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MATRIX FORMING CAPABILITIES OF THREE CALCIUM DILUENTS

Jones W. Bryan, Jr., Ph.D. [1,2] and J. David McCallister, Ph.D. [3]
Medical University of South Carolina
Department of Pharmaceutical Sciences Charleston, SC 29425

Abstract: The formulation of drug substances with excipients capable of forming a matrix structure is an approach which has been successfully applied to sustain medicament release following oral administration. Investigations of materials which possess matrix forming properties have been limited to a few polymeric substances such as polyvinyl chloride, polyethylene, acrylic copolymers, and cellulose derivatives [1-5]. Calcium sulfate dihydrate, dibasic calcium phosphate dihydrate, and tribasic calcium phosphate have previously been used as fillers/diluents in the formulation of solid dosage forms. All three diluents exhibit poor solubility in media of pH 1.1 and are practically insoluble in media of pH 4.0 to 7.5. In addition, when blended with one of three drug candidates and compressed these materials sustain drug release via a matrix diffusional process at higher pH corresponding to that of the human intestine. These findings led to an investigation of these calcium diluents as matrix forming agents in sustained release solid dosage forms.

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[1] Schering-Plough Corp., Animal Health Formulation Research, 2000 Galloping Hill Road, K-11-2 J4, Kenilworth, NJ 07033.

[2] To whom correspondence should be addressed.

[3] Medical University of South Carolina, Department of Pharmaceutical Sciences, 171 Ashley Avenue, Charleston, SC 29425.

BACKGROUND AND INTRODUCTION

The goal of most solid dosage forms is to achieve immediate release of the drug candidate to ensure rapid absorption into the systemic circulation. Therefore, formulation is normally approached with the idea of adding excipients to promote disintegration and rapid dissolution. The diluents calcium sulfate dihydrate, dibasic calcium phosphate dihydrate, and tribasic calcium phosphate have significantly lower solubilities (Merck Index) than other commercially available diluents such as lactose. This characteristic difference has led formulators to favor the more soluble diluents in the development of solid dosage forms intended for immediate release.

With inert excipients constituting up to 95% of some formulations the effect of their physical and chemical characteristics on medicament release becomes a concern. A study was conducted by Koparkar et al [6] to determine the intrinsic dissolution rates (IDR) of lactose and calcium salts and their effect on drug release. Data from this study indicate a direct relationship between IDR of the filler/diluent and rate of medicament release. It was concluded that in the formulation of solid dosage forms, the IDR of the filler may be as important as its compressibility and physical stability.

The study presented here was initiated to evaluate the effect of the solubility of three calcium diluents on release of medicament from solid dosage forms in media corresponding to that of the human gastrointestinal tract. The calcium salts show matrix forming/sustained release capabilities in media of pH 4.0 to 7.5 where they are practically insoluble. However, in media of pH 1.1 they exhibit gradual erosion due to their relatively higher solubility hence, a destruction of the matrix structure and failure to achieve a sustained release profile. Additional studies were performed to evaluate the inclusion of other excipients to impart a more acid resistant character on the diluent/drug blend and to assist in maintaining the matrix structure.

EXPERIMENTAL

Materials:

The materials were used as received unless specified otherwise. Dibasic calcium phosphate dihydrate USP powder, calcium sulfate dihydrate NF powder, and acacia were

TABLE 1

Solubility Data of Three Calcium Diluents

pH	Solubility of Calcium Diluent (mg/ml)		
	Calcium Sulfate	Dibasic	Tribasic
1.1	8.023	17.390	9.710
4.0	5.205	7.316	2.218
5.5	5.470	4.290	0.338
6.5	2.850	1.200	0.025
7.5	0.068	0.068	0.020

The values presented in the table are average values of triplicate runs.

purchased from Amend Drug and Chemical Company (Irvington, New Jersey). Magnesium stearate was purchased from Ruger Chemical Company (Irvington, New Jersey). Acetaminophen USP powder was donated by Mallinckrodt, Inc. (Raleigh, NC). Carbopol 934P was donated by BF Goodrich Company (Cleveland, Ohio).

Equipment:

1. Pharma Test Type PTW S six vessel dissolution apparatus.
2. Hewlett Packard Model 8451A Diode Array Spectrophotometer.
3. Carver Press.
4. Thomas Engineering, Inc. 7 mm standard concave tooling.
5. Manesty Model F3 single station tablet press.

Solubility Profiles:

Solubility profiles of calcium sulfate dihydrate, dibasic calcium phosphate dihydrate, and tribasic calcium phosphate were generated by placing an excess of diluent into a series of 1000 ml dissolution vessels containing media of pH 1.1, 4.0, 5.5, 6.5, and 7.5. Each system was allowed to equilibrate under agitation at 37°C. Samples were obtained via a two micron filter and diluent concentration was determined by the USP titration for calcium [7]. The results of these determinations appear in Table 1 and Figure 1.

