DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 15(9), 1455-1473 (1989)

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

MODIFIED DRUG RELEASE FROM BEADS PREPARED WITH COMBINATIONS OF TWO GRADES OF MICROCRYSTALLINE CELLULOSE

Evone S. Ghali, George H. Klinger and
Joseph B. Schwartz
School of Pharmacy
Philadelphia College of Pharmacy & Science
Philadelphia, PA 19104

ABSTRACT

In previous work, the use of binary drug - diluent mixtures with various grades or types of microcrystalline cellulose were shown to exhibit varying degrees of release from beads prepared by extruder/marumerizer technology.

Copyright © 1989 by Marcel Dekker, Inc.

RIGHTSLINK

In this work beads of suitable physical appearance were prepared with varying proportions of two grades of microcrystalline cellulose (Avicel PH-101 and Avicel RC-581) and 10% drug. In-vitro dissolution results varied with the proportion and the grade of the microcrystalline cellulose and with the dissolution medium utilized. Microcrystalline cellulose beads remained intact in water or in acid, but beads with the microcrystalline cellulose / carboxymethylcellulose sodium product exhibited gel structures in water and remained as beads in acid. The quantity of gel formation increased with an increasing level of the carboxymethylcellulose sodium product.

INTRODUCTION

The technique of preparing spheres[1-4] from extrusion of a moist powder bed followed by rounding on a rapidly rotating, serrated plate is finding increasing interest and acceptance within the pharmaceutical industry. This is due to the fact that a wide range of drug level is possible and one can obtain high drug loading in this physical form.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

Spheres are also of interest for use in controlled release delivery systems.[5]

Microcrystalline cellulose (MCC) products have been shown to spheronize as single components[6]. The application of the extruder/marumerizer technique to binary drug-diluent mixtures with different grades of microcrystalline cellulose was also demonstrated, and these formulations were shown to exhibit varying degrees of release[7]. Cellulosic materials such as carboxymethylcellulose sodium (CMC) have also been used in water swellable hydrophilic matrices in controlled release technology[8-10].

Previous work has shown also that Avicel PH-101 appears to be an ideal matrix material for the preparation of pellets with low drug loading; these beads remain intact during dissolution testing in water. The Avicel RC-581 appears to be more applicable to the preparation of pellets containing a high dose of drug. If the drug level is low (and at higher levels of this product containing CMC), rods rather than beads were obtained (under identical processing conditions) and a gel structure was observed during dissolution testing in water[7].

In the present investigation, beads are

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

prepared with varying proportions of the MCC products (Avicel PH-101 and Avicel RC-581), and 10% theophylline or 10% chlorpheniramine maleate. The purposes of this study were to manufacture beads of suitable physical appearance by combining two grades of microcrystalline cellulose, and to observe the physical behavior of these mixtures during dissolution testing in water and in acid (gel vs beads).

EXPERIMENTAL

Materials

The matrix materials include: microcrystalline cellulose (MCC), NF (Avicel PH-101, FMC Corporation, Philadelphia, PA) and microcrystalline cellulose with carboxymethylcellulose sodium (Avicel RC-581, FMC Corporation).

The model drugs used in this study are: chlorpheniramine maleate, USP, (provided by FMC Corporation, Philadelphia, PA) and anhydrous theophylline, USP (Knoll Fine Chemicals, New York, NY). They were selected because of their different solubilities.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

Pellet Manufacturing

The formulations listed in Table 1 were prepared at a constant batch size of 0.5 kg for each of the two drugs. The active ingredient and variable proportions of the two grades of microcrystalline cellulose were blended in a planetary mixer (Kitchen Aid Model K 5SS, Hobart Corporation, USA). Purified water was added to form a wet mass of suitable consistency. The wet

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

TABLE 1
Bead Formulations

Drug % w/w	Avicel PH-101 % w/w	Avicel RC-581 % w/w
10	90	-
10	70	20
10	55	35
10	40	50
10	20	70
10	-	90

