-vitro theophylline release was determined using the paddle method of the USP XX1 dissolution test apparatus (model AT7, Sotax CH-4008, Basel, Switzerland). 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. The weight of spheres used was 400 mg. Samples of 3 ml volume were collected at various predetermined time intervals using an automated fraction collector (model C613, Sotax, Switzerland) equipped with a piston pump (model CY7-50, Sotax, Switzerland) over a 12 hour period. The drug concentrations of the samples were

determined by direct measurement of the UV absorbance at 273 nm using a Hitachi U-2000 Spectrophotometer after appropriate dilution. Each test was run in sets of six and the average percentage of drug release versus time was calculated and plotted.

The dissolution medium used throughout the in-vitro studies was distilled water. However, to determine the pH dependence of drug release, different dissolution media, namely 0.1 M HCl, phosphate buffer BP of pH 4 and pH 7 were used. The batch of pellets containing theophylline, microcrystalline cellulose and glyceryl monostearate in a ratio of 10:5:5 was chosen for these studies. In addition, the effect of agitation rate on the rate of drug release was also evaluated on this batch of pellets. The different stirring speeds employed were 50, 75, 100, 125 and 150 rpm.

RESULTS AND DISCUSSION

Drug Release Profiles of Pellets

The drug release profiles of pellets containing theophylline and microcrystalline cellulose in various proportions are shown in Figure 1. The drug release was rapid and essentially complete within 4-6 hours. Though the pellets remained intact at the end of the dissolution period, it is apparent that the retarding effect of the matrix formed with microcrystalline cellulose alone could not produce sufficiently sustained drug release. This is consistent with the findings of O'Connor and Schwartz (8) where poor sustained release effect was observed when microcrystalline cellulose was used alone as the matrix material, even at a high microcrystalline cellulose to theophylline ratio of 9:1.

However, it was found in the present study that incorporation of glyceryl monostearate into the formulation could markedly improve the sustained release behaviour. Figure 2 shows the drug release profiles of pellets containing various quantities of glyceryl monostearate. At a constant drug to excipient ratio, the drug release rate could be modified in a predictable manner by varying the amount of glyceryl monostearate. Thus, the incorporation of glyceryl monostearate into the pellets produced a matrix that has greater retarding effect than when microcrystalline cellulose was used alone. However, at high concentrations of glyceryl monostearate (25% and above), flaking was observed during spheronisation, but could be circumvented by the addition of 10-15% of lactose, without any significant effect on the drug release rate as shown in Figure 3. Alternatively, the flaking could be reduced by first melting glyceryl monostearate in hot distilled water, followed by the addition of theophylline to form a slurry prior to mixing with the microcrystalline cellulose. Thus, this procedure was employed in the preparation of the pellets.

The drug release profiles were also plotted according to square root of time kinetics as shown in Figure 4. It can be seen that a relatively linear relationship was obtained, indicating that the drug release could be described by the diffusion controlled model proposed by Higuchi (9).