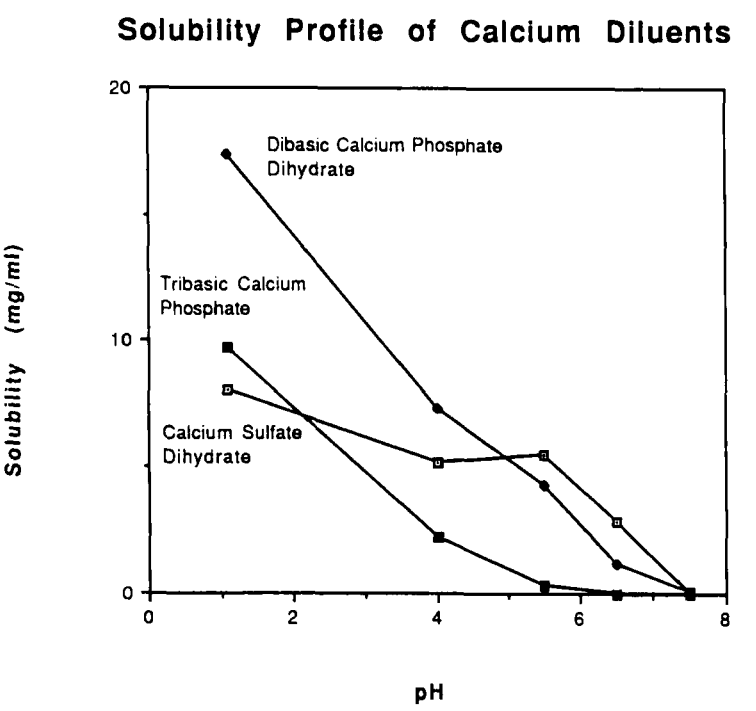

FIGURE 1
Solubility profiles of dibasic calcium phosphate dihydrate, tribasic calcium phosphate, and calcium sulfate dihydrate.

Acetaminophen powder USP was chosen as the model drug due to its relatively pH independent solubility profile over the range of interest. A solubility profile was generated by placing an excess of drug into a series of 1000 ml dissolution vessels containing media of pH 1.1, 4.0, 5.5, 6.5, and 7.5. The systems were allowed to equilibrate under constant agitation at 37°C. Samples were obtained via a 0.45 micron filter and drug concentration was determined by spectrophotometric analyses and observation of Beer's Law. A Hewlett Packard Diode Array Spectrophotometer was used for the analyses at a wavelength of 244 nm. Results appear in Table 2 and Figure 2.

Tablet Preparation and Dissolution Testing:

a. Single Surface:

Experimental tablets totalling 400 mg were prepared by blending 100 mg of acetaminophen and 300 mg of diluent in a small weigh boat with a microspatula. The blend was

TABLE 2

Solubility Data of the Model Drug Acetaminophen

pH	Solubility of Acetaminophen (mg/ml)
1.1	23.25
4.0	20.97
5.5	20.94
6.5	20.40
7.5	19.65

The values presented in this table are average values of triplicate runs.

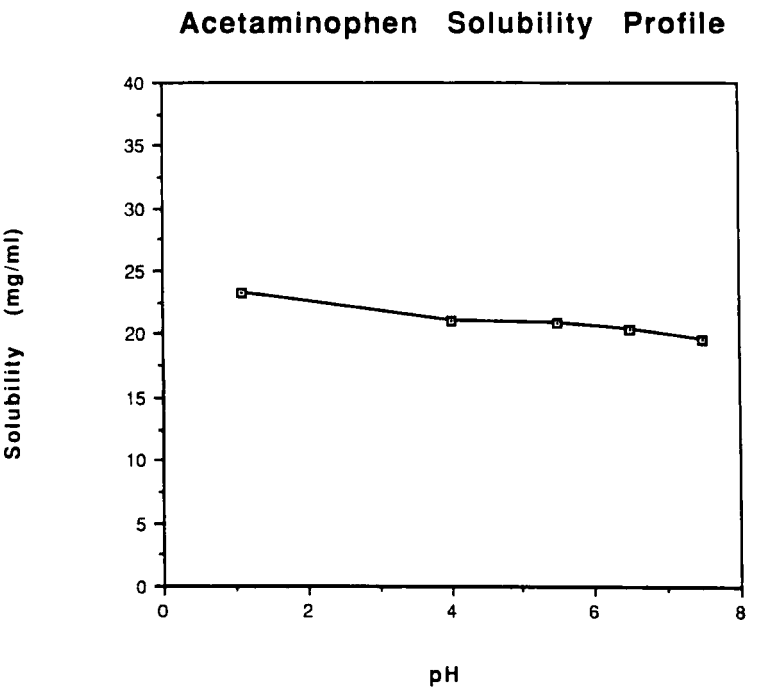

FIGURE 2
Solubility profile of the model drug acetaminophen.

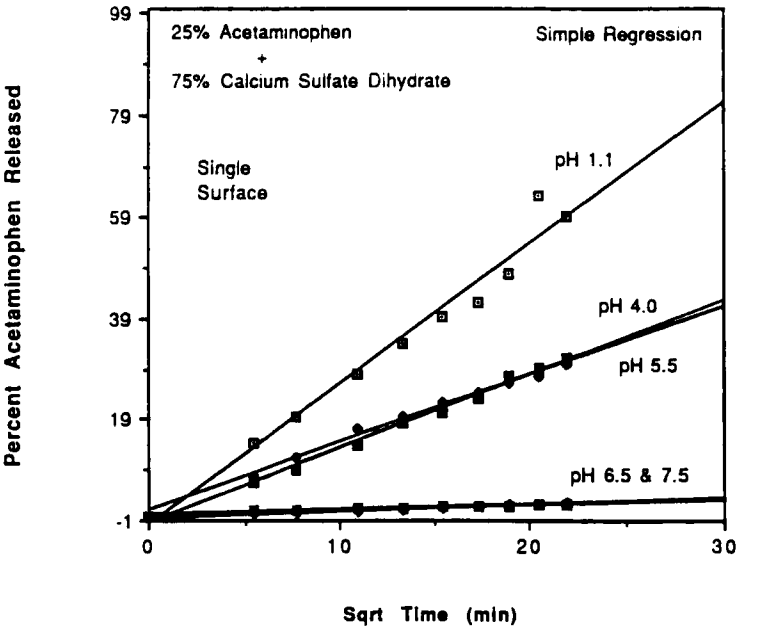

FIGURE 3

Regression of percent acetaminophen released from a single tablet surface on square root of time. The formulation contains drug (25%) and calcium sulfate dihydrate (75%), and profiles were generated in media of pH 1.1, 4.0, 5.5, 6.5, and 7.5.