RIGHTSLINK

granulations were passed through an extruder (Model EXDS-60, LUWA Corporation, Charlotte, NC). The extruder was operated at 50 rpm and fitted with 1.5 mm screens. The extrudate was transferred to the spheronizer (Marumerizer, Model Q-230, LUWA corporation) and processed at 1000 rpm. The spheres were collected after a 1-5 minute residence time and dried overnight on paper lined trays in a conventional hot air oven at a temperature of 40°C.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

Testing

Physical testing included particle size analysis by sieving (US standard sieves) and bed density determination by a standard graduated cylinder method. Dissolution testing was performed in both distilled water and 0.1N HCl, using USP/NF method I at a basket rotational speed of 50 rpm. Beads of a specified mesh cut (16/30) were selected for dissolution studies to compare samples over a 2 hour period. Samples were analyzed by UV spectroscopy at a wavelength of 272 nm for theophylline and 264 nm for chlorpheniramine maleate.

RIGHTSLINK

RESULTS AND DISCUSSION

At a 10% level for each of the drugs, beads were successfully manufactured with all combinations of the MCC products as listed in Table 1. It was

TABLE 2
Physical Properties of
10% Chlorpheniramine Maleate Beads

% Avicel RC581	-	20	35	50	70	90
% Avicel PH101	90	70	55	40	20	-
Density						
Bulk	0.69	0.58	0.69	0.69	0.71	0.71
Tapped	0.70	0.68	0.69	0.71	0.71	0.77
Sieve Analysis						
% Retained on						
8	0	0	0	0	0	0
12	1.2	1.0	2.0	0	1.0	0.1
16	29.6	35.0	43.0	51.0	41.0	27.7
20	48.1	56.0	47.0	47.0	56.0	60.0
30	18.9	8.0	6.0	2.0	2.0	13.0
40	1.9	1.0	2.0	0	0	0.7
pan	0.4	0	0	0	0	3.2

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

found that more granulating liquid (water) is required for an acceptable granulation and that longer residence time are needed to round the beads, as the levels of Avicel RC-581 are increased. If these slight changes are made, the beads are all rounded and of excellent appearance.

The physical properties including sieve analysis as well as bed density results for bead formulations with both drugs are listed in Tables 2 and 3. The sieve analysis data indicate a very narrow particle size range for most of these products even with the variation in the MCC products.

Single Diluents

Previous work in our laboratories has shown that Avicel RC-581 products form a gel in the basket / water dissolution test and that Avicel PH-101 products yield intact beads after testing (Figures 1 and 2).

The in-vitro distilled water dissolution profiles for beads of binary mixtures with the two drugs and the two Avicel products are shown in Figures 3 and 4. The same phenomenom was observed

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

TABLE 3
Physical Properties of
of 10% Theophylline Beads

% Avicel RC581	-	20	35	50	70	90
% Avicel PH101	90	70	55	40	20	-
Density						
Bulk	0.75	0.74	0.78	0.83	0.78	0.81
Tapped	0.76	0.78	0.79	0.86	0.83	0.86
Sieve Analysis						
% Retained on						
8	0	0	0	0	0	0
12	0	1.0	0	0.4	1.0	0
16	18.0	90.1	64.7	64.9	38.7	28.5
20	49.0	8.9	33.3	31.7	48.5	55.5
30	27.0	0.1	2.0	2.8	11.3	15.7
40	5.0	0	0	0.1	0.3	0.3
pan	2.0	0	0	0	0.1	0

for both of the drugs in this study. It is obvious that diffusion of the drug through the gel plug is slower than that through the pores of the intact beads; therefore release is slower.

