DRUG DEVELOPMENT AND INDUSTRIAL PHARMACY, 14(7), 875-894 (1988)

USE OF BUFFERS IN MATRIX CAPSULE FORMULATIONS

S. N. Pagay, Ph.D.

Department of Pharmaceutical Sciences

Sterling-Winthrop Research Institute

Rensselaer, NY 12144

ABSTRACT

Relatively few reports have appeared in the literature on the formulation of the hydrophilic matrix capsule as compared to the matrix tablet. This study was concerned with the development of a matrix capsule formulation to control the release rate of the drug specifically through the incorporation of buffers. One of the characteristics of hydrophylic matrix drug delivery systems is that the initial rate of release is high. The release rate is gradually brought under control as the diffusional barrier of hydrating polymers is established. Many weak bases are more soluble at a gastric pH than at neutrality. Such drugs are generally unsuitable for matrix systems since constant rates of drug release under the dynamic conditions of increasing pH make release rate control difficult. However, by using an appropriate buffer system it was possible to suppress the initial release in acid by decreasing the solubility of the drug within the environment of the capsule matrix thereby controlling the rate of drug

release. A buffered matrix capsule of an investigational drug was administered to normal healthy subjects in order to examine if a sustained plasma profile could be achieved. The absorption rate of the drug was calculated according to the Wagner-Nelson method. A dissolution test method was developed which correlated well with the in vivo data by selecting appropriate buffers and agitation rates. Capsule formulations exhibiting several different release rates between 6 and 24 hours were then prepared. The dissolution test conditions used for the drug release study were based upon the in vivo - in vitro correlation.

INTRODUCTION

An investigational drug (Compound I) has a short biological half life and targeted for a long term treatment. To reduce the dosing frequency of the drug, it was necessary to develop a prolonged release oral solid dosage formulation (e.g. matrix capsule) which could be processed on conventional manufacturing equipment.

Hydroxypropyl methyl cellulose (HPMC) polymers of different viscosities and chemistries are commonly used as matrices and were, therefore, considered as possible candidates for this formulation. The sustained release mechanism of matrix systems is dependent upon many variables, for instance, rate and extent of moisture permeation into the matrix, rate of gelation of the polymer and the dissolution and diffusion rate of the drug. In addition, the drug may be released after matrix erosion.[1]

When a matrix-filled capsule is exposed to moisture, the hard gelatin shell is dissolved and the moisture is allowed to penetrate the formulation. When this happens, the HPMC present in the formulation forms a gel layer matrix. As the moisture continues to intrude the capsule, the dry powder

formulation within the gel layer is hydrated, forming additional gel layers. Simultaneous erosion of the outer gel layer may also occur. The drug is then released over several hours by either diffusing through the gel or by eroding with the gel layers, or both, resulting in prolonged action of the drug.[2]

Release rate mechanisms have been proposed for the different matrix drug delivery systems.[1,3,4] These systems generally display a rapid initial release rate. For example, the prototype formulation of Compound I matrix capsule (Formula 1) released nearly 40% of the drug within the first hour while the remaining 60% is released gradually over the next several hours in 0.1N hydrochloric acid.

One of the reasons for this initial burst of release is that the drug from the capsule surface is dissolved before polymer gelling takes place. To minimize this escape of the drug from the capsule surface into solution, the rate of polymer hydration must be very fast. Another reason is the solubility of the drug in the test medium. For example, the solubility and the release rate of a weakly acidic or basic drug is influenced by the pH of the dissolution medium (i.e. in vitro test medium or gastrointestinal fluids).

Compound I is a weakly basic drug and both the solubility and the release rate are greater in an acid medium (e.g. gastric fluid) than in a neutral one (e.g. intestinal fluid), resulting in an increased release rate initially. Since the release rate is influenced partly by the environmental pH as well as by the formulation, it is difficult to achieve a near constant release rate throughout the GI tract for a controlled release product. However, by adding an appropriate buffer to the formulation, it should be possible to control the release rate from a matrix.

OBJECTIVES

The specific objectives of this study were as follows:

1. Use antacids and buffers to control the release rate by altering the drug's solubility within the matrix.
2. Generate a plasma level profile by testing a representative matrix capsule formulation in normal subjects. (For comparison, an aqueous solution and a conventional capsule were used as standard preparations.)
3. Develop an in vitro dissolution test to correlate percent drug released with the in vivo data (percent drug absorbed).
4. Use this dissolution test method to evaluate matrix formulations with different release rates.