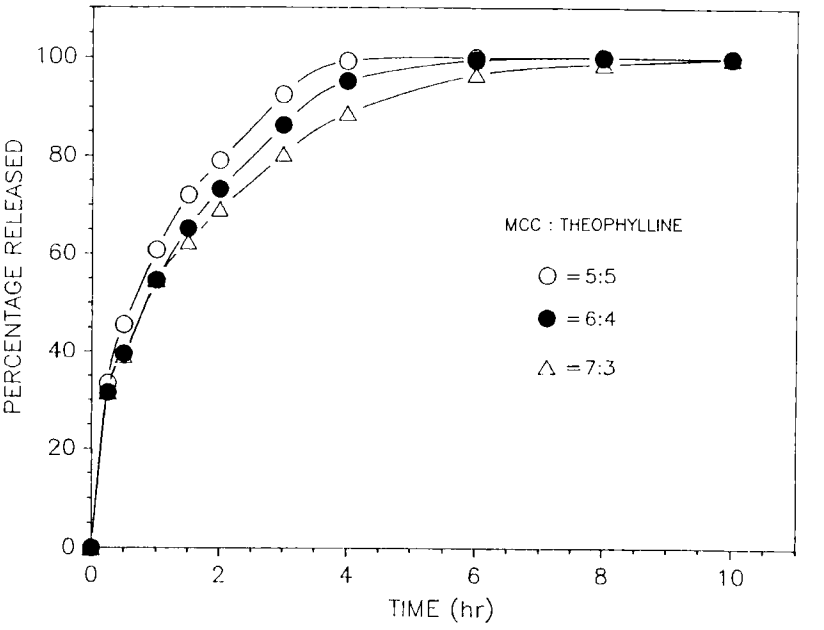

FIGURE 1
In-vitro theophylline release from pellets containing different proportions of microcrystalline cellulose (MCC) and theophylline.

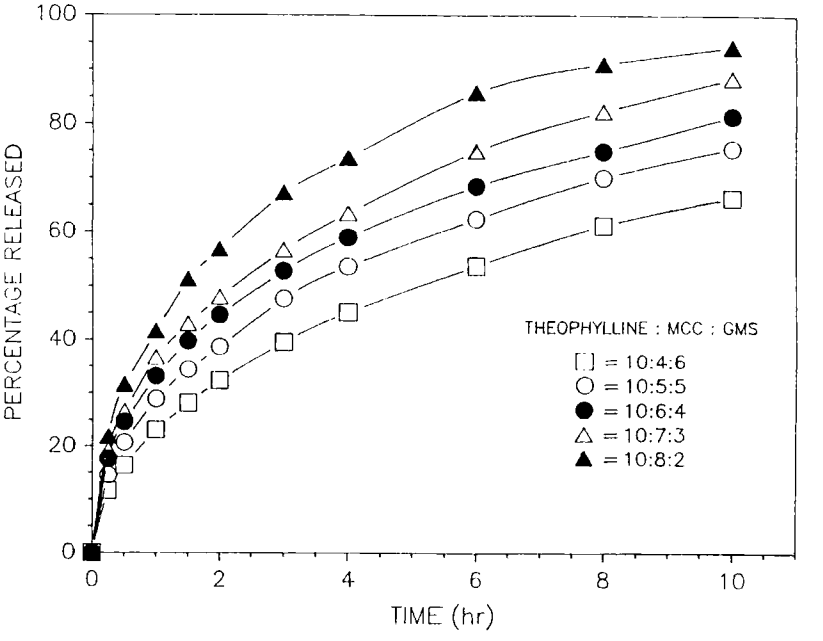

FIGURE 2
In-vitro theophylline release from pellets containing different proportions of microcrystalline cellulose (MCC) to glyceryl monostearate (GMS).

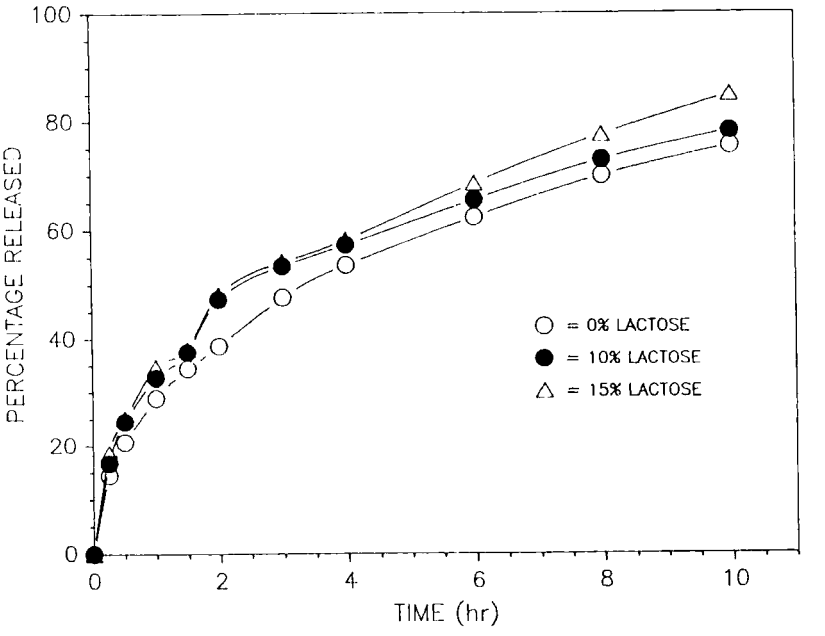

FIGURE 3

In-vitro theophylline release from pellets containing lactose monohydrate. The proportion of theophylline:MCC:GMS of the pellets was 2:1:1.

