DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 11(9&10), 1837-1857 (1985)

SPHERONIZATION II: DRUG RELEASE FROM DRUG-DILUENT MIXTURES

R.E. O'Connor and J.B. Schwartz
Philadelphia College of Pharmacy & Science
Philadelphia, PA 19104

ABSTRACT

Pellets were prepared from wet granulations using an extruder and spheronizer. Binary mixtures of active ingredient and different types of Avicel microcrystalline cellulose products have been processed and evaluated to determine the effect of varying the drug, the diluent, and the drug-diluent ratio. Physical properties including in-vitro drug release profiles were evaluated for the uncoated pellets. Anhydrous Theophylline, USP and Quinidine Sulfate, USP were evaluated at drug-diluent ratios from 10:90 to 80:20. Chlorpheniramine Maleate, USP and Hydrochlorothiazide, USP were incorporated into one system to study the influence of more extreme values of aqueous solubility on drug release. Drug release was found to vary with the drug, diluent, and the drug-diluent ratio.

0363-9045/85/1109-1837$3.50/0

INTRODUCTION

Pellets for pharmaceutical uses are of interest for both conventional dosage forms and controlled release delivery systems. It has been reported in a recent survey (1) that over 80% of the respondents from the pharmaceutical industry and academia are actively engaged in the research and development of drug delivery systems.

In an earlier report (2), materials used to manufacture pellets were evaluated with commercially available equipment, namely an extruder and spheronizer. In that study, the Avicel microcrystalline cellulose (MCC) products were found to be amenable to the spheronization process as single components. As a logical extension, this study has been expanded to include simple drug-diluent mixtures, so that drug release could also be investigated. The literature contains several references (3-5) to drug release from coated or specially formulated pellets. The emphasis in this report, however, is directed toward drug release from uncoated pellets consisting of binary mixtures of drug and diluent.

In the present study, two active ingredients, theophylline and quinidine sulfate, were incorporated into three diluents or matrix materials at three drug-diluent ratios: 10:90, 50:50, and 80:20. These

two drugs are of current interest in controlled release dosage forms and are even represented by several marketed products. The three diluents were selected from those Avicel MCC products studied previously and are Avicel PH-101, Avicel RC-581, and Avicel CL-611. Two additional drugs, chlorpheniramine maleate and hydrochlorothiazide, were selected as soluble and insoluble model compounds, respectively, and were evaluated in the system prepared with Avicel PH-101 at a drug-diluent ratio of 10:90.

It is the authors' contention that this experimental plan will provide a useful data base for future research and formulation efforts, as well as, insight into the application of this process to controlled release.

EXPERIMENTAL

Materials

The matrix materials include: Microcrystalline Cellulose, NF (Avicel PH-101, FMC Corporation, Philadelphia, PA) and two types of Microcrystalline Cellulose and Carboxymethylcellulose Sodium, NF (Avicel RC-581 and Avicel CL-611, FMC Corporation).

The active ingredients used in this study include: Chlorpheniramine Maleate, USP (VitaAmerican Corporation, Little Falls, NJ), Hydrochlorothiazide, USP (supplied for this study by E. R. Squibb & Sons,

Inc., Princeton, NJ), Quinidine Sulfate, USP (supplied for this study by the FMC Corporation, Philadelphia, PA), and Anhydrous Theophylline, USP (Knoll Fine Chemicals, New York, NY).

Pellet Manufacturing

The dry powders were preblended for 5 minutes in a planetary mixer (Hobart Model A-200T, Hobart Corporation, Hobart, NY). Batch size was held constant at 1.0 kilogram of dry solid. Purified Water, USP was added to the mixing powders in the planetary mixer to achieve the proper consistancy for extrusion. The wetted mass was passed through the extruder (Model EXDS-60, LUWA Corporation, Charlotte, NC). The extruder was operated at 50 rpm and was fitted with 1.5 mm screens. The extrudate was then processed in the spheronizer (Marumerizer, Model Q-230, LUWA Corporation) immediately following extrusion. The spheronizer was operated at 1000 rpm and was fitted with a 2 mm scored friction plate. Product was collected after a two minute residence time. The spheronized product was dried on paper lined trays either by air or in a hot air oven (Stokes Model-38C, Pennwalt Corporation, Warminster, PA).

