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A new type of a pH-independent controlled release tablet

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Summary

The release of weakly basic drug such as papaverine HCl from sustained-release formulations is dependent on the environmental pH in the gastrointestinal fluid. Precipitation of the poorly soluble free base occurs within the formulation in the intestinal fluid. Precipitated drug is no longer capable of release from the formulation. pH-independent release tablet was prepared by compressing the mixture of papaverine HCl, polyvinyl pyrrolidone (PVP) and citric acid followed by coating the lateral site of the tablet with ethylcellulose. The tablet was shaped into a cylindrical type. When the composition ratio of citric acid to drug was more than about 3.5, the tablet showed a pH-independent release. The percentage of drug release was not influenced by the drug content when the composition ratio of the matrix remained constant. Release rate was controlled by a surface area which could release the drug, and the amount of citric acid or PVP-K 30 incorporated into the matrix. Release rate can be altered freely while maintaining the pH-independent release characteristic by combining the different composition matrices. By simulating these results, drug released as a function of time has been calculated, giving results in good agreement with experiments.

Introduction

During the last decade, many controlled-release drug delivery systems for oral administration have been developed by using various techniques. There have been some reports that release profiles of drugs from these systems are independent of environmental pH values (Theeuwes, 1975; Bechgaard and Baggensen, 1980; Kohri et al., 1986, 1989). These formulations can be expected to provide a constant release of a drug during the transit through the gastrointestinal tract in spite of the variation in pH values. Moreover, there are well-known systems where drug release from the formulation can be changed by using enteric coating polymers when the formulation transfers from stomach to small intestine. However, no systems have been developed that permit drug release to be changed freely while maintaining pH-independent drug release. Such a system will reduce the variation of absorption which is ascribed to the fluctuation of gastric pH or gastric emptying time. This is also useful for increasing absorption of a drug which has low solubility at neutral pH values such as basic drugs. Furthermore, this system will be useful for increasing the bioavailability of drugs

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which encounter the first-pass effect, since it will be possible that the metabolic activity of the enzyme is saturated by considerable drug release during the initial stage and that this is followed by sustained release, or since it will also be possible that the sustained release rate can be increased with time.

In this study papaverine HCl, of which it has been reported that the bioavailability of a sustained-release formulation was much less than that of a conventional one (Arnold et al., 1977; Meyer et al., 1979), was used as a model drug. We tried to prepare a formulation which can change the release rate of the drug freely while maintaining pH-independent release. We also investigated the simulation of the release profile for this formulation.

Materials and Methods

Materials

Papaverine HCl (Sigma, St. Louis, MO), polyvinyl pyrrolidone K 90 (Kollidon 90, PVP-K 90, BASF), polyvinyl pyrrolidone (Kollidon 30, PVP-K 30, BASF), ethylcellulose (100 cp, Wako Pure Chemical Industry, Osaka), and citric acid (Wako Pure Chemical Industry, Osaka) were used. All other chemicals were reagent grade.

Preparation of the tablet

Papaverine HCl, PVP-K 90, PVP-K 30 and citric acid were dried under reduced pressure at ambient temperature for 2 days. The dried materials were passed through a 100-mesh sieve and were then mixed and compressed to a cylindrical tablet by a single-punch machine (Model KT-2, Okada Seiko Co.). A tablet with a diameter of 5 mm, length of 10 mm and weight of 240 mg was used for release studies except the explanation of the tablet size in this article. The tablet hardness was 20 ± 1.5 (mean $\pm$ S.D., $n = 20$) kg/cm^2 (Monsanto Hardness tester). The tablet was coated with 5% ethylcellulose in ethyl acetate on the lateral surface by using a paintbrush and dried under reduced pressure at ambient temperature for 1 day. The shape of the tablet is illustrated in Fig. 1. Compositions of the tablets prepared in this study are listed in Table 1. A layered tablet