then compressed on a Carver Press under 4000 lbs of pressure using 7 mm standard concave tooling. Prior to dissolution testing, each tablet was coated on all but one surface with spermaceti wax. This was done to standardize the total surface area exposed to the dissolution medium.

Drug release profiles were obtained by subjecting tablets containing drug and diluent to media of pH 1.1, 4.0, 5.5, 6.5, and 7.5. The USP paddle method was employed at 50 RPM and the test medium was maintained at 37°C. Samples were taken by an automated sipper device fitted with a two micron filter at 0.5, 1, 2, 3, 4, 5, 6, 7, and 8 hours. Results, regression analyses, and corresponding statistics are presented in Figures 3, 4, and 5.

b. Whole Tablets:

Whole tablets were prepared by weighing the excipients, screening through a 10 mesh sieve, blending in a laboratory model twin shell v-blender, weighing 400 mg aliquots of the

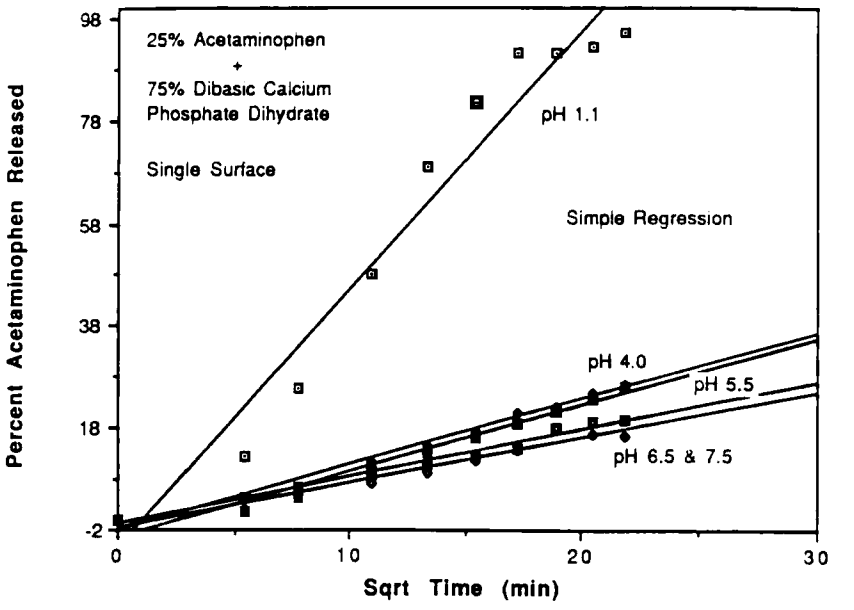

FIGURE 4

Regression of percent acetaminophen released from a single tablet surface on square root of time. The formulation contains drug (25%) and dibasic calcium phosphate dihydrate (75%), and profiles were generated in media of pH 1.1, 4.0, 5.5, 6.5, and 7.5.

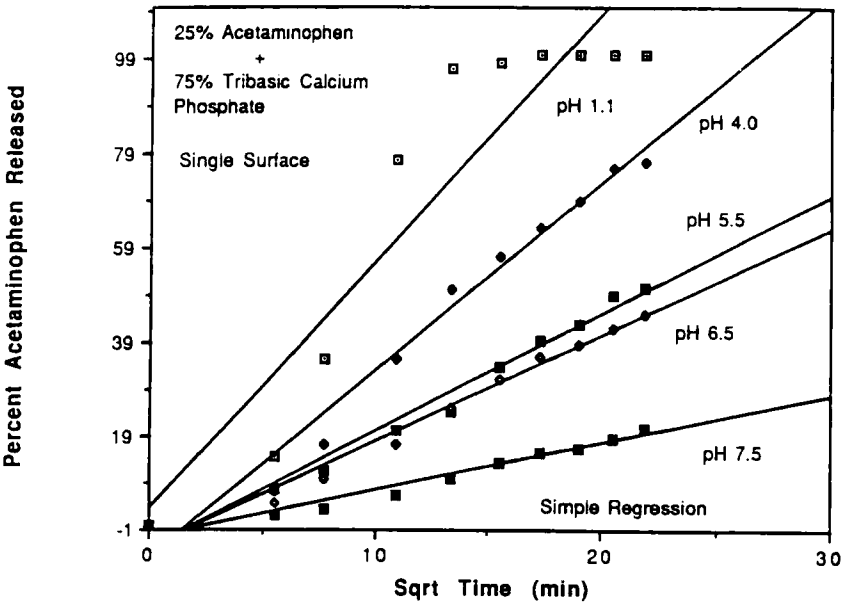

FIGURE 5

Regression of percent acetaminophen released from a single tablet surface on square root of time. The formulation contains drug (25%) and tribasic calcium phosphate (75%), and profiles were generated in media of pH 1.1, 4.0, 5.5, 6.5, and 7.5.

blend, and compressing on a single station tablet press (Manesty F3) equipped with 7 or 9 mm standard concave tooling (Thomas Engineering). The press was instrumented with a transducer type strain gauge (Measurement Systems, Inc.) to monitor compression force applied during tablet manufacture.