Physical Testing

Physical testing included particle size analysis by sieving, density determination, and friability

evaluation using an abrasion wheel and glass beads, as described in an earlier report (2). The geometric mean diameter (d'g) was determined from the sieve analysis data using a log-probability plot as discussed by Martin (6).

Dissolution testing was performed in 900 ml of distilled water at 37 degrees Celsius using USP/NF Method I at a basket rotational speed of 50 rpm over a four hour time period. All samples were analyzed by UV spectroscopy at a maximum wavelength determined by an absorbance versus wavelength scan.

RESULTS AND DISCUSSION

The manufacturing results are presented in a processing summary (Table I) for the binary mixtures of theophylline and matrix material. In general, the results demonstrate that active ingredient can be incorporated into pellets under these simple mixing and processing conditions. The physical appearance of the products varied as a function of drug concentration. At a drug-diluent ratio of 10:90, the matrix material used was the predominant factor in determining the physical appearance of the spheronized products. Thus, the Avicel PH-101 product which formed the most spherical placebo pellets (2) also formed the best pellets at this concentration. At a drug-diluent ratio of 50:50, the products were overall the most acceptable in

Table I- Processing Summary for Binary Mixtures of Theophylline and Specified Matrix Material

Matrix Material	Drug-Diluent Ratio	Processes Completed: Granulation/Extrusion	Spheronization	Pellet Description
Avicel PH-101	10:90	Yes	Yes	Spherical
	50:50	Yes	Yes	Spherical
	80:20	Yes	No	None
Avicel RC-581	10:90	Yes	Yes	Spheres & Short Rods
	50:50	Yes	Yes	Spherical(*)
	80:20	Yes	Yes	Spherical Agglomerates
Avicel CL-611	10:90	Yes	Yes	Longer Rods
	50:50	Yes	Yes	Spherical(*)
	80:20	Yes	Yes	Spherical(*)

(*) Some product more irregular in shape

appearance for all three matrix materials. At a drug-diluent ratio of 80:20, a complete reversal in pellet acceptability occurred with respect to that at the 10:90 ratio. In fact, the Avicel PH-101 did not yield acceptable pellets and those prepared with Avicel CL-611 were the most spherical in appearance.

Therefore, based solely on physical appearance, Avicel PH-101 appears to be the ideal matrix material for the preparation of pellets containing low dose medicaments. Conversely, Avicel RC-581 and Avicel CL-611 appear to be more applicable to the preparation of pellets containing a high dose of drug, at least by this simple processing method.

The results of physical testing are reported in Tables II, III, and IV for pellets containing theophylline in Avicel PH-101, Avicel RC-581, and Avicel CL-611, respectively.

In general, the particle size distributions for these pellets represent a narrow distribution relative to that produced by conventional wet granulation. The percentage of the batch found in a 12/30 mesh cut decreased with increasing active concentration for all the matrix materials tested. The sieve analysis data, as well as, the calculated geometric mean diameter, indicate that increasing the active concentration results in smaller particles for the pellets prepared

Table II- Physical Testing Data for Avicel PH-101 as a Matrix Material

	% Theophylline			
	0(*)	10	50	80
Sieve Analysis Percent Retained on Mesh #				
8	0.36	0.30	0.06	
12	5.71	2.80	3.82	N
16	37.05	42.68	22.62	O
20	47.06	49.79	35.36	
30	9.51	4.32	26.61	P
40	0.28	0.06	9.57	E
Pan	0.03	0.05	1.95	L
				L
				E
Geometric Mean Diameter (micrometers)	1010	980	760	T S
Density (g/ml)	0.78	0.76	0.76	
Friability (%)	3.07	1.29	20.38	

(*) Data taken from Reference (2)

Table III- Physical Test Data for Avicel RC-581 as a Matrix Material

	% Theophylline			
	0(*)	10	50	80
Sieve Analysis Percent Retained on Mesh #				
8	0.00	0.00	0.04	1.99
12	1.06	0.50	2.73	24.31
16	21.61	33.84	44.76	45.22
20	63.87	55.49	42.32	25.24
30	12.48	8.35	8.85	3.19
40	0.98	1.42	1.23	0.04
Pan	0.00	0.40	0.07	0.00
Geometric Mean Diameter (micrometers)	880	860	900	1800
Density (g/ml) Bulk(Tapped)	0.83(0.83)	0.81(0.85)	0.78(0.82)	0.76(0.78)
Friability (%)	1.89	0.80	2.74	1.70