TABLE 1

Composition ratio of components in the tablet and tablet properties

Tablet	Papaverine HCl	PVP-K 90	PVP-K 30	Citric acid	Weight (mg)	Diameter (mm)	k_1 [a] (mg h$^{-1/1.21}$)	Release characteristic
A	1	7.5	–	7.5	240	5	2.56	I [b]
B	1	10.5	–	5.0	240	5	2.10	I
C	1	12.5	–	2.5	240	5	1.79	D [c]
D	1	15.0	–	–	240	5	1.46	D
E	1	–	7.5	7.5	240	5	8.98	I
F	1	2.5	5.0	7.5	240	5	5.51	I
G	1	5.0	2.5	7.5	240	5	3.68	I
H	1	1.25	6.25	7.5	240	5	6.77	I
I	1	3.75	3.75	7.5	240	5	4.29	I
J	2	7.0	–	7.0	240	5	5.37	I
K	3	6.5	–	6.5	240	5	7.59	D
L	2	9.33	–	4.67	240	5	4.17	D
M	3	8.67	–	4.33	240	5	6.15	D
N	1	7.5	–	7.5	800	9	9.53	I
O	2	7.0	–	7.0	800	9	17.55	I
P	1	7.5	–	7.5	200	5	2.85	I

[a] The value of k_1 at pH 1.1 was calculated from Eqn 4.
[b] pH-independent release.
[c] pH-dependent release.

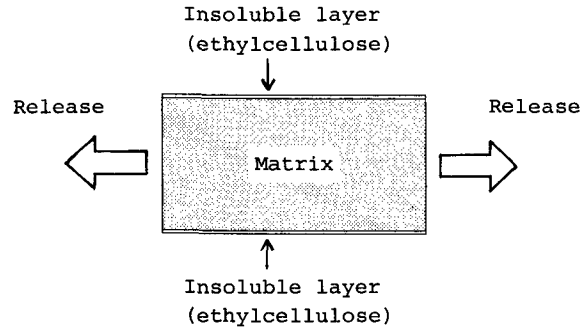

Fig. 1. Cross-section of the tablet employed.

which showed unique release characteristics was also prepared. Namely, the mixture which differed in composition of the central matrix was compressed on both sides of the central one. Several more kinds of mixture can be combined to this compressed part by compression and the lateral site of the tablet then coated by ethylcellulose.

Drug release study

The JP-XI rotating basket method was employed for in vitro release studies of papaverine HCl from tablets. The releasing vessel was kept at a constant temperature in a water bath of 37 ± 0.5 °C. McIlvaine buffer and 0.1 N HCl were used as dissolution media. The ionic strength of each medium was adjusted to 0.42 M by adding NaCl. The shaft of the basket was rotated at 150 rpm. 5 ml samples were removed at appropriate intervals and the same volume of fresh medium was immediately added to the dissolution vessel to maintain the original volume. The sample solutions were analyzed spectrophotometrically at 252 nm. It was ascertained that the drug was released from the tablet completely.

Solubility

The solubility of papaverine HCl in 0.1 N HCl and McIlvaine buffer was determined by adding excess papaverine HCl to the media at 37 °C. After equilibration the aliquot was filtered immediately using a membrane filter with pore size of 0.45 μm (Toyo Roshi Co.) and diluted appropriately with the same medium. The samples were analyzed by spectrophotometry at 252 nm.

Results

Solubility of papaverine HCl

The solubility of papaverine HCl at 37 °C as a function of pH in a saturated buffer solution is shown in Table 2. Maximum solubility was observed at a pH value of about 4. It was also observed that solubility at pH 4.0 was about 500-fold larger than that at pH 7.0.

Effect of citric acid in the matrix on drug release

We studied the effect of citric acid on decreasing the surface pH of the tablet. As shown in Fig. 2, the variation in release rates decreased with increasing extent of incorporation of citric acid into the tablet, since the surface pH of the tablet decreased to about 1.5 even though the pH value of the bulk was 7.0. The surface pH was measured using a pH test paper in contact with a tablet. These low pH values were almost the same as that of the saturated solution of citric acid in pH 7.0 buffer solution. It was also found that the release rate of the drug from the tablet increased with increasing amount of citric acid. Furthermore, it is probable that the drug was not released from the coating site of the tablet, since no drug was released from the tablet of which all sites were coated by ethylcellulose.