EXPERIMENTAL

A. Matrix Formulation

The formulations were developed using USP/NF excipients. HPMC (Methocel®) less than 80 mesh was the major component of each of the formulae. Magnesium hydroxide and citrate buffer were selected in an attempt to control the pH of the cellulosic gel matrix. Lactose was used as a soluble filler while talc and magnesium stearate were employed as the flow and lubricating agents, respectively.

B. Capsule Preparation

1. The Wet Granulation Method

The formulations containing magnesium hydroxide were prepared according to the wet granulation method. First the drug was mixed with magnesium hydroxide and a small portion (2 mg/capsule) of Methocel K4M.[2] The mixture was passed through an 80 mesh hand screen and

blended in a twin-shell blender,[5] and was then transferred into a Hobart mixer.[6] A sufficient amount of water was added to the system to form a damp, powder-free granulation. The granulation was next dried in a drying oven[7] at 50°C until the moisture level was less than 2% and was then passed through a Homoloid mill[8] using a size 0 screen and knives impact forward. The remaining Methocel was passed through an 80 mesh screen and combined with the granulation. Finally the mixture of talc, and magnesium stearate was passed through an 80 mesh hand screen and added to the system to form a homogeneous blend.

2. Dry Powder Blend Method

The reference matrix capsule (Formula 1) and the formulations containing citrate buffer were prepared as dry powder blends. The drug was mixed with Methocel K4M[2] (Formula 1) and with Methocel K4M, sodium citrate and citric acid (Formula 5 and 6).

The mixture was then passed through an 80 mesh hand screen and blended in a twin shell blender. The talc and magnesium stearate were combined, passed through an 80 mesh hand screen and added to the system to form a homogeneous blend.

3. Capsule Filling

The powder blends and granulation prepared for the different formulations were filled in hard gelatin capsules using a high speed capsule filling machine.[9] Capsule size 1 was used for Formulae 2, 5 and 6. The remaining formulations were filled in size 2 capsule.

C. Release Rate Measurement

The USP Paddle Dissolution Test Method[10] was used throughout the in vitro release rate measurement studies. Two sets of dissolution test conditions were followed:

Method I: USP Paddle rotated at 90 RPM. The dissolution test medium was 500 mL 0.1 N hydrochloric acid.

During the initial development work, Method I was used to obtain the release rate profiles of matrix capsule formulations.

Method II: USP Paddle rotated at 50 RPM. The dissolution test medium was 500 mL 0.1 N hydrochloric acid. After one hour the pH of the test medium was changed to 7.5 using THAM[11] buffer.

Method II was used to obtain the in vivo - in vitro correlation and to determine the relative rates of different buffered matrix capsule formulations.

D. Evaluation of Sustained Release Profile of the Buffered Matrix Capsule in Humans

In vivo data (percent absorbed-time) was obtained by administering a Compound I matrix capsule formulation containing magnesium hydroxide (Formula 2) to 10 normal healthy subjects in a randomized, open label three-way crossover study. The drug was given after overnight fasting. Plasma samples were taken every 15 minutes for 1.5 hours and then at 2, 3, 4, 5, 6, 8, 10, 12 and 16 hour intervals. For the sake of comparison, a conventional (immediate release) capsule and a solution were tested in a similar fashion. Each subject was administered all three formulations.

RESULTS AND DISCUSSION

The major problem encountered during the development of a matrix drug delivery system stems from the initial high release rate of the drug. The initial release rate is dependent upon the rate of polymer hydration needed to form the gel and the solubility of the drug. With this in mind,