(*) Data taken from Reference (2)

Table IV- Physical Testing Data for Avicel CL-611 as a Matrix Material

	% Theophylline			
	0(*)	10	50	80
Sieve Analysis Percent Retained on Mesh #				
8	0.24	0.00	3.05	19.78
12	1.08	0.02	21.63	26.90
16	49.02	59.27	60.18	36.72
20	45.55	38.46	13.60	14.61
30	3.98	2.04	1.42	1.76
40	0.13	0.16	0.12	0.18
Pan	0.00	0.05	0.00	0.05
Geometric Mean Diameter (micrometers)	1020	1020	1280	1420
Density (g/ml) Bulk(Tapped)	0.80(0.80)	0.81(0.83)	0.80(0.80)	0.81(0.82)
Friability (%)	0.89	0.10	0.60	1.24

(*) Data taken from Reference (2)

with Avicel PH-101 and larger particles for those prepared with Avicel RC-581 and Avicel CL-611. As previously reported (2), some degree of vertical orientation was necessary to obtain the particle size results reported for the non-spherical pellets.

Pellet density appears to be unaffected by changes in the drug-diluent ratio. The pellet densities are generally greater than those usually produced during a conventional wet granulation.

The friability appears to increase with increasing active concentration. The large increase for Avicel PH-101 was accompanied by the physical characteristic of softness and may, in part, explain the failure to form satisfactory product at a drug-diluent ratio of 80:20. All other products could be qualitatively classified as hard pellets and could be expected to withstand rough handling.

The in-vitro dissolution results for pellets containing theophylline have been summarized in Table V and represent the percent dissolved at 30 and 60 minutes. These early sampling times are of interest to demonstrate the delayed release characteristics of these pellets by this test method. Dissolution data are also presented in graphical form to facilitate comparison and discussion of trends. The results of dissolution testing were somewhat surprising, since

Table V- Dissolution Summary for Pellets Containing Theophylline

Drug-Diluent Ratio	Avicel Type	Percent Dissolved at Time = T	
		T = 30 minutes	T = 60 minutes
10:90	PH-101	46.9	65.8
	RC-581	9.4	16.2
	CL-611	6.3	12.6
50:50	PH-101	69.5	88.1
	RC-581(1)	38.3	49.7
	CL-611(1)	14.8	25.5
80:20	PH-101(2)	53.9	77.0
	RC-581	27.1	48.6
	CL-611	29.7	60.3

(1) 16/20 Mesh Cut used for testing
(2) Salvaged particles from spheronizer used for testing