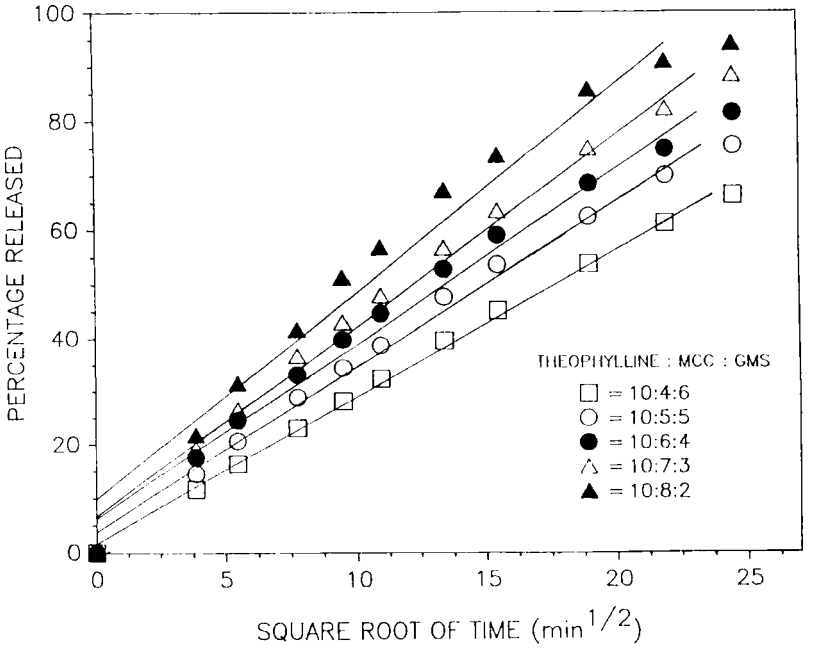

FIGURE 4

Plot of percentage theophylline release versus square root of time.

Lipophilic excipients have been shown to be able to retard the drug dissolution of a dosage form (10). Thus, the ability of glyceryl monostearate to retard the rate of drug release from the pellets may be attributed to its lipophilic property. Incorporation of glyceryl monostearate caused an increase in the lipophilicity of the pellet matrix, leading to a decrease in the effective interfacial area between the drug and the dissolution medium, resulting in a reduction of wettability (11). Consequently, there is a slower rate of water penetration and dissolution of the drug within the pellets and hence a slower rate of drug release.

Referring to Figure 5, it is interesting to note that when the proportion of microcrystalline cellulose to glyceryl monostearate was kept constant (1:1), the rate of drug release was relatively insensitive to changes in the drug to excipient ratio from 3:5 to 6:5. An appreciable change in drug release rate was observed only when the drug to excipient ratio was above 6:5. From these results and also those shown in Figure 2, it is apparent that the ratio of glyceryl monostearate to microcrystalline cellulose has a greater influence on the drug release than the drug to excipient ratio.

The Effect of Drying Temperature, Duration of Drying and Storage Time

The drug release profiles for pellets treated at different temperature and duration of drying are shown in Figure 6. It can be seen that the drug release profiles for pellets dried at 30, 35 and 40°C for different durations are almost superimposible, indicating that the rate of drug release was not affected by both drying temperature and the duration of drying.

However, an appreciable increase in the rate of drug release was observed when the pellets were dried at 60°C. In addition, the drug release rate was also found to increase with an increase in the duration of drying. Since this temperature is slightly higher than the melting point of glyceryl monostearate (approximately 57°C), the physical properties of the pellets could have been altered, rendering them more porous. Therefore, it is important to use a lower temperature (less than the melting point of glyceryl monostearate) in the drying of the pellets.