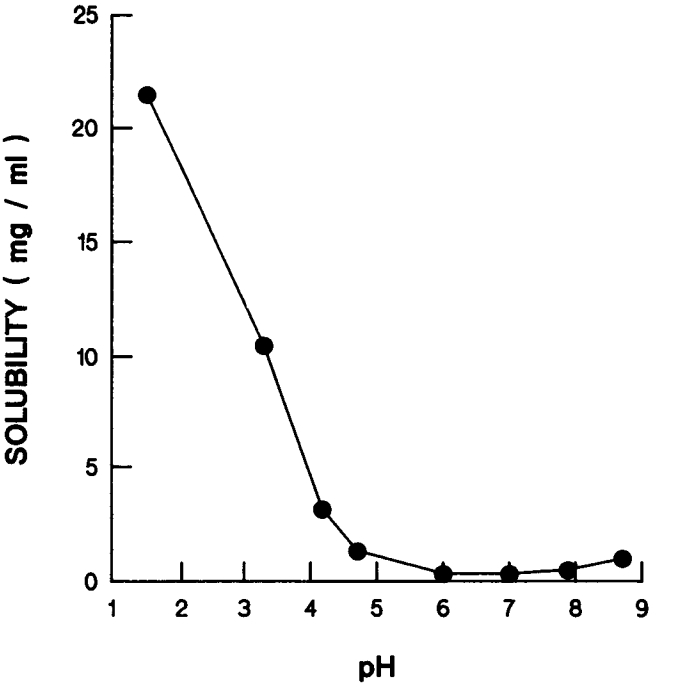

FIGURE 1

pH - solubility profile of the drug.

Methocel K was selected for this study, because it has the fastest hydration rate of all the Methocel chemistries (A, E or F)[2]. The release rate can be modified to some extent by altering the concentration, viscosity or chemistry of HPMC within the formulation. However, the hydration rate is not the only factor controlling the release rate profile when influenced by the pH changes, e.g. changes in the gastrointestinal fluid.

The pH solubility profile of a drug is a factor that can dramatically influence its release rate through the matrix system. For example, Compound I has a pKa at 4.1 and 8.3, and its solubility is 40 times greater at pH 1.5 than it is at pH 7, as shown in Figure 1. This increased solubility

TABLE 1

Release Rate Modification of the Buffered Matrix Capsule (Formula 2) by Altering the Level of the Buffering Component and by Using the Different Viscosity Grades of Hydroxypropyl Methyl Cellulose (Methocel®)

Component	Formula 1 mg/capsule	Formula 2 mg/capsule	Formula 3 mg/capsule	Formula 4 mg/capsule	Formula 5 mg/capsule	Formula 6 mg/capsule
Compound I	15.0	15.0	15.0	15.0	15.0	15.0
Lactose USP	76.0	—	53.0	—	—	—
Methocel K 4000 CPS USP	154.0	160.0	60.0	130.0	145.0	145.0
Methocel K 100 CPS USP	—	—	30.0	—	—	—
Magnesium Hydroxide USP	—	90.0	60.0	67.5	—	—
Citric Acid USP	—	—	—	—	26.0	95.0
Sodium Citrate USP	—	—	—	—	116.0	35.0
Talc USP	30.0	30.0	23.0	28.0	30.0	30.0
Magnesium Stearate NF	5.0	5.0	4.0	4.5	5.0	5.0
TOTAL WEIGHT	280.0	300.0	245.0	245.0	337.0	325.0

NOTE: Formula 1 is a reference matrix capsule.

Formulae 2 to 6 are buffered matrix capsules with different release rates.

TABLE 2

Effect of Methocel Concentration (in Formula 1) on the Release Rate of the Drug

mg/cap	Methocel[a] % (w)	% Released In One Hour	Hours to Release 100%
110	39	49 (0.1)	6
140	50	45 (1.4)	7
154	55	38 (1.6)	7
168	60	38 (0.5)	7

[a] The concentrations (mg/capsule) of the remaining components were the same as in Formula 1, except for lactose. The amount of lactose was adjusted so that the total weight was 280 mg/capsule.

NOTE: 1. Dissolution test method I was used.

2. All values are mean ± S. D.

3. Number of samples = 6

also favors a rapid initial release rate in the acidic pH of the gastric environment.

This study shows how the release rate can be controlled by the addition of an appropriate buffer into matrix formulation.

Reference Matrix Capsule

Before incorporating the buffer into the system, a reference matrix capsule (Formula 1) was prepared. Table 1 describes this formulation. To develop this formulation with the slowest release rate, the effects of Methocel concentration, viscosity and particle size were evaluated.

Table 2 shows how different concentrations of Methocel (39%, 50%, 55% and 60%) influence the release rate of the drug. To keep the formula

TABLE 3

Effect of Methocel Viscosity (in Formula 1) on the Release Rate of the Drug

Methocel Viscosity (CPS)	% Released In One Hour	Hours to Release 100%
850[a]	44 (1.3)	5
4,000	38 (1.6)	7
15,000	37 (1.6)	7
100,000	35 (1.8)	8

[a]Blend of 50% each of HPMC 4000 and 100 cps viscosity grades.