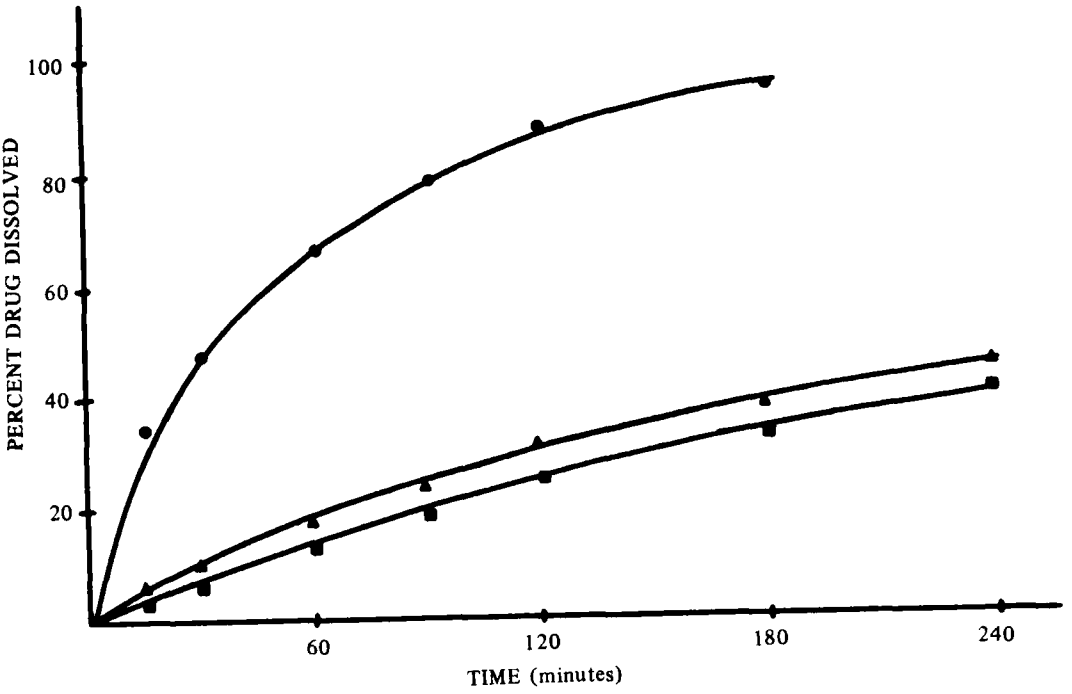

Figure 1. Dissolution profiles for pellets containing 10% theophylline in different Avicel MCC types. (KEY: ● Avicel PH-101, ▲ Avicel RC-581, ■ Avicel CL-611)

none of the pellets tested yielded an immediate release profile.

The dissolution profiles for pellets containing theophylline in each diluent at a drug-diluent ratio of 10:90 are shown in Figure 1. These release profiles were found to be the slowest of all three drug-diluent ratios and appear to be dependent on the diluent. The pellets containing Avicel PH-101 as the matrix

material exhibited 100% release after 3 hours of dissolution testing, while those containing either Avicel RC-581 or CL-611 exhibited only 40% release after 4 hours. The physical appearance of the basket contents after dissolution testing may explain the delayed release from these pellets. The results of dissolution testing for pellets prepared with Avicel PH-101 have been attributed to their non-disintegrating nature. Intact drugless pellets remained in the basket after testing; this phenomenon would be expected of an inert matrix release system (7). The pellets prepared with Avicel RC-581 or Avicel CL-611 appear to have a similar release system, since these pellet systems formed a swollen gelatinous plug in the dissolution basket assembly. These latter two systems can be best described as water-swellable hydrogel matrix systems (7).

The results of an extended dissolution test for pellets containing theophylline in Avicel RC-581 at a drug-diluent ratio of 10:90 is shown in Figure 2. Testing was extended over a 12 hour time period to determine the release profile under constant test conditions. The first four hour segment of this dissolution profile is superimposable on the previous four-hour profile (Figure 1). It is obvious that release continues over a 12 hour time period.

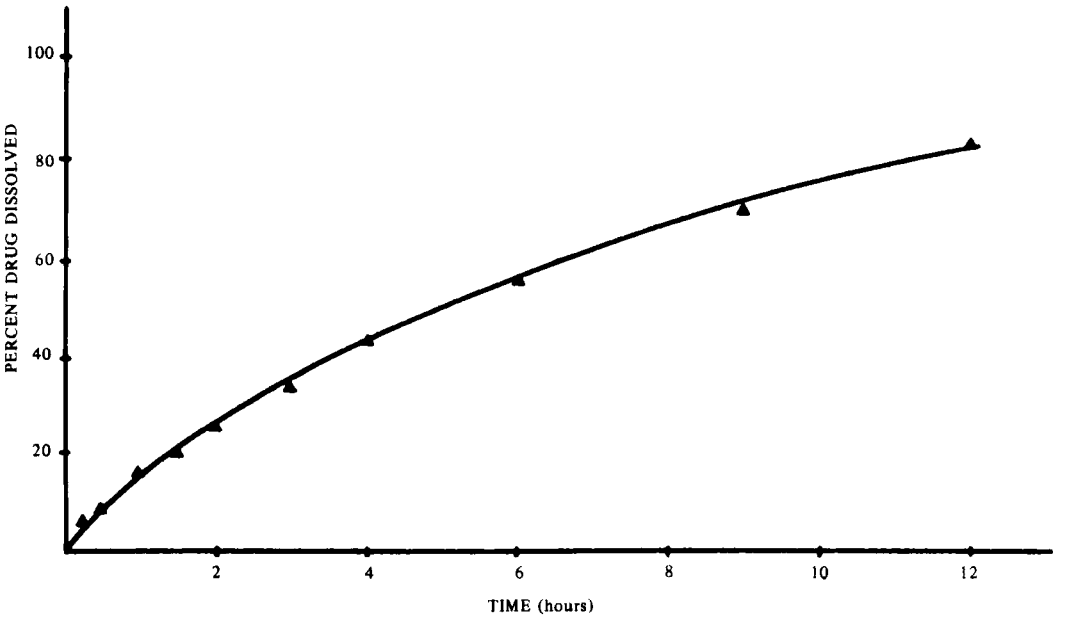

Figure 2. Dissolution profile for pellets containing 10% theophylline in Avicel RC-581 with an extended time axis.