Effect of drug content in the tablet on drug release

The effect of drug content in the tablet on drug release was examined by using the matrices which showed pH-independent drug release in Fig. 2. In

TABLE 2

Solubility of papaverine HCl in the final pH of the medium at 37 °C

pH	Solubility (μg/ml)
1.16	3991
2.79	5396
4.11	8585
5.00	4100
5.08	3383
5.40	1565
6.00	47
6.67	22
7.00	16

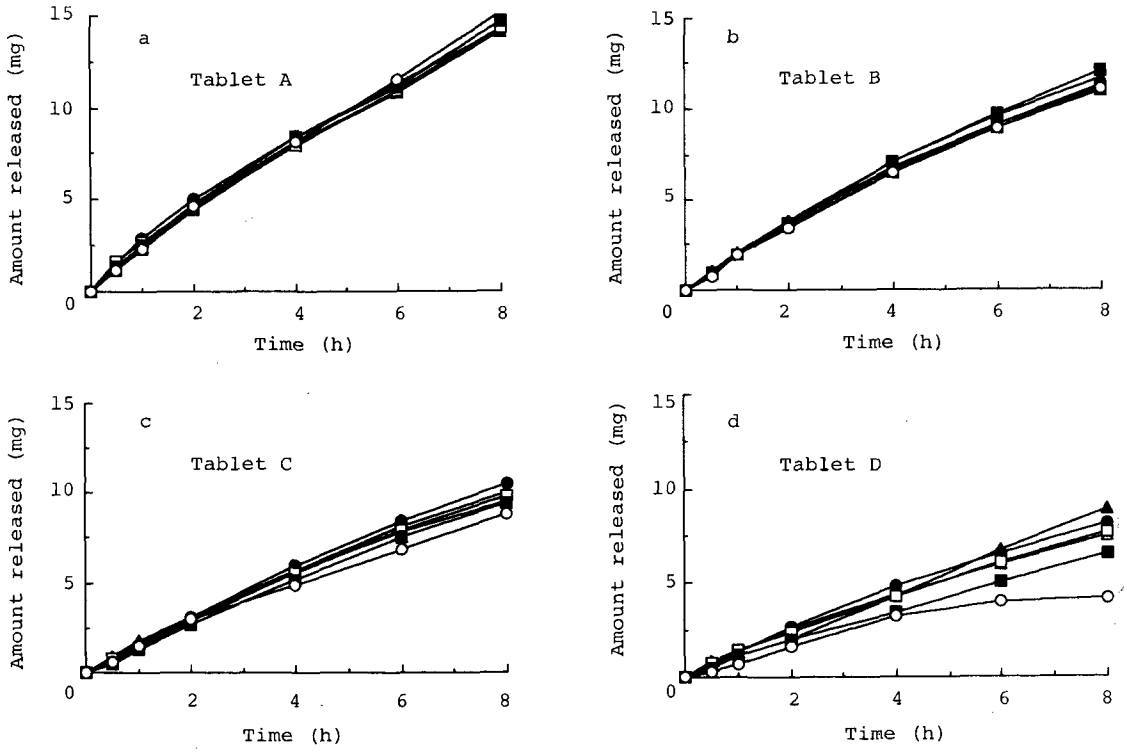

Fig. 2. Effect of citric acid on the release of papaverine HCl from tablets in various pH media. (●) pH 1.1; (△) pH 2.8; (▲) pH 3.8; (□) pH 4.8; (■) pH 5.9; (○) pH 7.0.