It was also observed that at 60°C, the pellets were sticky, leading to agglomeration of the pellets in the fluid bed drier and this was more pronounced with an increase in the duration of drying. Interestingly, the rate of drug release of the pellets dried at 60°C for 60 min was found to be closely similar to that of pellets prepared using microcrystalline cellulose as the sole matrix material.

Figure 7 shows the drug release profiles of the pellets obtained initially and after storing for 6 months at ambient temperature. It can be noted from the plots that the drug release profiles were not significantly altered after 6 months for both durations of drying employed. Thus, the pellet matrix appeared to be stable and the duration of drying has no effect on its stability during storage. Furthermore, the drug release from the pellets was also found to be independent of pH (Figure 8) as well as the agitation rate (Figure 9).

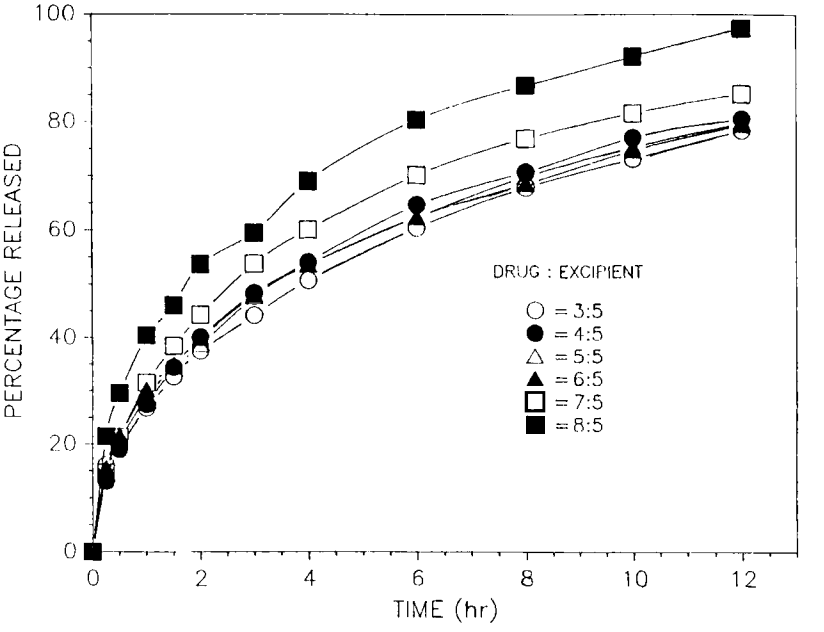

FIGURE 5

In-vitro theophylline release from pellets containing different drug to excipients ratio, (excipients comprised equal parts of MCC and GMS).

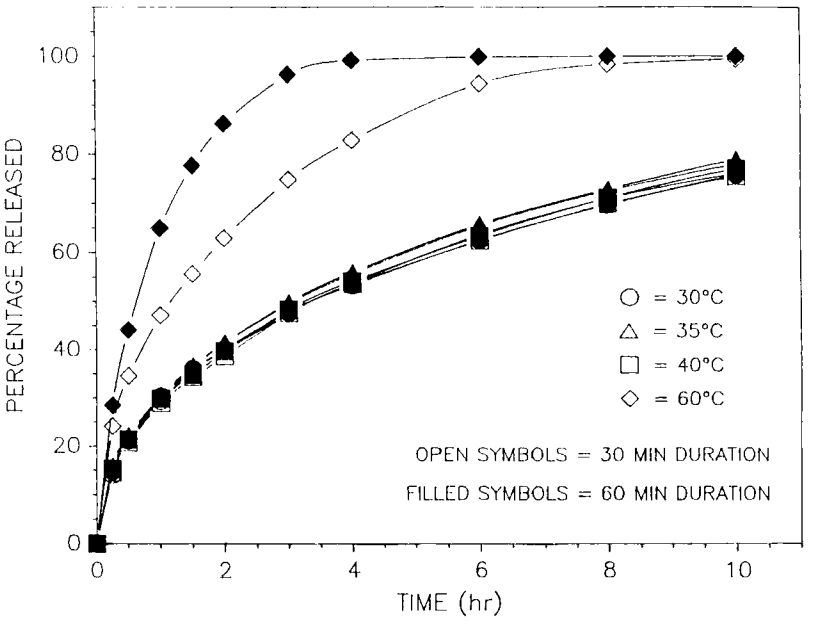

FIGURE 6

In-vitro theophylline release from pellets dried at different temperature and duration of drying.