When acid is used as the dissolution medium

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

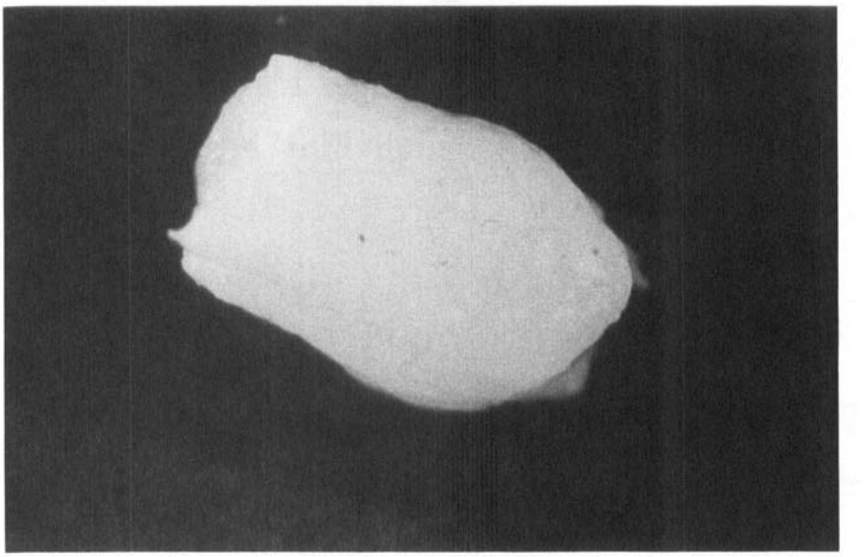

FIGURE 1
Gel Structure

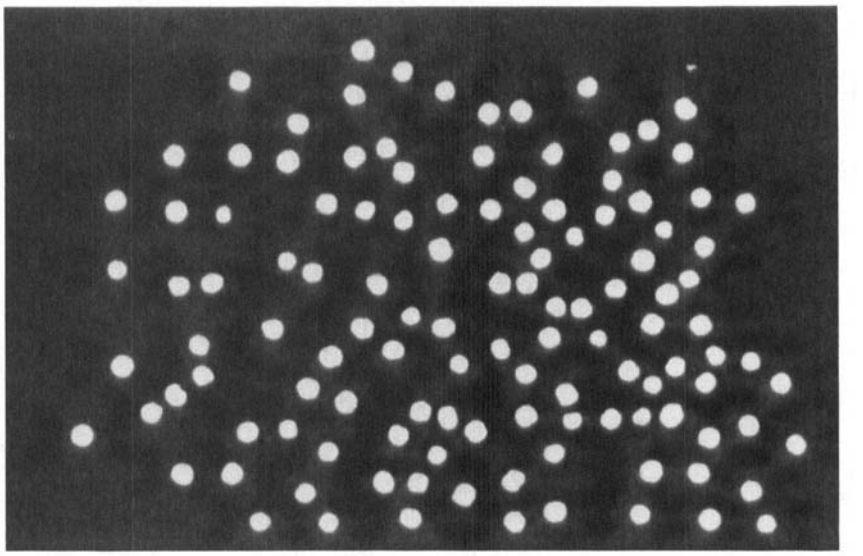

FIGURE 2
Intact Beads

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

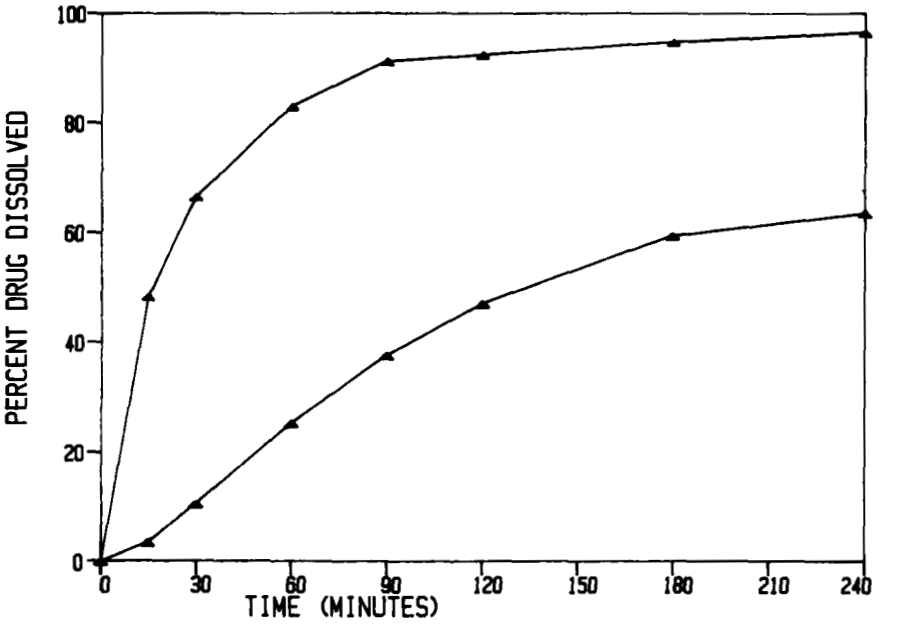

FIGURE 3

Dissolution Profiles of 10% Theophylline Beads in Water. Key: △ 90% PH-101; ▲ 90% RC-581.

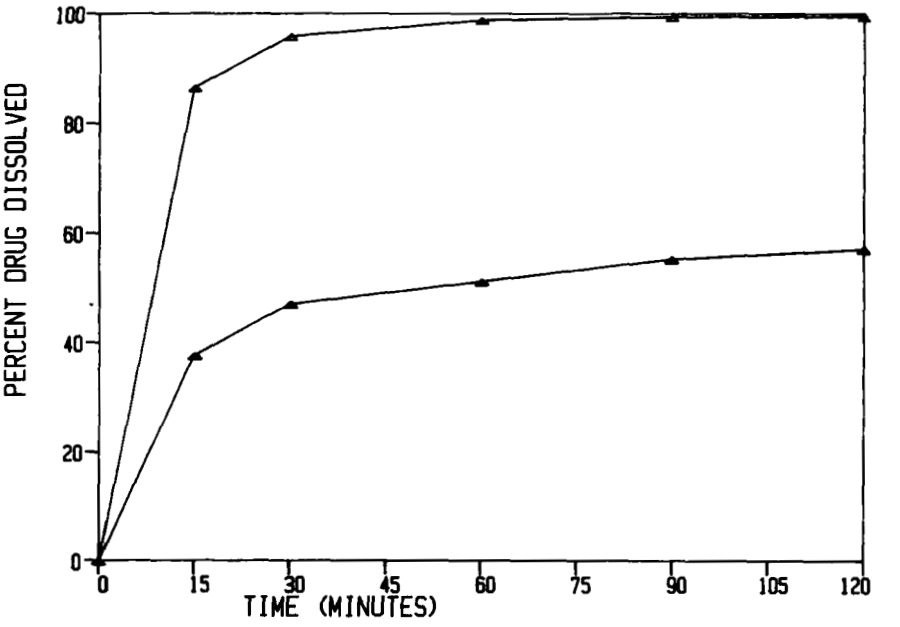

FIGURE 4

Dissolution Profiles of 10% CPM Beads in Water. Key: △ 90% PH-101; ▲ 90% RC-581.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

for the same beads, the results are different (Figures 5 and 6). No gel plug is formed from the products containing carboxymethylcellulose sodium; the drug release is rapid; and the beads appear to remain intact. This phenomenon has been shown previously to occur also in buffer at higher pH values and to be a function of the ionic strength of the dissolution medium, and not the pH[11].