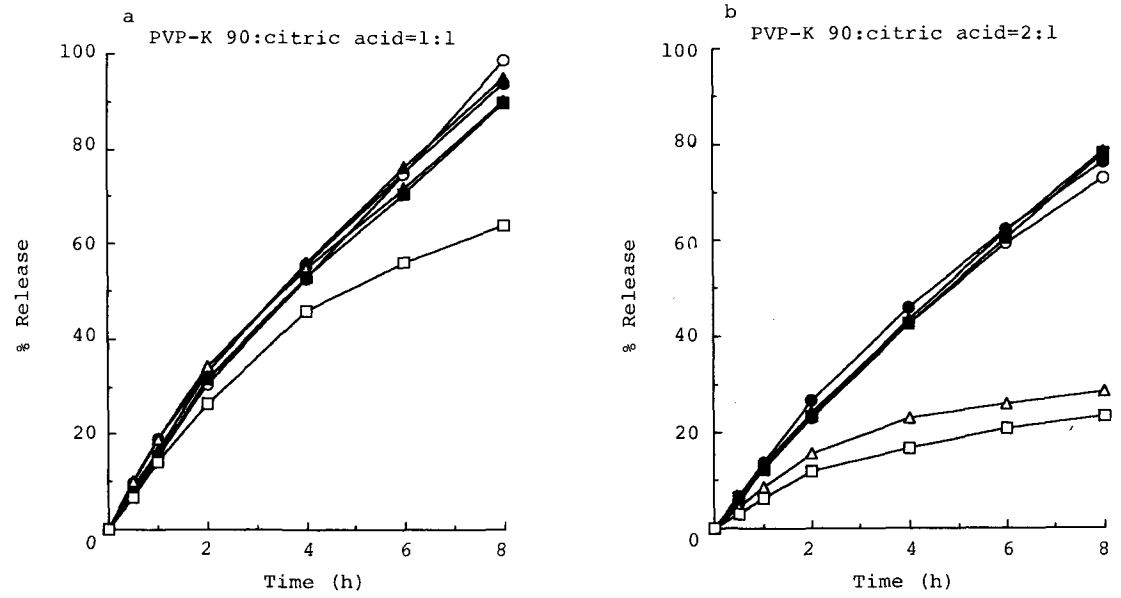

Fig. 3. Release profiles of papaverine HCl from tablets containing various amounts of drug at pH 1.1 (closed symbols) and pH 7.0 (open symbols). (●, ○) 15 mg; (▲, △) 30 mg; (■, □) 45 mg. (a) (●, ○) Tablet A; (▲, △) tablet J; (■, □) tablet K. (b) (●, ○) Tablet B; (▲, △) tablet L; (■, □) tablet M.

the case of the matrix containing a composition ratio of PVP-K 90 to citric acid of 1 : 1, pH-independent drug release was obtained when 15 or 30 mg of the drug was contained in the matrix (tablets A and J) as shown in Fig. 3a. Tablet K, however, which contained 45 mg of the drug, showed pH-dependent drug release (Fig. 3a). In the case of the matrix containing a composition ratio of PVP-K 90 to citric acid of 2 : 1, pH-independent drug release was achieved only when 15 mg of the drug was present in the matrix (tablet B) as shown in Fig. 3b. The maximum drug content for the pH-independent release tablet was varied according to the composition ratio of the matrix. Precipitation of the crystalline drug in the matrices (tablets K–M) which exhibited pH-dependent drug release was found after a release study at pH 7.0. The percent release of the drug at pH 1.1 from the tablet which showed pH-dependent release was equal to that at pH 1.1 and 7.0 from the tablet which showed pH-independent release when the composition ratio of the matrix was constant (Fig. 3a and b).

Control of drug release

The release rate from the tablet was controlled while maintaining pH-independent release by incorporating PVP-K 30, a low viscosity type of PVP, into the tablet. As shown in Fig. 4, the drug release rate increased with increasing content of PVP-K 30.

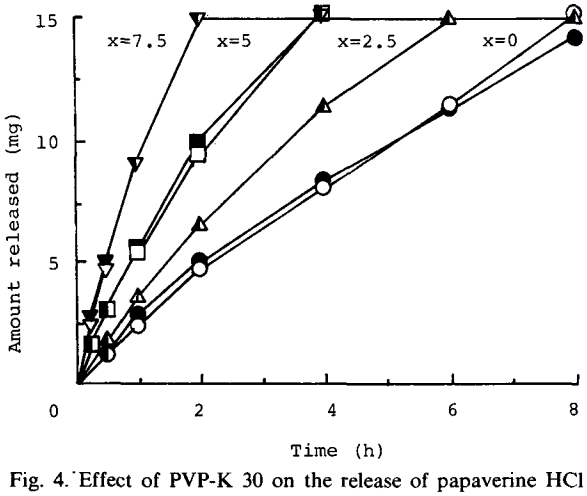

Fig. 4. Effect of PVP-K 30 on the release of papaverine HCl from tablets at pH 1.1 (closed symbols) and pH 7.0 (open symbols). The composition ratio of the tablet is expressed as follows: papaverine HCl : PVP-K 90 : PVP-K 30 : citric acid = 1 : 7.5 − x : x : 7.5. x, content ratio of PVP-K 30 to drug in the tablet.