The dissolution profiles for pellets containing theophylline in each diluent at a drug-diluent ratio of 50:50 are shown in Figure 3. These profiles exhibit the same trend as that established at a drug-diluent ratio of 10:90. In addition, the difference in drug release between pellets prepared with Avicel RC-581 and those prepared with Avicel CL-611 is more apparent at this drug concentration. Comparison of Figures 1 and 3 supports the hypothesis that drug release is dependent on the nature of the diluent or matrix material.

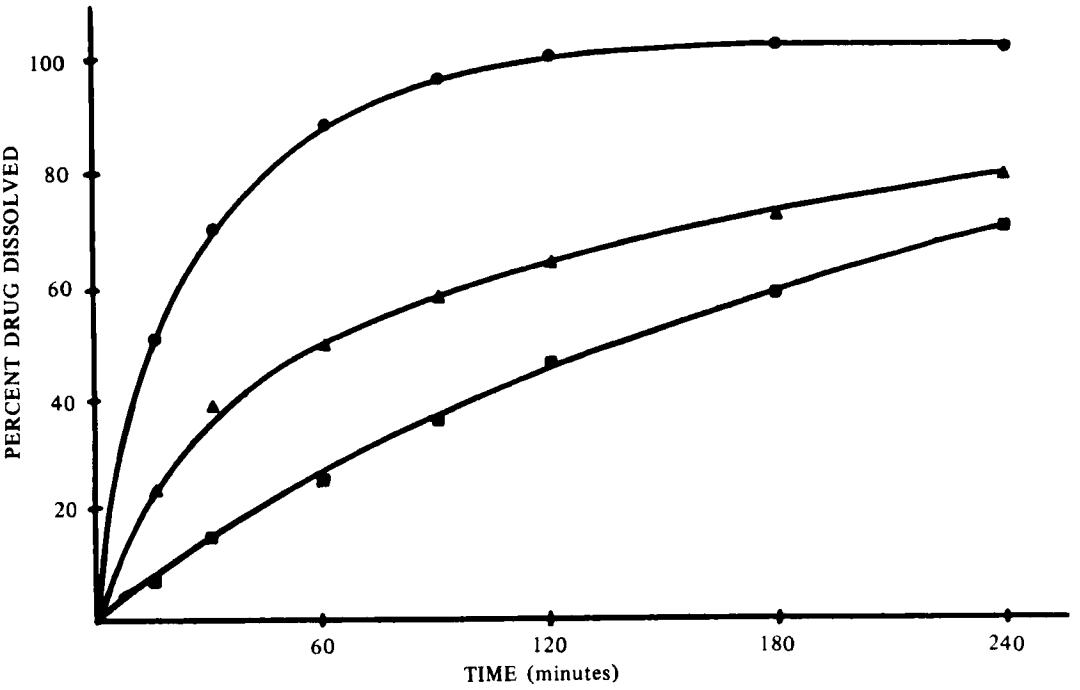

Figure 3. Dissolution profiles for pellets containing 50% theophylline in different Avicel MCC types. (KEY: ●Avicel PH-101, ▲ Avicel RC-581, ■ Avicel CL-611)

The dissolution profiles for theophylline in Avicel CL-611 at drug-diluent ratios of 10:90, 50:50, and 80:20 are shown in Figure 4. A direct relationship appears to exist between drug concentration and drug release. Therefore, drug release was also found to be dependent on the drug-diluent ratio.