Dissolution tests were performed by placing the tablets in a series of baskets which were lowered into dissolution vessels (Pharma Test, Model PTW S) containing 1000 ml of 0.1N HCl. Testing was conducted for two hours under constant agitation at 50 RPM with the dissolution media being maintained at 37°C. At the completion of the initial two hour testing period the baskets were removed from the vessels, the 0.1N HCl was replaced with preheated phosphate buffer (pH ≈ 7.2), and testing was resumed for an additional six to eight hours. Samples were taken at one hour intervals via an automated sampling device fitted with two micron filters. Percent drug released data was generated by spectrophotometric analysis and comparison of sample absorbance values to those of a series of standard solutions. Analysis was performed at wavelengths of 244 nm for acetaminophen, 270 nm for theophylline, and 266 and 264 nm for chlorpheniramine maleate. Data was reported as percent drug released versus square root of time via a computer software program on-line with the spectrophotometer (Hewlett Packard, Model 8451A). Least squares linear regression statistics and data analysis was performed on the Statistical Graph and Plotting Program.

RESULTS AND DISCUSSION

The solubility profiles of the pharmaceutical diluents: calcium sulfate dihydrate, dibasic calcium phosphate dihydrate, and tribasic calcium phosphate are presented in Figure 1. All three calcium salts exhibit their highest solubility at pH 1.1 with a decrease to practically insoluble levels at pH 6.5 and 7.5. These diluents have shown the ability to sustain model drug release from a single tablet surface for eight to ten hours in media of pH 4.0 to 7.5 (Figures 3, 4, and 5). These release characteristics coupled with the ability to remain intact throughout the release process suggests the existence of a matrix type drug delivery system. However, in media of pH 1.1 release occurs much more rapidly due to erosion of the dosage form associated with the gradual solubilization of the diluent. Regression analysis of the percent drug released on the square root of time showed a strong linear relationship in the pH range of 4.0 to 7.5

TABLE 3

Regression Statistics for Acetaminophen Release vs Square Root of Time from Calcium Sulfate Dihydrate Vehicle as a Function of pH.

	pH of Test Medium				
Statistic	1.1	4.0	5.5	6.5	7.5
R-Squared	.993	.999	.998	.978	.994
C.O.D.	.970	.994	.992	.938	.961
Corr.	.985	.997	.996	.969	.980

TABLE 4

Regression Statistics for Acetaminophen Release vs Square Root of Time from Dibasic Calcium Phosphate Dihydrate Vehicle as a Function of pH.

	pH of Test Medium				
Statistic	1.1	4.0	5.5	6.5	7.5
R-Squared	.989	.997	.996	.987	.991
C.O.D.	.956	.987	.983	.954	.969
Corr.	.978	.994	.991	.977	.984

TABLE 5

Regression Statistics for Acetaminophen Release vs Square Root of Time from Tribasic Calcium Phosphate Vehicle as a Function of pH.

	pH of Test Medium				
Statistic	1.1	4.0	5.5	6.5	7.5
R-Squared	.971	.993	.994	.994	.988
C.O.D.	.867	.975	.977	.978	.961
Corr.	.931	.987	.988	.989	.981

where the dosage forms remain intact. Conversely, this relationship was not as strong at pH 1.1 where the diluent solubilities are highest and the dosage form slowly eroded (Tables 3, 4, and 5). These findings conform to Higuchi's mathematical description of matrix diffusional release, wherein, he states that drug release should exhibit a linear relationship with the square root of time [1-5].

A challenge to the use of these calcium diluents as matrix forming agents in sustained release solid dosage forms is their protection from the acidic environment of the gastrointestinal tract for up to two hours following oral administration. Once the dosage form passes into the more basic environment of the intestine the calcium diluents are able to regain their matrix forming ability. A screening study was initiated to evaluate the effect of the addition of other excipients to impart an acid resistant nature on the diluent/drug blend. Results indicate that Carbopol 934P (1-5%) and acacia (10-25%) impart gel-forming and binding characteristics to the formulation of drug and diluent. In the presence of 0.1N HCl the Carbopol gels very slightly forming a thin protective barrier over the exterior of the dosage form without compromising the matrix structure formed by the calcium diluent. The presence of this barrier at the dosage form/dissolution medium interface allows for release of drug deposited on the immediate exterior of the dosage form while limiting dissolution of the poorly soluble calcium diluent. Acacia is a natural gum which possesses viscosity increasing characteristics and is a commonly used binder in the formulation of solid dosage forms. When wetted the binding characteristics of acacia are increased which enhances the cohesion of the formulation excipients. Its effect on the gelling capabilities of Carbopol 934P is beyond the scope of this presentation. It was previously claimed that an admixture of at least 5% cross-linked acrylic acid polymer with calcium hydroxide, magnesium oxide, or magnesium hydroxide can obtain the same degree of sustained release as that obtained with a greater amount of polymer and none of the basic compound [8]. However, addition of acacia allows for the use of as little as 1% Carbopol 934P. This small amount of gelling agent is only needed as a protective mechanism in the presence of acidic media. These vehicles employ calcium diluents of which direct compression grades are commercially available [9,10].