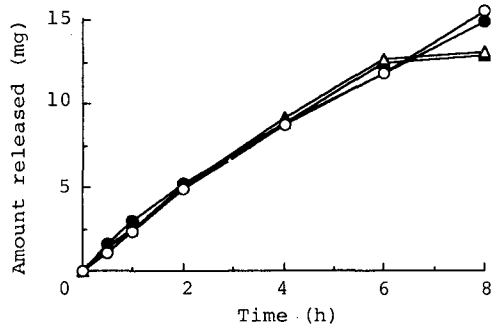

Fig. 5. Effect of the tablet weight on the release of papaverine HCl from tablets at pH 1.1 (closed symbols) and pH 7.0 (open symbols). (●, ○) 240 mg, tablet A; (▲, △) 200 mg, tablet P.

Effect of tablet weight on drug release

As shown in Fig. 5, drug release was investigated from tablets with the same diameters and composition ratios of the matrices but differing in tablet weights. Two tablets which weighed 200 and 240 mg (tablets P and A) released drug completely in 6 and 8 h, respectively. It was also found that the amount of drug released from these tablets was identical in spite of the variation in tablet weight.

Effect of tablet diameter on drug release

The drug release profile from a tablet of diameter 9 mm was compared with that for a diameter

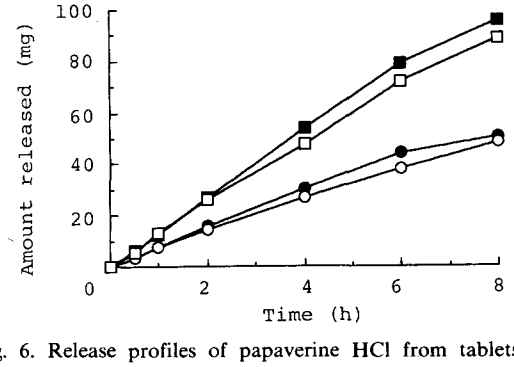

Fig. 6. Release profiles of papaverine HCl from tablets of diameter 9 mm at pH 1.1 (closed symbols) and pH 7.0 (open symbols). (●, ○) Tablet N; (■, □) tablet O.

of 5 mm. We prepared a tablet of 9 mm diameter and weight of 800 mg. In the release study at pH 7.0, the dissolution medium was replaced completely by fresh medium at 4 h after sampling to inhibit precipitation resulting from the low solubility of the drug at pH 7.0. As shown in Fig. 6, however, the release rate at pH 1.1 was slightly higher than that at pH 7.0, since sink conditions were probably not completely maintained at pH 7.0 under the conditions of this dissolution study. Tablet N which weighed 800 mg in Fig. 6 has the same tablet composition as tablets A and P which weighed 200 and 240 mg in Fig. 5. The amount of drug released from tablet N (Fig. 6) was about 3–3.5-fold greater than that of the latter at all times measured (tablets A and P in Fig. 5). This value is equal to the ratio of the surface area of tablets with diameters of 9–5 mm.

Simulation of drug release rate

According to Langer and Peppas (1981), the diffusional release of a drug from a polymeric matrix can be described by:

$$M_t/M_\infty = k_0 t^{n^*} \quad (1)$$

or

$$M_t = k_0 M_\infty t^{n^*}$$

where M_t/M_∞ is the fractional release of drug, t is the release time, k_0 is a constant incorporating structural and geometric characteristics of the controlled-release device, and n^* is the release exponent, indicative of the mechanism of drug release. Experimental data showed that the amount of drug release was not dependent on M_∞ or tablet weight, but was proportional to the drug content ratio in the tablet when the diameter and composition ratio of the matrix are equal, so that Eqn 1 was modified to the following:

$$M_t = k_1 \sqrt[n]{t} \quad (2)$$

where n equals $1/n^*$ and k_1 is the rate constant concerned with the drug content in the tablet.

It was also clear that the amount of drug release was proportional to the surface area of the tablet. Thus, if the surface area of the tablet with a diameter of 5 mm is regarded as unit surface area, then k_1 for the tablet which has a diameter other than 5 mm is expressed as follows:

$$k_1 = kd^2/25 \quad (3)$$

where d is the diameter of the surface for release from a tablet and k is the rate constant for a tablet which has a diameter of 5 mm.