NOTE: 1. Dissolution test method I was used.

2. All values are mean ± S.D.

3. Number of samples = 6.

weight the same, lactose was used. The release rate decreases as the concentration of Methocel is increased, leveling off at a Methocel concentration of 55 to 60%. Consequently, Formula 1 was developed at a 55% Methocel concentration.

Table 3 shows the effect of different viscosity grades of Methocel (55% concentration), on the release rates. Only minor differences in the release rates existed between Methocel 4000, 15,000 and 100,000 cps viscosities. The release rate was slightly faster, however, when Methocel 850 cps was used. Methocel 4000 cps was, therefore, incorporated into Formula 1.

TABLE 4

Effect of Methocel Particle Size (in Formula 1) on the Release Rate of the Drug

Methocel Particle Size (micron)	% Released In One Hour	Hours to Release 100%
> 177[a]	85 (5.1)	4
< 177	38 (1.6)	7

[a]Equivalent of U.S. standard 80 mesh.

NOTE: 1. Dissolution test method I was used.

2. All values mean ± S. D.

3. Number of samples = 6.

The effect of the particle size of Methocel on the release rate was also studied. Release rate of < 80 mesh Methocel particle size was compared to a similar formulation containing > 80 mesh Methocel. The results (both formulations contain 55% Methocel, Table 4) showed that when the particle size was not controlled (> 80 mesh Methocel), the gel became too porous, allowing the drug to escape freely. In this case, the matrix capsule behaved like a conventional capsule.

In sum, Formula 1 containing 55% Methocel K, with a 4000 cps viscosity and < 80 mesh particle size resulted in a matrix capsule with the slowest release rate.

Buffered Matrix Capsule

Formula 2, shown in Table 1, differed from Formula 1, by the addition of an antacid (90 mg of magnesium hydroxide per capsule). The magnesium hydroxide provided a means of controlling the pH of the matrix when it was exposed to an acidic pH environment. Formula 1 had no magnesium hydroxide and contained lactose as a filler.

Figure 2 compares the release rates of these two matrix capsules. The dissolution test was performed according to Method I. The buffered matrix capsule, Formula 2, released 19% (S.D. 0.6) drug in one hour compared to 38% (S.D. 1.6) for Formula 1 during the same time period. Therefore, by using an antacid, the initial release rate of the drug was decreased by 50%. Furthermore, Formula 2 released 100% drug in nine hours as compared to the reference matrix capsule, Formula 1, which released the same amount in seven hours.

In Vivo - In Vitro Correlation

The buffered matrix capsule formulation containing magnesium hydroxide, Formula 2, was tested in humans to determine if sustained plasma levels could be achieved and if a dissolution test method could be developed which would correlate with the absorption rate of the sustained release formulation.

Table 5 shows the Cmax and Tmax values for the buffered matrix capsule and for the standard preparations (conventional capsule and an aqueous solution). The release rate for the buffered matrix capsule, Formula 2, was sustained but very slow. Notice that the Cmax of the buffered capsule is only 18% that of the conventional capsule. This means that the initial drug release is well controlled. Otherwise, the Cmax would