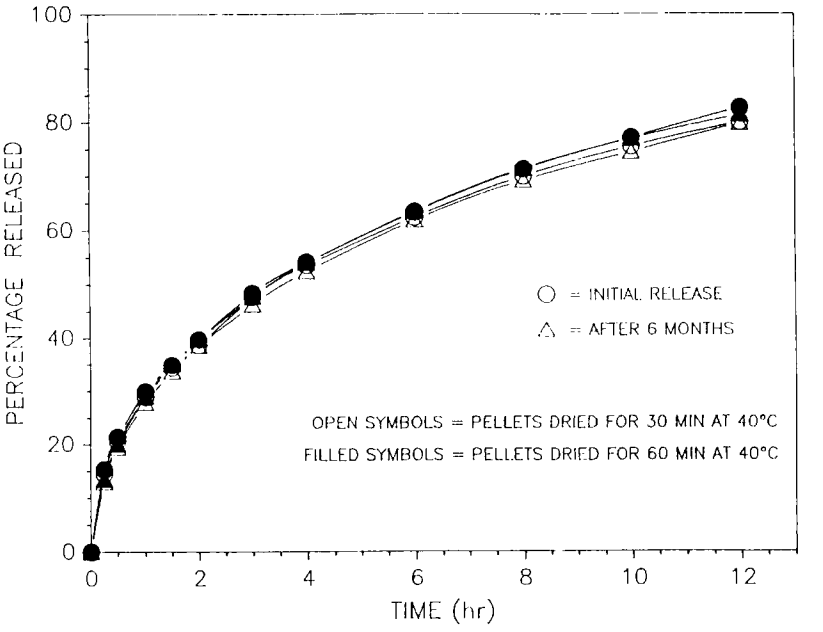

FIGURE 7
In-vitro theophylline release from pellets as a function of storage time.

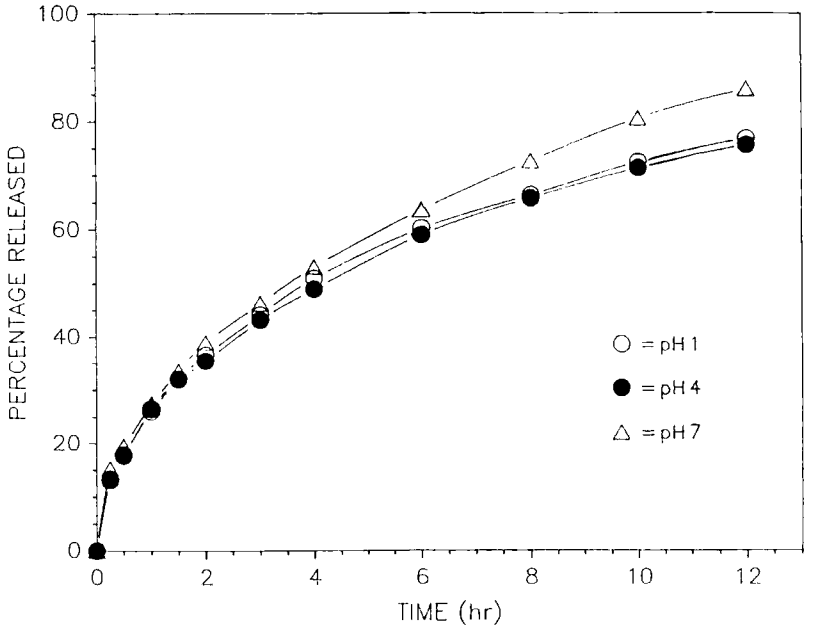

FIGURE 8
In-vitro theophylline release from pellets under different pH conditions.