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

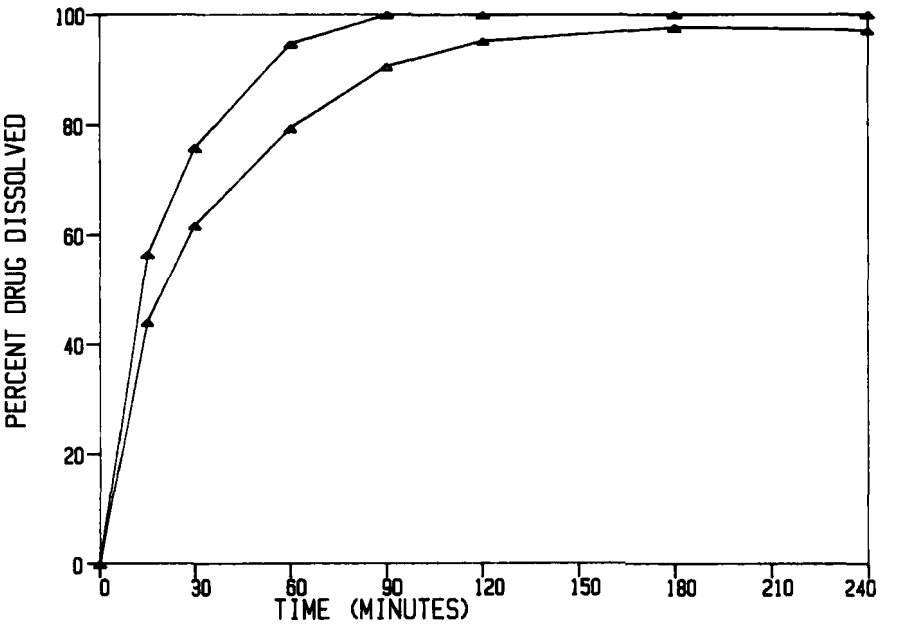

FIGURE 5

Dissolution Profiles of 10% Theophylline Beads in 0.1 N HCl. Key: △ 90% PH-101; ▲ 90% RC-581.

RIGHTSLINK

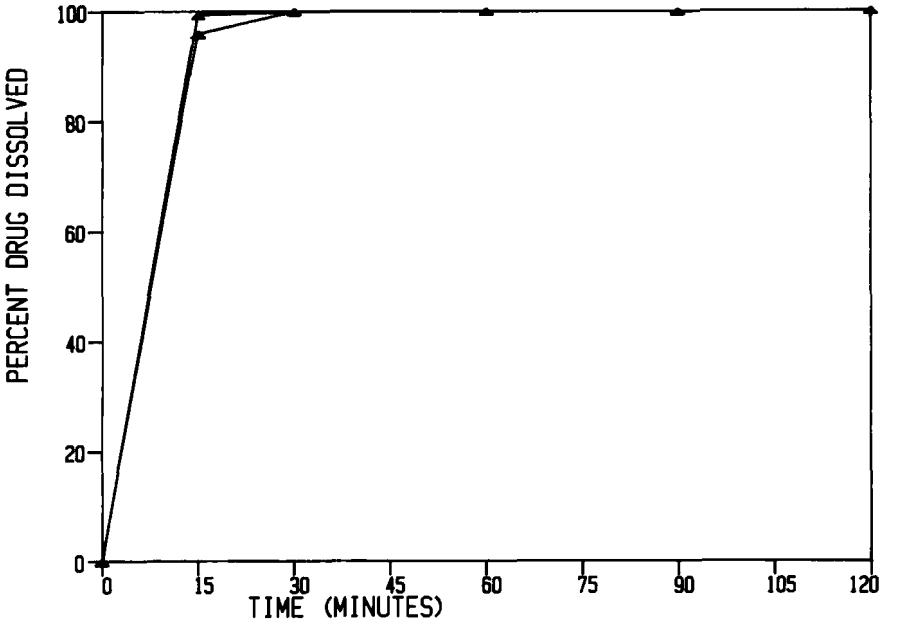

FIGURE 6

Dissolution Profiles of 10% CPM Beads in 0.1 N HCl. Key: ▵ 90% PH-101; ▲ 90% RC-581.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

Diluent Ratios

The dissolution results in water are shown in Figure 7 for the beads containing anhydrous theophylline prepared with combinations of the two grades of microcrystalline cellulose, and in Figure 8 for the soluble drug, chlorpheniramine maleate, with the same excipients. Dissolution of both drugs decreases as the Avicel RC-581 level