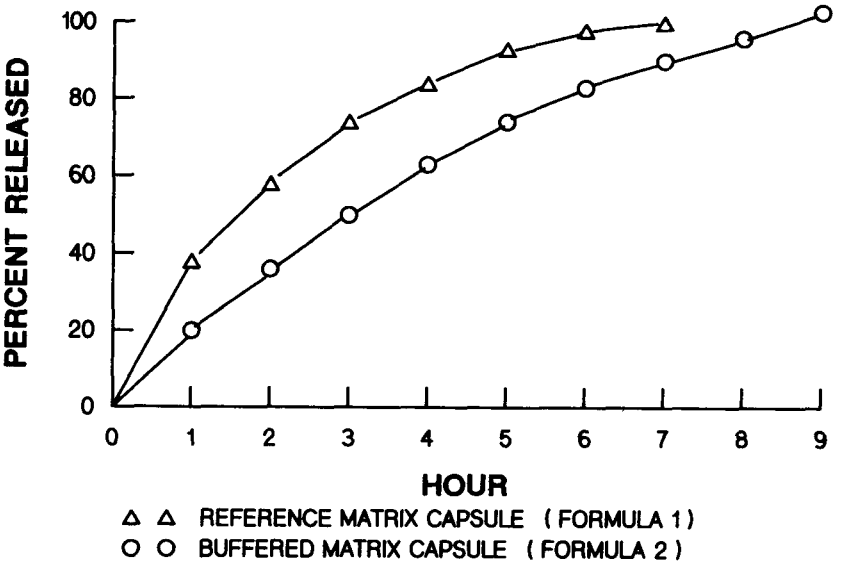

FIGURE 2

Comparison of release rates of the reference matrix capsule Formula 1 and a buffered matrix capsule Formula 2. Dissolution test method I was used.

TABLE 5

Comparison of C_{max} and T_{max} Values for the Buffered Matrix Capsule (Formula 2), Conventional Capsule and the Aqueous Solution Obtained From the Clinical Study

FORMULATION	C_{max} (Ng/mL)	T_{max} (Hour)
Buffered Matrix Capsule (Formula 2)*	90.7 ($\pm$ 61.2)	1.75 ($\pm$ 0.98)
Conventional Capsule*	512.0 ($\pm$ 98.0)	0.57 ($\pm$ 0.17)
Aqueous Solution**	256.0 ($\pm$ 78.5)	0.38 ($\pm$ 0.08)

*Administered at time 0
**The 50% dose was administered at time 0 and the remaining at 6 hour

NOTE: All values are mean $\pm$ S. D.
Number of subjects = 10

be higher. Formula 2 also has a more prolonged Tmax, about 3 fold greater than that for the conventional capsule.

The Wagner-Nelson Method[12] was used to determine the drug absorption rate profile of this formulation. Dissolution tests were performed at various agitation rates and test media pHs to determine which conditions gave the best correlation between the absorption rate and the in vitro release rate profile.

Figure 3 shows the in vivo - in vitro correlation between the percent drug absorbed versus percent drug released with a correlation coefficient of 0.99. The dissolution test conditions (Method II) included a change in pH after one hour from 1.5 to 7.5 and an agitation rate maintained at 50 RPM.

At the test conditions outlined above, the formulation containing magnesium hydroxide (Formula 2) released 100% of the drug in 24 hours. Using Method I, the same formulation released 100% of the drug in nine hours.

The presence of magnesium hydroxide in Formula 2 influenced mostly the initial release rate of the drug during the first hour (Formula (1) 38%, Formula (2) 19%). This can be shown by comparing the apparent release rates of Formulae 1 and 2 after the first hour. The apparent release rate in the acid medium (Method I) for both formulations was 10%/hour; and the release rate when determined at pH 7.5 (Method II) was 4.1%/hour for Formula 1 and 3.5%/hour for Formula 2.

The results of this part of the study show that Formula 2 containing magnesium hydroxide influenced the initial release rate both in dissolution testing and in a human bioavailability study. The results also indicate that the dissolution test method (Method II) correlated with the in vivo data.

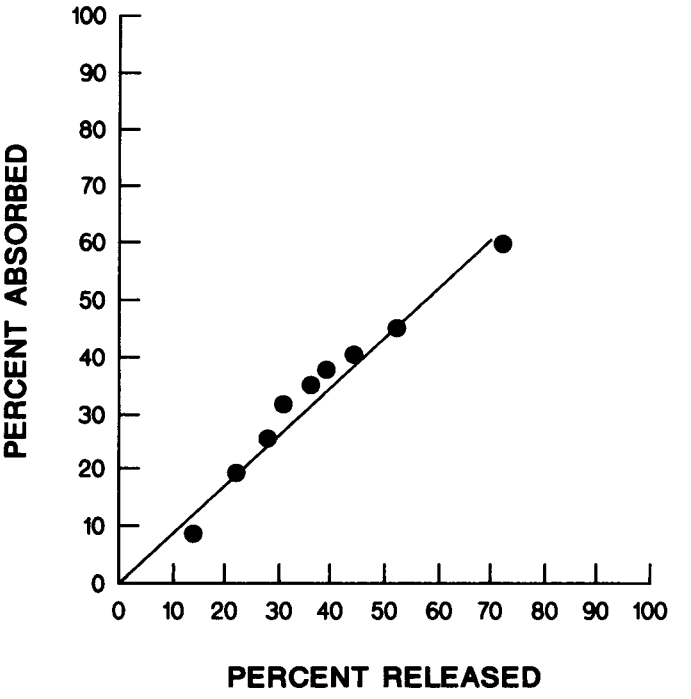

FIGURE 3

Correlation between percent drug absorbed and percent drug released (Dissolution Test Method II) for the buffered matrix capsule Formula 2.