Calcium sulfate dihydrate was chosen as diluent in the initial release studies due to its insolubility at pH 1.1 relative to the other diluents. It was found that a formulation containing calcium sulfate dihydrate, Carbopol 934P (1-5%), acacia (10-25%), and magnesium stearate (0.5%) resulted in a vehicle capable of sustaining drug release for ten to twelve hours (Figure 6). Release occurred via a matrix diffusional delivery system with a solid mass remaining after testing.

Dibasic calcium phosphate dihydrate possesses solubility and sustained release characteristics similar to calcium sulfate dihydrate in media of pH 4.0 to 7.5. Six 400 mg

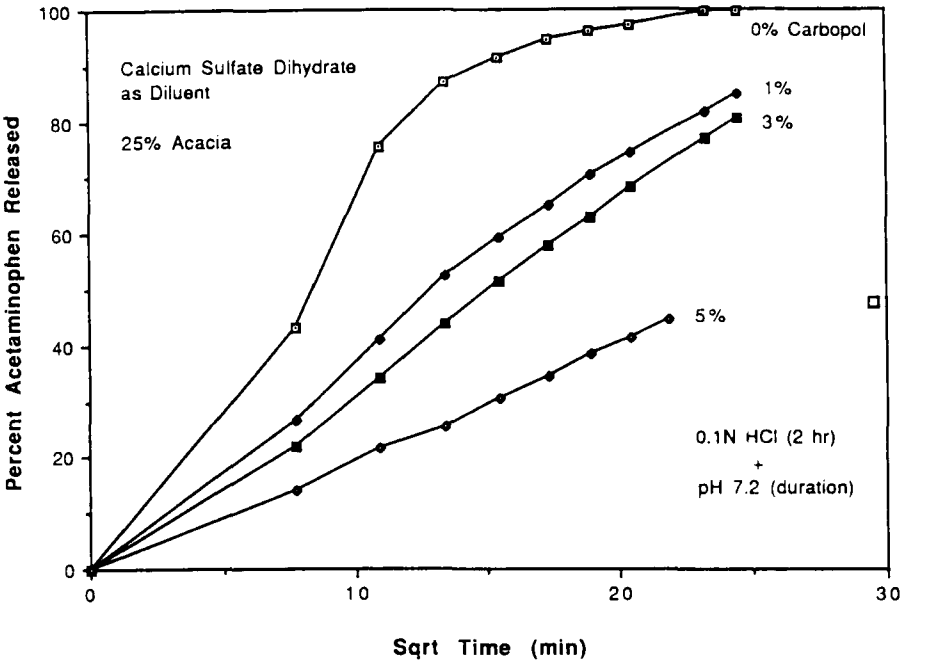

FIGURE 6

Percent acetaminophen released versus square root of time from whole tablets containing drug (20%), Carbopol 934P (0-5%), acacia (25%), magnesium stearate (0.5%), and calcium sulfate dihydrate.

whole tablets were tested with each containing acetaminophen (20%), Carbopol 934P (5%), acacia (25%), and magnesium stearate (0.5%) with dibasic calcium phosphate dihydrate as diluent. The tablets were placed in a basket apparatus and subjected to 0.1N HCl for two hours and phosphate buffer (pH 7.2) for eight hours while rotating at 50 RPM at 37°C. The data indicate an average of 36% drug released in the first two hours with near 100% release in ten hours. It is important to note the data distribution at each sampling interval as reflected by the standard deviation and percent relative standard deviation values (Table 6). These statistics substantiate the existence of a highly consistent release profile from the six dosage forms tested.

An additional study was conducted to evaluate the effect of the level of Carbopol 934P on release. Levels of 0, 1, 3, and 5% were tested and it was evident that drug release increased significantly with decreasing Carbopol levels (Table 7). The 1% vehicle released its entire drug content in the first two hours while the 3% vehicle sustained drug release for eight hours as compared to ten hour release for the 5% vehicle. Observations of the dosage forms during

TABLE 6

Acetaminophen Release from Vehicle with Dibasic Calcium Phosphate Dihydrate as Matrix Forming Agent.

Time (min)	% Acetaminophen Released							
	Tablet No.							
	1	2	3	4	5	6	SD	%RSD
60	22	23	24	23	23	27	1.6	6.9
120	35	37	37	36	37	39	1.4	3.9
180	49	54	53	51	53	55	1.9	3.6
240	57	63	61	59	62	62	2.1	3.5
300	64	69	68	65	69	70	2.3	3.4
360	71	75	74	70	76	76	2.6	3.6
420	76	80	80	75	82	83	3.2	4.0
480	83	87	86	82	88	90	2.9	3.3
540	90	95	92	90	94	96	2.5	2.7
600	94	100	98	96	98	99	2.0	2.1

FORMULATION:

EXCIPIENT	LEVEL (%)
Acetaminophen	20
Carbopol 934P	5
Acacia	25
Magnesium Stearate	0.5
CaHPO4 2H20	qs to 100 gm

testing revealed the existence of a loosely defined pasty matrix which slowly eroded throughout the release period. In comparison, the vehicle employing calcium sulfate dihydrate maintained a solid matrix. The difference in the release rates exhibited by these two vehicles may be related to the solubility characteristics of the individual calcium diluents.

A least squares linear regression analysis of percent drug released versus the square root of time was performed on the dibasic calcium phosphate dihydrate vehicle to evaluate matrix release characteristics. The analysis indicates a linear relationship which is strongest with the 5% Carbopol level and weakest with 1% Carbopol (Figure 7).

Acetaminophen has been employed as the model drug to this point due to its relatively pH independent solubility profile. Additional studies were conducted to evaluate release of the more

TABLE 7

Acetaminophen Release from Vehicle with Dibasic Calcium Phosphate Dihydrate as Diluent with Three Levels of Carbopol 934P.