RIGHTSLINK

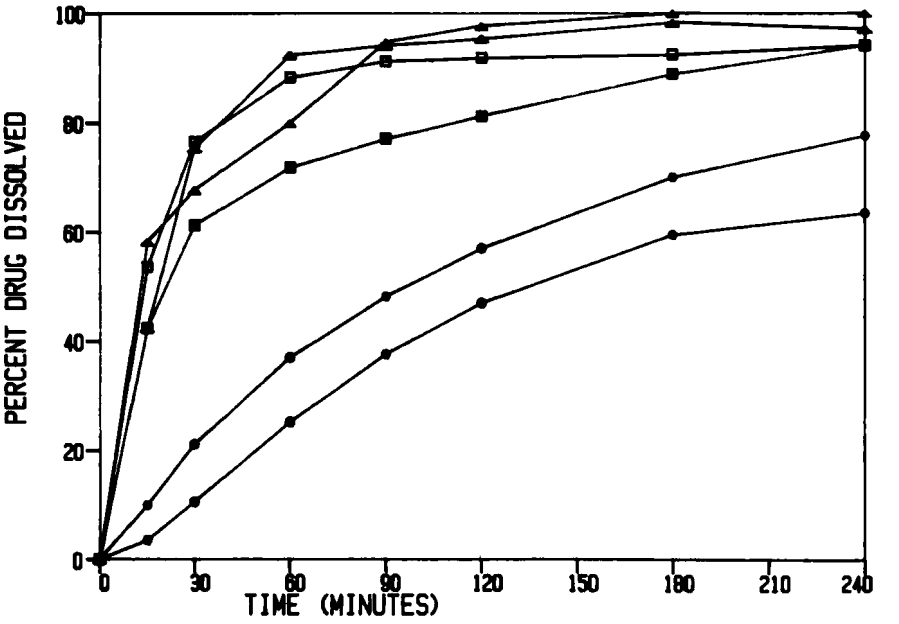

FIGURE 7

Dissolution Profiles of 10% Theophylline Beads in Water. Key: △ 0% RC-581; ▲ 20% RC-581; □ 35% RC-581; ■ 50% RC-581; ○ 70% RC-581; ● 90% RC-581.

increases. This is expected since one can observe that the size of the swollen gelatinous plug in the basket after testing increases with higher levels of Avicel RC-581.

Figure 9 shows the dissolution profiles of the same 10% theophylline formulations except that testing was performed in 0.1N HCl. The drug release

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

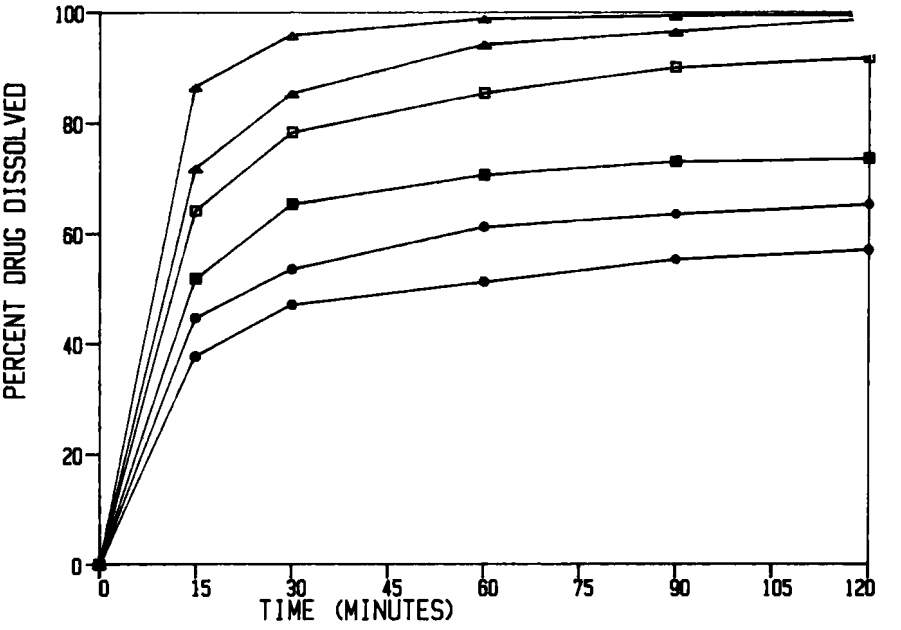

FIGURE 8

Dissolution Profiles of 10% CPM Beads in Water.
Key: △ 0% RC-581; ▲ 20% RC-581; □ 35% RC-581;
■ 50% RC-581; ○ 70% RC-581; ● 90% RC-581.