This data supported the use of this method to evaluate new matrix formulations.

Release Rate Modification

According to the results of the in vivo - in vitro correlation, Formula 2 released 100% of the drug over 24 hours. To enhance the overall release rate, Formulae 3 and 4 were developed by decreasing the amount of magnesium hydroxide which is present in Formula 2. In addition, the porosity of the matrix was increased by decreasing the concentration and the viscosity of the polymer. Formulae 3 and 4 are shown in Table 1.

Upon exposure to an environment of pH 7.5, the magnesium hydroxide in Formulae 3 and 4, like Formula 2, is expected to have little control over the release rate since the drug is least soluble at that pH. When a buffer such as citrate is used, the release rate of the drug can be controlled both in an acidic and in a neutral pH environment. Use of a citrate buffer will control the solubility of the drug within the matrix between pH 1.5 - 7.5. Modifications of the pH caused by the gastrointestinal transit of the matrix capsule should not affect the release rate of the drug in this matrix, since the matrix pH can be controlled by the formulation itself and not by the pH of the gastrointestinal fluid. The buffer capacity of the matrix should, however, be greater than that of the gastrointestinal fluid.

Citric acid-sodium citrate is a useful buffering agent in a pH range of 3 to 6. Based upon the pH solubility profile of Compound I (shown in Figure 1), the solubility of the drug at pH 3 was found to be 10 mg/mL and at pH 5 was 1 mg/mL. Matrix capsule formulations were developed using citrate buffer to achieve a pH of 5 (Formula 5) and 3 (Formula 6) in solution. These formulations are also described in Table 1.

The release rate profile of Formulae 3, 4, 5 and 6 are displayed in Figure 4. For comparison, the release rates of the reference matrix capsule and the prototype buffered matrix capsule Formulae 1 and 2, respectively are also shown in this figure. All formulations were tested using the dissolution Method II which was shown to give the best in vivo - in vitro correlation. Table 6 summarizes the release rates of the different formulations (% released in one hour and hours to release 100% drug).

It can be seen here that Formula 3 released 35% (S.D. 2.6) of the drug in one hour and 100% in nine hours while Formula 4 released 24% (S.D. 1.7) in one hour and 100% in 16 hours.

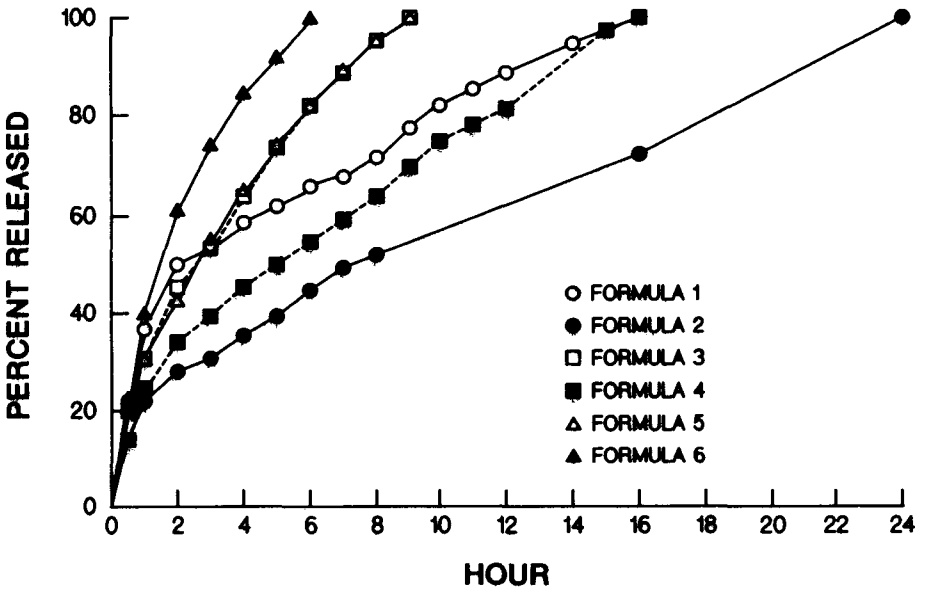

FIGURE 4

Comparison of release rates of prototype matrix capsules Formulae 1 to 6. Dissolution test method II was used.