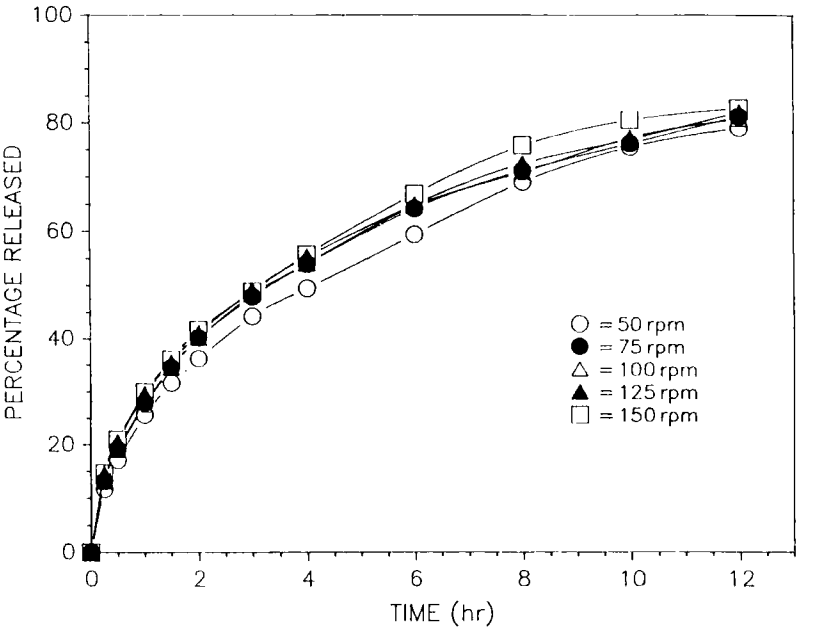

FIGURE 9
In-vitro theophylline release from pellets under different agitation rate.

Such pH independence was also observed by Yuen et. al. (12) with their sustained release theophylline pellets in which a coating method was used to control the drug release. On the other hand, the independence on agitation rate or stirring speed may indicate that the drug release which proceeded via a diffusion process, is internalised and occurring within the pellets. This is because if the diffusion is occurring in a static layer of fluid surrounding the pellets, then changes in agitation rate or stirring speed will drastically alter the release profile (13). In both of these two later studies, the pellets also remained intact without any visible swelling, and no fragmentation or erosion was observed. The integrity of the pellets is essential for achieving the controlled release effect.

CONCLUSION

A novel multiparticulate matrix controlled release preparation of theophylline with satisfactorily in-vitro dissolution rate was successfully prepared using an extrusion-spheronisation technique. The rate of drug release could be modified in a predictable manner by varying the amount of glyceryl monostearate in the formulation. Also, the rate of drug release was stable after storage for 6 months and was essentially independent of pH and agitation rate.

ACKNOWLEDGMENTS

The authors would like to thank Ho Yan Hor Company, Malaysia, for its support and generous supply of some materials used in this study.

REFERENCES

1. M.H. Jacobs, R.M. Senior and G. Kessler, J. Am. Med. Ass., 235, 18 (1976).
2. J. Urquhart, Drugs, 23, 207 (1982).
3. 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.
4. J.S. Rowe, Pharm. J., 231, 538 (1983).
5. H. Bechgaard, Acta Pharm. Technol., 28(2), 149 (1982).
6. 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.
7. P.J. Harrison, J.M. Newton and R.C. Rowe, J. Pharm. Pharmacol., 37, 686 (1985).
8. R.E. O'Connor and J.B. Schwartz, Drug Dev. Ind. Pharm., 11, 1837 (1985).
9. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
10. G. Levy and R.H. Gumton, J. Pharm. Sci., 1139 (1963).
11. U.V. Banakar, in "Pharmaceutical Dissolution Testing", U.V. Banakar, ed., Marcel Dekker Inc., New York, 1991, p. 133.
12. K.H. Yuen, A.A. Deshmukh and J.M. Newton, Drug Dev. Ind. Pharm., 19(8), 855 (1993).
13. C. Tapia, G. Buckton and J.M. Newton, Int. J. Pharm., 92, 211 (1993).