Time (min)	% Acetaminophen Released					
	Level of Carbopol 934P					
	1%		3%		5%	
60	62.8	68.7	38.2	35.2	22.4	25.5
120	94.8	100.2	63.3	61.2	34.4	37.7
180	98.0	101.4	75.6	74.1	49.4	52.4
240	99.0	101.4	81.3	79.6	57.5	61.2
300	99.4	101.5	85.7	84.6	65.6	68.3
360	99.4	101.5	90.6	90.4	73.5	74.1
420	99.4	101.5	98.0	95.3	79.2	79.7
480	99.4	101.5	100.1	95.9	85.8	85.5
540	99.4	101.5	100.2	95.9	95.2	91.2
600	99.4	101.5	100.2	96.0	100.8	97.2

FORMULATION:

EXCIPIENT	LEVEL (%)
Acetaminophen	20
Carbopol 934P	as specified
Acacia	25
Magnesium Stearate	0.5
$CaHPO_4 \cdot 2H_2O$	qs to 100 gm

practical sustained release candidates theophylline and chlorpheniramine maleate. Results indicate a 63% release of theophylline from a vehicle of Carbopol 934P (5%), acacia (25%), magnesium stearate (0.5%), and calcium sulfate dihydrate. A 93% drug release occurred from the same formulation with dibasic calcium phosphate dihydrate as diluent (Table 8, Figure 8). Percent relative standard deviations calculated for each sampling interval reveal consistent release profiles from triplicate runs of each formulation. To demonstrate the mechanisms by which release occurs the solids masses which remained after testing of the calcium sulfate dihydrate dosage forms were dried overnight and weighed. These three dosage forms possessed final weights of 212, 229, and 216 mg from an initial weight of 400 mg which suggests the existence of a nondisintegrating matrix delivery system. In comparison, the three vehicles

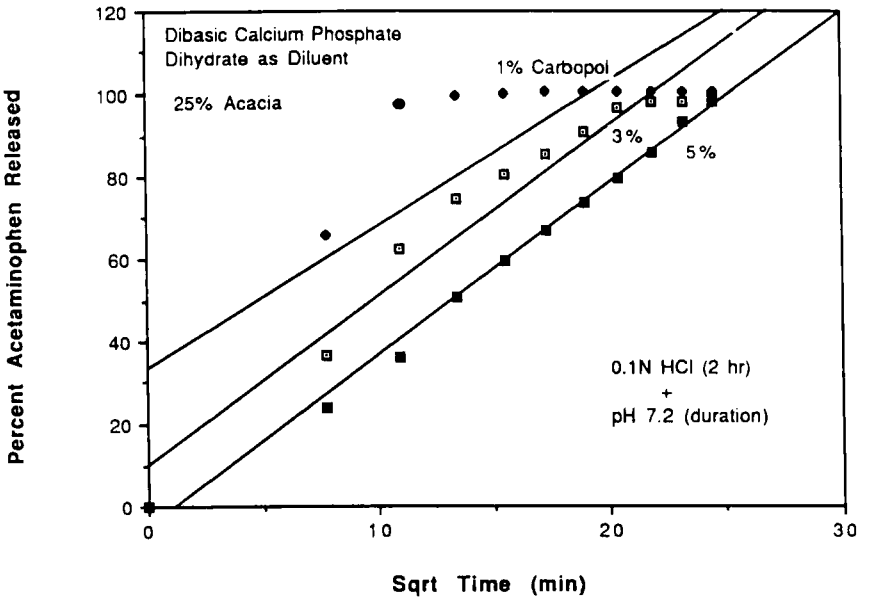

FIGURE 7

Regression of percent acetaminophen released on square root of time from whole tablets containing drug (20%), Carbopol 934P (1-5%), acacia (25%), magnesium stearate (0.5%), and dibasic calcium phosphate dihydrate.

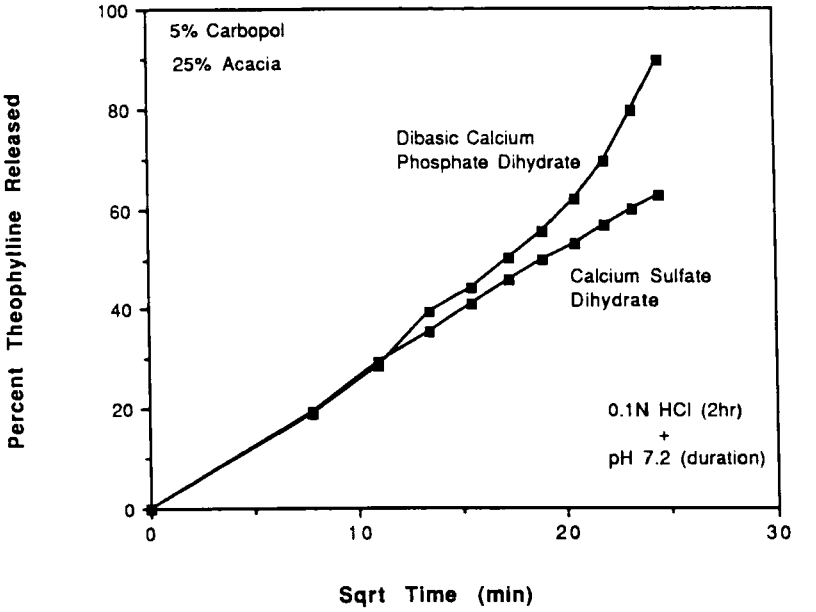

FIGURE 8

Percent theophylline released versus square root of time from whole tablets containing drug (25%), Carbopol 934P (5%), acacia (25%), magnesium stearate (0.5%), and either dibasic calcium phosphate dihydrate or calcium sulfate dihydrate.