Compared to Formula 2, the initial release rate of Formulae 3 and 4 was increased, but the overall release rate for 100% of the drug release was also enhanced. This will allow complete release of the drug during the g.i. transit.

The release rate data of the buffered capsule Formula 5 (pH 5.0) shows that 31% (S.D. 2.2) of the drug released in the first hour and the remaining 70% in the next eight hours.

The release rate of Formula 6 containing citrate pH3 buffer shows that 40% (S.D. 2.6) of the drug was released in one hour and 100% in six hours. This clearly demonstrates that the release rate is indeed controlled by the pH of the matrix rather than the pH of the dissolution test medium

TABLE 6

Summary of Release Rates of Prototype Matrix Capsules

Formula	Buffer/ Antacid	% Released (S.D.) In One Hour	Hours to Release 100%
1	None	38 (1.6)	16
2	Magnesium Hydroxide	19 (0.6)	24
3	Magnesium Hydroxide	35 (2.6)	9
4	Magnesium Hydroxide	24 (1.7)	16
5	Citrate pH 5	31 (2.2)	9
6	Citrate pH 3	40 (2.6)	6

Formula 1 - Reference matrix capsule

Formula 2 - 6 -Release rate modifications through the use of antacids and buffers

NOTE: 1. Dissolution test method II was used.

2. All values are mean ± S. D.

3. Number of samples = 6

(in this case pH 7.5). The reference matrix capsule (Formula 1) took 16 hours for 100% drug release as compared to Formula 6 which took only six hours. The initial release rates of both Formulae 1 and 6 are similar.

CONCLUSION

To control the release rate in a changing pH environment, the buffering agent should be effective within the microenvironment of the matrix and the matrix should be porous enough for fluid penetration and dissolution of the buffer. These conditions will allow the drug to diffuse out of the matrix at a rate depending solely upon the concentration gradient between the matrix and the dissolution media.

A matrix drug delivery system always produces an initially high release rate followed by a more gradual rate. For those compounds whose solubility is influenced by pH modification, an appropriate buffer system can be used to adjust the solubility within the matrix. This in turn will control the initial, as well as, the overall release rate of the drug.

SUMMARY

1) Using HPMC matrix with appropriate buffers and antacids, formulations with different release rates were developed.

2) The ^{C}max of the buffered matrix capsule was decreased by a factor of 5 from that of the conventional capsule; and the ^{T}max was prolonged by a factor of 3. This shows that drug release from the buffered matrix capsule can be controlled over a prolonged period of time.

3) An in vitro dissolution test was developed to correlate percent drug release with percent drug absorbed (determined by the Wagner-Nelson Method).

4) Using the in vitro dissolution test method, release rates were measured for the various buffered matrix formulations.

5) It was shown empirically that the release rates from HPMC matrix formulations were controlled by the presence of the buffering agent and not by the pH of the dissolution test medium.

REFERENCES AND NOTES

1) Bamba, M., Puisieux, F., Marty, J. P. and Cartensen, J. T., Int. J. Pharm., 2, 307 (1979).

2) Dow Chemical Company, Midland, MI.

3) Higuchi, T., J. Pharm. Sci., 52, 1145 (1963).

4) Desai, S. J., Simonelli, A. P. and Higuchi, W. I., J. Pharm. Sci., 54, 1459 (1964).

5) Patterson-Kelly Company, East Stroudsburg, PA.

6) Hobart Corporation, Guilderland, NY.

7) Despatch Industries, Inc., Mississauga, Ontario Canada.

8) The Fitzpatrick Company, Chicago, IL.

9) H&K Capsule Filling Machine Model 334, Bosch Packaging Corp., Piscatway, NJ.

10) Hanson Research Corp., Northridge, CA

11) T-395, Fisher Scientific, Fairlawn, NJ.

12) Wagner, J. G. and Nelson, E., J. Pharm. Sci., 52 610 (1963).