The release data from experiments were treated according to Eqn 2 and n was calculated by the method of least squares. We obtained 1.21 ± 0.09 (mean ± S.D., 70 experiments) as the value of n. Thus, we can simulate the drug release profiles of

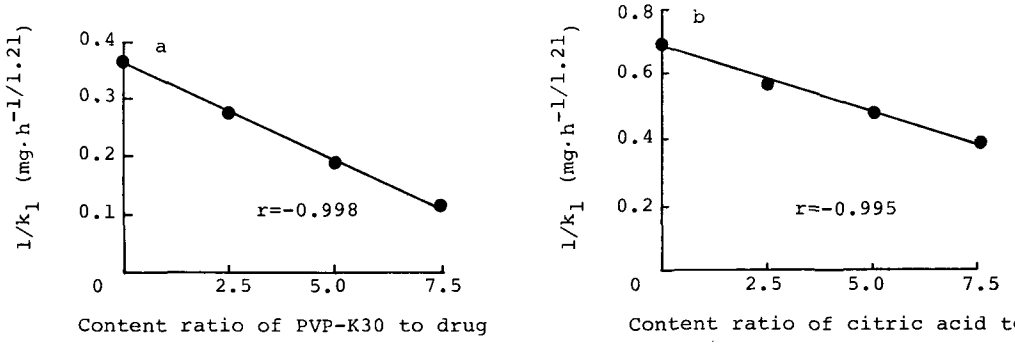

Fig. 7. Correlation between $1/k_1$ and composition ratio of PVP-K 30 (a) or citric acid (b) in the matrix. The composition ratio of the tablet is expressed as follows: (a) papaverine HCl : PVP-K 90 : PVP-K 30 : citric acid = 1 : 7.5 − x : x : 7.5. x, content ratio of PVP-K 30 to drug in the table. (b) papaverine HCl : PVP-K 90 : citric acid = 1 : 15 − y : y. y, content ratio of citric acid to drug in the tablet.

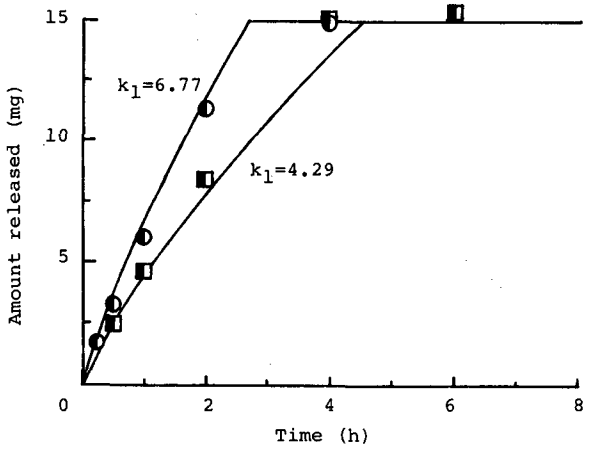

Fig. 8. Release profiles of papaverine HCl from tablet H (●, ○) and tablet I (■, □) at pH 1.1 (closed symbols) and pH 7.0 (open symbols). Each point represents an experimental value. Each line shows a calculated release curve.

tablets prepared in this study by the following equation:

$$M_t = k_1 \sqrt[1.21]{t} \quad (4)$$

The values of k_1 at pH 1.1 calculated by using Eqn 4 are listed in Table 1. These values fitted the experimental results well. For instance, tablets A, J and K have the same composition ratio of matrices (PVP-K 90 : citric acid = 1 : 1), therefore the amount of drug released from them at pH 1.1 was proportional to the drug content ratio (Fig. 3a). These results reflect their k_1 values shown in Table 1. Moreover, the value of k_1 for tablet N is about 3.7-fold larger than that of tablet A (Table 1). This value corresponds to the ratio of the surface areas or of the amounts of drug released from the two tablets.

The relationship between the k_1 value and the amount of excipient in the tablet is shown in Fig. 7. A linear relationship was found between the reciprocal k_1 value and the content of PVP-K 30 (Fig. 7a) or citric acid (Fig. 7b) in the tablet.

Thus, we simulated drug release rate by using these relationships. For instance, in the case of the content ratio of PVP-K 30 in the formulation being 6.25 and 3.75, we determined k_1 values of 6.77 and 4.29, respectively (Fig. 7a). The simulation curves of drug release were obtained after substituting these k_1 values into Eqn 4. Fig. 8 demonstrates good agreement between the theoretical and experimental amounts of drug release at different times even though tablets (tablets H and I) which have different compositions are used.