TABLE 8

Theophylline Release from Vehicle Containing Either Calcium Sulfate Dihydrate or Dibasic Calcium Phosphate Dihydrate as Diluent.

Time (min)	% Theophylline Released							
	Calcium Diluent In Formulation							
	Calcium Sulfate Dihydrate			%RSD	Dibasic Calcium Phosphate			%RSD
60	19	20	19	1.6	19	NA	19	.37
120	29	30	29	1.5	29	27	29	4.9
180	35	36	35	.58	39	40	39	1.4
240	41	41	41	.37	46	42	45	4.5
300	46	46	45	.25	53	47	51	6.0
360	50	50	49	.42	58	51	57	7.0
420	53	53	53	.43	64	57	64	5.1
480	57	57	56	.41	73	63	73	8.5
540	60	60	59	.29	82	71	85	9.7
600	63	63	62	.18	94	82	93	7.4

FORMULATION:

EXCIPIENT	LEVEL (%)
Theophylline	25
Carbopol 934P	5
Acacia	25
Magnesium Stearate	0.5
$CaHPO_4 \cdot 2H_2O$ or $CaSO_4$	qs to 100 gm

containing dibasic calcium phosphate dihydrate as diluent almost totally eroded yielding three insignificantly small masses. These results illustrate how the calcium sulfate dihydrate vehicle functions to sustain release via a nondisintegrating matrix compared to an erodible matrix when dibasic calcium phosphate dihydrate is used.

Acetaminophen and theophylline have solubilities of ≈ 22 mg/ml and 10 mg/ml in 0.1N HCl and therefore provide an indication of the release characteristics of poorly and moderately soluble drug candidates from these sustained release vehicles [11,12]. Release of the more highly soluble chlorpheniramine maleate (50 mg/ml) is an additional test of the sustained release capabilities of this vehicle [13]. A study of the release of chlorpheniramine maleate (10 mg)

TABLE 9

Chlorpheniramine Maleate Release from Vehicles Containing Calcium Sulfate Dihydrate as Diluent with Three Levels of Carbopol 934P.

Time (min)	% CHLORPHENIRAMINE MALEATE RELEASED					
	LEVEL OF CARBOPOL 934P					
	1%		3%		5%	
60	53	59	43	48	42	41
120	78	87	57	68	55	56
180	89	94	63	77	62	60
240	95	97	67	81	64	64
300	98	98	69	83	67	66
360	100	99	71	86	69	68
420	102	99	73	88	70	70
480	102	100	75	90	72	71
F.W.	151	150	243	210	244	238

F.W. = Final weight of tablet after testing and drying.

FORMULATION:

EXCIPIENT	LEVEL (%)
Chlorpheniramine Mal.	2.5
Carbopol 934P	as specified
Acacia	25
Magnesium Stearate	0.5
Calcium Sulfate	qs to 100 gm

from a 400 mg tablet containing Carbopol 934P (1-5%), acacia (25%), magnesium stearate (0.5%), and calcium sulfate dihydrate was conducted. Results (Table 9, Figure 9) indicate 82.5, 62.5, and 55.5% drug release from vehicles containing 1, 3, and 5% Carbopol 934P in the first two hours. These same vehicles released 101.5, 82.5, and 71.5% drug in eight hours. It is apparent that release of the more highly soluble chlorpheniramine maleate can be sustained for eight hours from the vehicle under investigation.

Initial drug release occurs from a nondisintegrating matrix due to direct contact of the dissolution medium (0.1N HCl) with drug deposited on the immediate exterior of the dosage form. It is therefore reasonable to believe that the initial rate of drug release is governed by the solubility of the drug candidate in 0.1N HCl. To illustrate this effect a comparison of initial

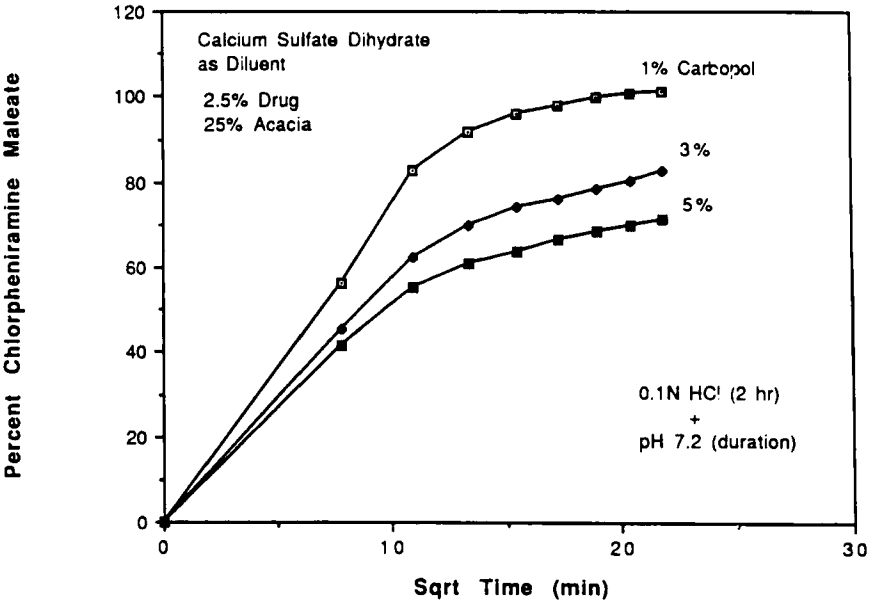

FIGURE 9

Percent chlorpheniramine maleate released versus square root of time from whole tablets containing drug (2.5%), Carbopol 934P (1-5%), acacia (25%), magnesium stearate (0.5%), and calcium sulfate dihydrate.