The results of manufacturing, physical testing, and dissolution testing for pellets containing quinidine sulfate were similar to those discussed for

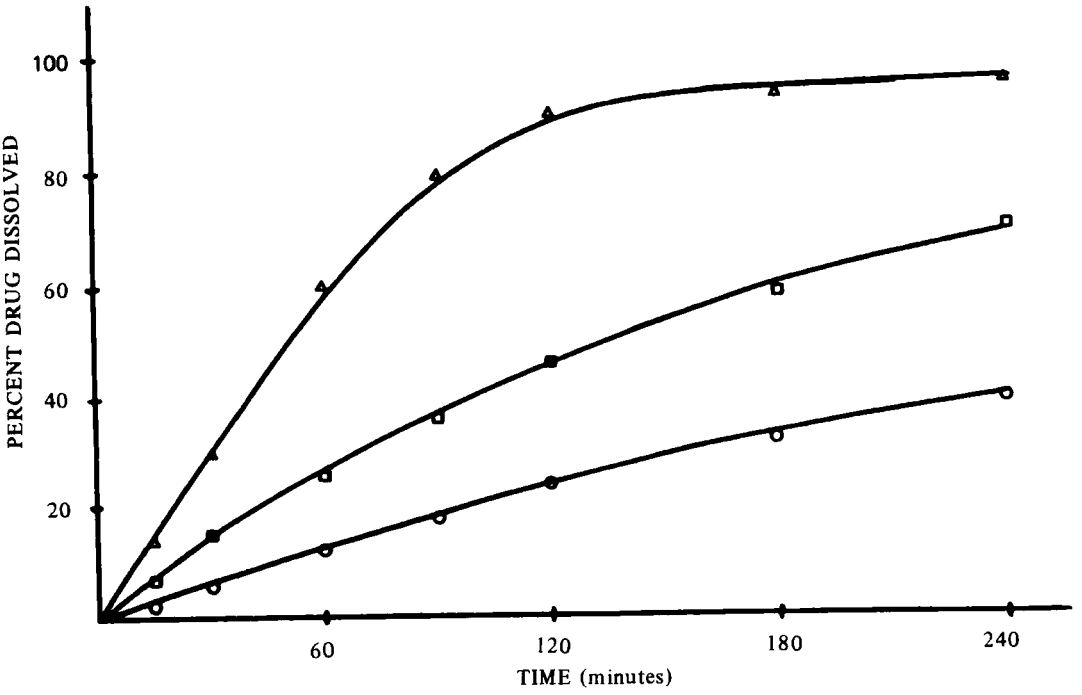

Figure 4. Dissolution profiles for pellets containing different concentrations of drug in Avicel CL-611. (KEY: ○ 10%, □ 50%, △ 80%)

pellets containing theophylline and, therefore, will not be presented in this paper. The dissolution profiles are probably similar for the two series of pellets due, in part, to the similar aqueous solubility of the two active compounds (Table VI).

The dissolution profiles for pellets containing Avicel PH-101 and various active ingredients (Table VI) at a drug-diluent ratio of 10:90 are shown in Figure 5. The results demonstrate that this system

Table VI- Some Physical Constants for Active Compounds

Compound	Maximum Wavelength	Solubility(*) (mg/ml)	USP XX Descriptive Term
Chlorpheniramine Maleate	262	160.0	Freely Soluble
Quinidine Sulfate	234	10.0	Sparingly Soluble
Theophylline, Anhydrous	272	8.3	Slightly Soluble
Hydrochlorothiazide	270	0.61	Very Slightly Soluble

(*) from the series, Analytical Profiles of Drug Substances, K. Florey, ed., Academic Press, NY.