Release from the layered tablet

Two kinds of layered tablets were prepared as shown in Fig. 9. Tablet Q consists of formulation I containing a drug and formulation II lacking drug. Tablet R consists of formulations I and III, which contains a larger amount of the drug than formulation I.

Tablet Q released drug from formulation I which was placed externally. After the complete erosion of formulation I, drug release ceased until

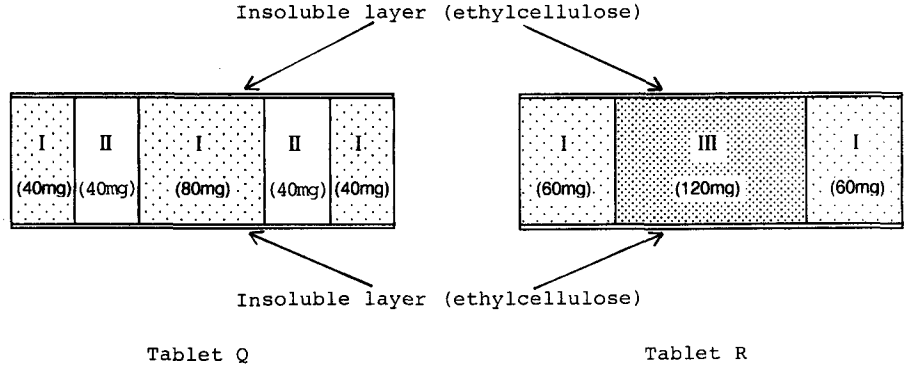

Fig. 9. Cross-sections of layered tablets of diameter 5 mm and weight 240 mg. Tablet Q consists of I (papaverine HCl : PVP-K 90 : citric acid = 1 : 7.5 : 7.5) and II (papaverine HCl : PVP-K 90 : citric acid = 0 : 8 : 8). Tablet R consists of I and III (papaverine HCl : PVP-K 90 : citric acid = 2 : 7 : 7). Each formulation weight is shown in parentheses.

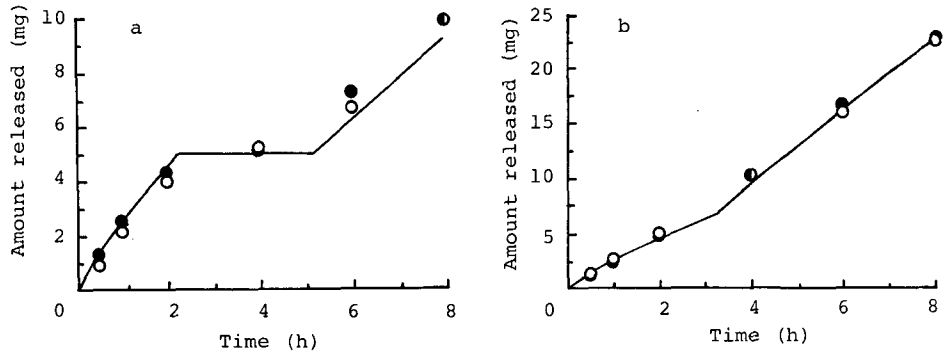

Fig. 10. Release profiles of papaverine HCl from tablet Q (a) and tablet R (b) at pH 1.1 (closed symbols) and pH 7.0 (open symbols). Each point represents an experimental value. Each line shows a calculated release curve.

formulation II had dissolved. Consecutively, drug was released from the central part (formulation I), at the same rate as in the initial stage. Accordingly, it was shown that tablet Q released drug intermittently. Tablet R initially released drug at the same rate as that of tablet Q at the outset. After erosion of formulation I, drug was released at a higher rate from formulation III due to the larger amount of drug in this matrix than in formulation I. Tablet R showed a different release profile in which the release rate increased with time. It was apparent that drug release from tablets Q and R was pH-independent (Fig. 10). Good agreement is also indicated between the theoretical and experimental amounts of drug released at different times for tablets Q and R as shown in Fig. 10.