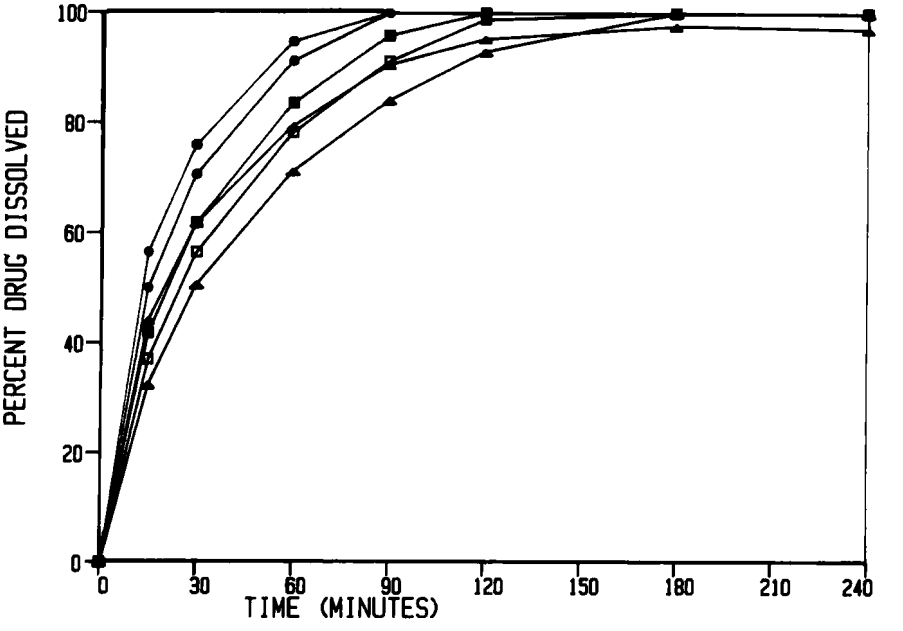

FIGURE 9

Dissolution Profiles of 10% Theophylline Beads in 0.1 N HCl.
Key: △ 0% RC-581; ▲ 20% RC-581; □ 35% RC-581; ■
50% RC-581; ○ 70% RC-581; ● 90% RC-581.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

was found to be nearly the same from the different products, and all pellets remain intact in the basket after dissolution. The effect of gel forming material, if any, is slight.

The drug release from pellets containing 10% chlorpheniramine maleate (Figure 10) prepared with varying proportions of Avicel PH-101 and Avicel RC-581 in 0.1 N HCl followed similar trends; no gel was formed. In this case the drug release is so