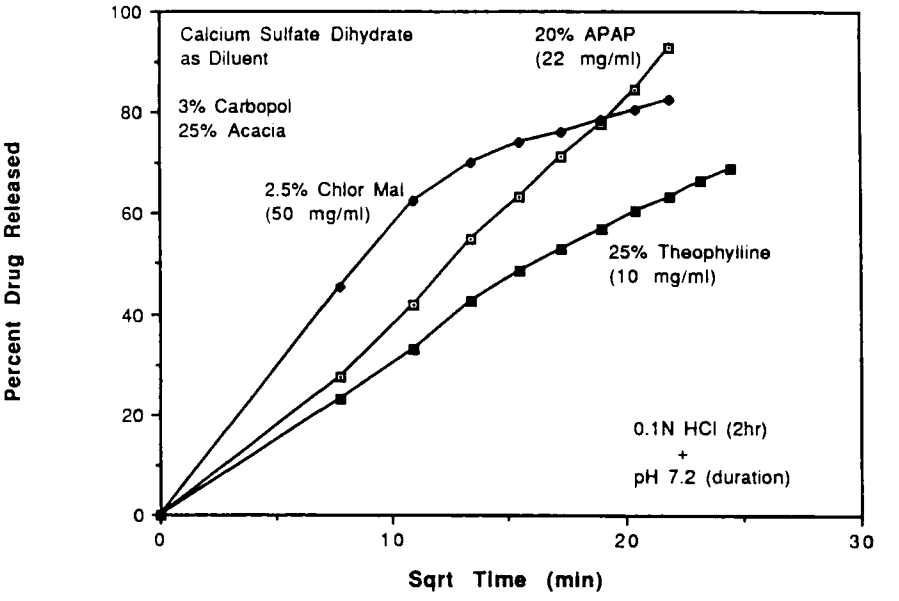

FIGURE 10

Percent drug released versus square root of time from whole tablets containing Carbopol 934P (3%), acacia (25%), magnesium stearate (0.5%), and calcium sulfate dihydrate, and either chlorpheniramine maleate (2.5%), acetaminophen (20%), or theophylline (25%).

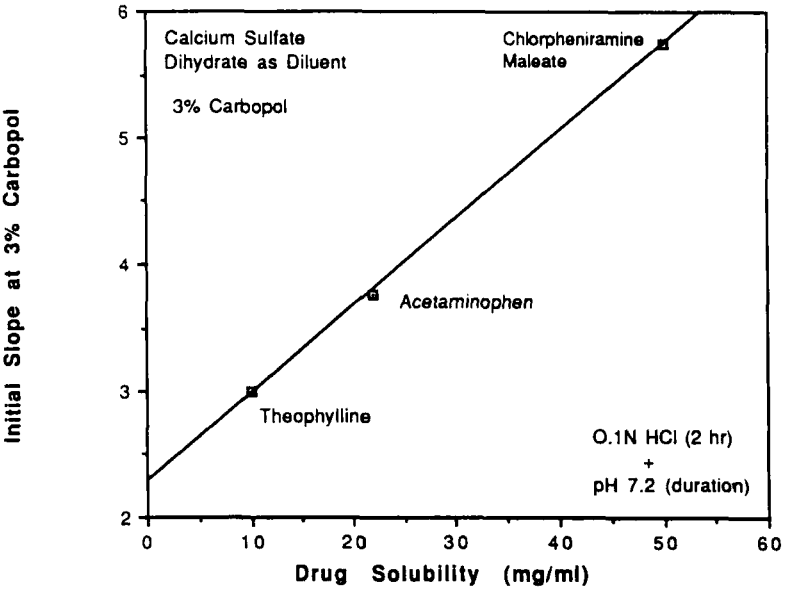

FIGURE 11

Initial slope of drug release profile versus drug solubility in 0.1N HCl from whole tablets containing Carbopol 934P (3%), acacia (25%), magnesium stearate (0.5%), calcium sulfate dihydrate, and either chlorpheniramine maleate (2.5%), acetaminophen (20%), or theophylline (25%).

drug release from vehicles containing Carbopol 934P (1 and 3%), acacia (25%), magnesium stearate (0.5%), and calcium sulfate dihydrate was performed. Figure 10 shows chlorpheniramine maleate (50 mg/ml) demonstrates the fastest release with acetaminophen (22 mg/ml) and theophylline (10 mg/ml) exhibiting slower release initially. The slope of the percent drug released versus the square root of time for the first two hours was calculated and plotted versus drug solubility. A direct relationship does exist with the more highly soluble chlorpheniramine maleate showing the fastest initial release followed by acetaminophen and theophylline, respectively. (Figure 11).

These results suggest that the application of calcium sulfate dihydrate and dibasic calcium phosphate dihydrate as matrix forming agents is feasible. Release profiles differ based on drug characteristics yet the rate of release can be predictably controlled by adjustment of the formulation variables. The simplicity of the formulation and manufacture of these dosage forms provide an alternative approach to their application in the formulation of sustained release solid dosage forms.

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