Discussion

During the course of gastrointestinal transit, drug may be exposed to various pH conditions ranging from 1 in the stomach to 7 in the intestine. It is also well known that gastric pH varies from 1 to 7 (Finholt and Solvang, 1968; Malagelada et al., 1976) and that drug remains in the stomach for varying lengths of time (Nimmo et al., 1973; Bates et al., 1974). Since most drugs are either weak acids or weak bases, their release from sustained-release formulations is pH-dependent. In particular, basic drugs encounter obstacles on release from such formulations under the neutral pH conditions due to low solubility at these pH values when gastric pH is increased or the gastric emptying rate is increased. The pH dependency of drug release from sustained-release formulations containing basic drugs has been demonstrated (Timko and Lordi, 1978; Donbrow and Friedman, 1979). This may result in variation in absorption or reduction of bioavailability for basic drugs.

The pH-solubility profile of papaverine HCl showing a maximum at about pH 4 is shown in Table 2. The solid phases in equilibrium with the solution at pH values lower and higher than about pH 4 are the salt and base of papaverine, respectively (Serajuddin and Rosoff, 1984). The decrease in solubility at lower pH values was attributed to the common ion effect of chloride owing to the addition of the hydrochloride salts and sodium chloride. The amount of sodium chloride increases when the pH of the medium is decreased in order to maintain a constant ionic strength. Thus, a reduction in the extent of dissociation of the hydrochloride salt decreases its solubility.

Papaverine HCl was preferentially released from tablets under acidic conditions as compared to neutral conditions (Fig. 2d). There are few available reports that the dissolution rate at the pH of low solubility is increased by incorporating an appropriate acidic compound (Thoma and Zimma, 1990) or buffering agent (Doherty and York, 1989) due to the change in surface pH of the matrix. We could reduce the surface pH of the tablet by incorporating citric acid and obtain a pH-independent release formulation of papaverine

HCl. The pH-independency of drug release was influenced by the ratio of citric acid to the drug. When this ratio was less than about 3.5, the drug was precipitated in the matrix during the release study at pH 7.0, so that the release patterns were no longer pH-independent. The release rate was controlled by the content of citric acid (Fig. 2a and b) or PVP-K 30 (Fig. 4). Water-soluble material such as citric acid or PVP-K 30 would be dissolved rapidly. Therefore, the effective surface area of PVP-K 90 would increase. Thus, the release rate was increased by increasing the proportion of these water-soluble components in the matrix. The rate-limiting step in this release would be the dissolution of PVP-K 90. The amount of drug release per unit time was also controlled by the surface area which could release drug. In general, if the surface of the tablet is saturated by a drug and the surface area for release is maintained constant, then the amount of drug released per unit time is considered to remain constant irrespective of the different drug content in the tablet. However, it was shown that the amount of drug released from this tablet per unit time was proportional to the amount of drug in the matrix (Fig. 6). Moreover, it was found that the erosion of the matrix was enhanced with time. Thus, it is unlikely that the release will be followed by a concentration gradient being established from the solubility of the drug at the surface pH to the drug concentration at the bulk pH. Ultimately, the drug would be considered to be released from the tablet with the erosion of the matrix before the surface of the tablet has attained saturation of the drug. It is possible that pH-independent drug release could be ascribed to this phenomenon as well as the reduction in the surface pH by incorporating citric acid into the matrix.

Release profiles of the drug from the tablet prepared in the present study could be expressed by Eqn 4. Eqn 4 was applicable in the cases of all the tablets prepared in this study at any pH values provided the drug did not precipitate in the formulation. The dependence of n^* on the diffusional mechanism has been summarized previously (Langer and Peppas, 1981). In this study, we determined n^* to be equal to 0.826, since n equalled 1.21. Thus, these release characteristics appear to be of a type corresponding to anomalous diffusion (Langer and Peppas, 1981).

When different compositions of formulations were combined, this layered tablet (Fig. 9) showed a unique release profile (Fig. 10). For instance, the drug was released at appropriate intervals, or drug release increased with time, while maintaining pH-independent release. Using the calculated values of k_1 and n, good agreement between the experimental and theoretical data was obtained for the release rates (Figs. 8 and 10). Hence, it is possible that the release rate of drug can be predicted in various cases with a different content of drug, differing composition ratio of the matrix, different tablet weight and differing surface area. The tablet prepared in this study is a new type of controlled-release formulation which shows predictively various release profiles with maintaining pH-independent release. This tablet can be available to use for many purposes such as reduction in the variation of absorption or increase in bioavailability for basic drugs or drugs which are hindered by the first-pass effect.

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