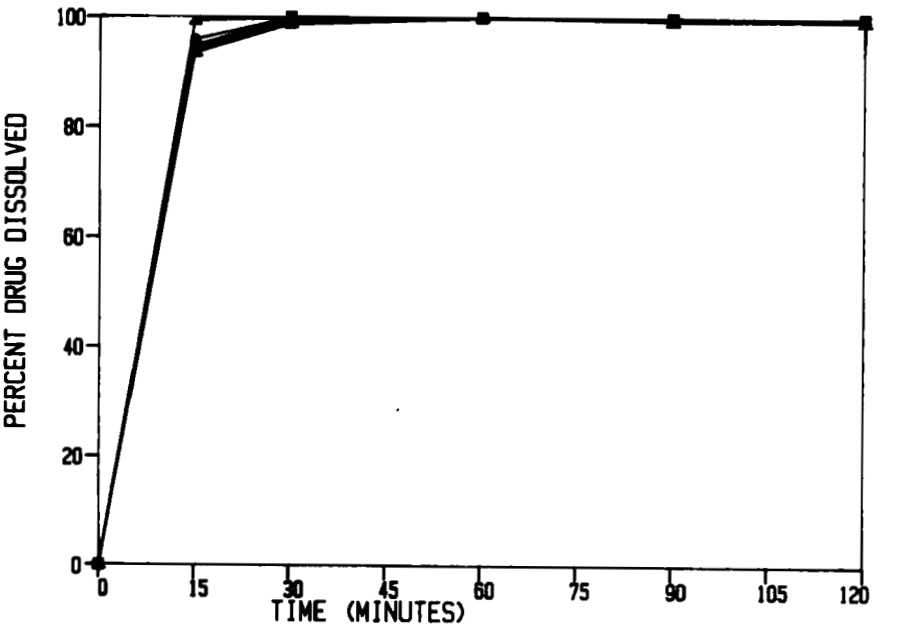

FIGURE 10

Dissolution Profiles of 10% CPM Beads in 0.1 N HCl. Key: △ 0% RC-581; ▲ 20% RC-581; □ 35% RC-581; ■ 50% RC-581; ○ 70% RC-581; ● 90% RC-581.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

rapid that the curves are almost identical, even though the beads remained intact in the dissolution basket after testing.

It is clear that the solubility of the drug plays a major role in drug release from these three component beads, as it does in the binary mixtures.

CONCLUSIONS

Beads of suitable physical appearance can be manufactured by combining two grades of microcrystalline cellulose (Avicel PH-101 and Avicel RC-581). The combination of Avicel PH-101 and Avicel RC-581 appears to provide more flexibility to the formulator for product manufacture and for modifying drug release under appropriate conditions. The behavior of the beads with combinations of MCC products changes in different solvents, and this may also give formulators some options for subsequent treatment (e.g., coating) and development into a final delivery system.

ACKNOWLEDGEMENT

The authors gratefully acknowledge Dr. R. O'Connor and Mr. G. D'Alonzo for their

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

helpful discussions and assistance with this manuscript.

REFERENCES

1. I.M. Jalal, H.J. Malinowski and W.E. Smith, J. Pharm. Sci., 61, 1466-1468 (1972).

2. C.W. Woodruff and N.O. Nuessle, ibid, 61, 787-790 (1972).

3. H.J. Malinowski and W.E. Smith, J. Pharm. Sci., 63, 285-288 (1974).

4. H.J. Malinowski and W.E. Smith, Pharm. Tech., 64, 1688-1692 (1975).

5. M.J. Gamlen, Chemist & Druggist, 13, 56 (December, 1969).

6. R.E. O'Connor, J. Holinej, J.B. Schwartz, Am. J. of Pharm., 156, 80-87 (1984)

7. R.E. O'Connor, J.B. Schwartz, Drug Dev. Ind. Pharm., 11, 1837-1857 (1985).

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK

8. P. Buri, E. Doelker, Pharm. Acta Helv., 55, 189-197 (1980).

9. P. DeHaan, CF Lerk, Pharm. Weekblad Sci. Ed., 6, 57-67 (1984).

10. V.H-L. Lee and J.R. Robinson, in "Sustained and Controlled Release Drug Delivery Systems," J.R. Robinson, ed., Dekker, NY, 1978, p. 136.

11. J.B. Schwartz, R.E. O'Connor and J.P. Remon "Pellets for Controlled Release: Effect of Processing, Test Methods and Ionic Strength on Drug Release from Two Hydrogel Systems," Proceedings of the 12th International Symposium on Controlled Release of Bioactive Materials, Geneva, Switzerland, July 8-12, 1985, p. 83-84.

Drug Development and Industrial Pharmacy Downloaded from informahealthcare.com by Biblioteca Alberto Malliani on 01/26/12
For personal use only.

RIGHTSLINK