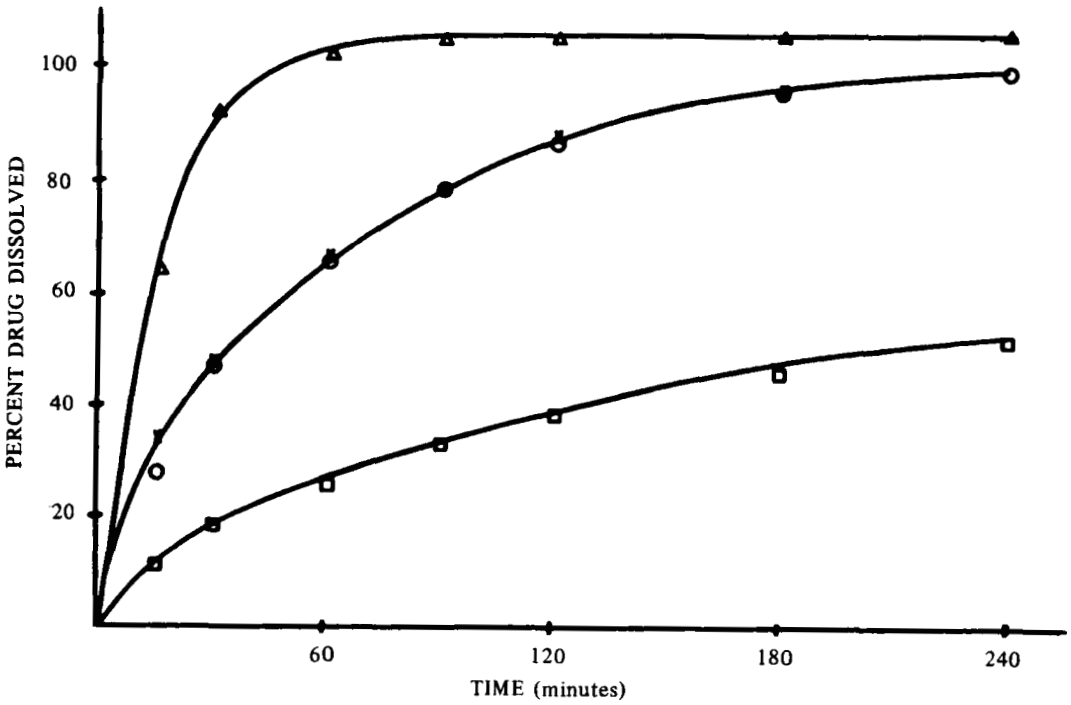

Figure 5. Dissolution profiles for pellets containing 10% drug in Avicel PH-101. (KEY: △ Chlorpheniramine Maleate, ○ Quinidine Sulfate, X Theophylline, □ Hydrochlorothiazide)

follows a direct correlation between aqueous solubility and drug release, which has been previously described by the Noyes-Nernst equation (8). These data suggest that drug release from this system is dependent on the properties of the drug, in particular, its aqueous solubility.

The influence of in-vitro dissolution test methodology on the results of any dissolution study is well documented in the literature and is worthy of further study for these test systems.

CONCLUSIONS

Based on the data and discussion presented in this paper, several conclusions can be made regarding this work. Drug release from these simple drug-diluent mixtures has been found to vary with the drug, the diluent, and the drug-diluent ratio under the specified test conditions. At least two different drug release systems have been identified, namely, the inert matrix and the swelling hydrogel matrix systems. It appears that the Avicel microcrystalline cellulose products have specialized properties that permit spheronization as single components and in binary mixtures of drug and diluent using only purified water as the granulating fluid.

ACKNOWLEDGMENTS

Presented at the 131st APhA Annual Meeting, IPT Section, Montreal, Canada, May, 1984.

Abstracted in part from a thesis submitted by R.E. O'Connor to the Philadelphia College of Pharmacy & Science in partial fulfillment of the Master of Science degree requirements, November, 1983. Mr. O'Connor is the 1984 & 1985 AFPE Manufacturing/ Industrial Pharmacy Fellow.

The authors thank the Elanco Division, Eli Lilly & Company, Indianapolis, IN for the gift of the equipment to the College; the LUWA Corporation, Charlotte, NC for current support in equipment operation; E. R. Squibb & Sons, Inc., Princeton, NJ for supply of material, and the FMC Corporation, Philadelphia, PA for their support and generous supply of materials used in this study.

REFERENCES

1. B.S. Hubert, Pharmaceutical Technology, August, 32 (1984).

2. R.E. O'Connor, J. Holinej, and J.B. Schwartz, Am. J. of Pharm., 156, 80 (1984).

3. J.B. Schwartz and H.Y. Ando, American Druggist, July, 41 (1983).

4. K.S. Murthy, R.U. Nesbitt, and M.R. Harris, Pharmaceutical Engineering, July-August, 19 (1983).

5. F.W. Goodhart, M.R. Harris, K.S. Murthy, and R.U. Nesbitt, Pharmaceutical Technology, April, 64 (1984).

6. A.N. Martin, J. Swarbrick, and A. Cammarata, in "Physical Pharmacy," 3rd ed., Lea & Febiger, Philadelphia, 1983, p. 494.

7. 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.

8. D.A. Wadke and H. Jacobson, in "Pharmaceutical Dosage Forms: Tablets," H.A. Lieberman and L. Lachman, eds., Vol. 1, Dekker, NY ,1980, p. 14.