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RESEARCH PAPERS

STUDIES ON DRUG RELEASE FROM A CARBOMER TABLET MATRIX

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ABSTRACT

The purpose of this investigation was to study the drug release mechanisms for tablet matrices of carbomer. Carbomer is a polymer of acrylic acid which is cross-linked with polyalkenyl polyether. The drug and the carbomer were blended and directly compressed into tablets using a laboratory Carver press. The influence of the level of carbomer, the type of drug, and the pH of dissolution media were investigated by measuring drug release kinetics. In general, the release of a relatively neutral molecule (e.g. theophylline) in the pH 7.2 phosphate buffer solution appears to exhibit nearly zero-order kinetics via a diffusion-controlled mechanism for all polymer levels studied (10-85%).

The drug release process based on diffusion can be described by the general expression:

$$M_t = k_1 t^{1/2} + k_2 t,$$

where M_t represents the amount of the drug released at time t, and k_1, k_2 are related to kinetic constants characteristic of the drug delivery systems. The release kinetics are modified when an ionic species, such as sodium salicylate, is incorporated into the tablet matrix.

INTRODUCTION

Carbomer as shown in Figure 1, is a polymer of acrylic acid which is cross-linked with polyalkenyl polyether. Carbomer, used in the present study, has a molecular weight of about 3 million. Carbomer readily hydrates, absorbs water, and swells. In addition, its hydrophilic nature, its cross-linked structure, and its essentially insolubility in water make carbomer a potential candidate for use in controlled release drug delivery systems.

Carbomer was first prepared and patented in 1957 [1]. Since then, a number of extended release tablet formulations which involve carbomer matrices have been patented [2]. Hudson [3] used Carbopol 934 as a binder and employed wet granulation method for the tablet formulation. From the experimental work, Hudson concluded that carbomer can be successfully employed in sustained release tablet bases. Lapidus and Lordi [4] studied some factors affecting the release of a water soluble drug from a compressed hydrophilic matrix. They observed that the release pattern appears to follow the theoretical relationship proposed by Higuchi [5,6] for solid drugs dispersed in solid matrices. They also reported that the decreased release rate of chlorpheniramine maleate in pH 7.5 buffer solution could be attributed to the increased gelation of the carbomer in an alkaline medium and the interaction of chlorpheniramine with the carbomer. Later, several investigators [7-9] confirmed that an addition of carbomer to timed release tablet formulations decreased the release rate of the drugs. The effects of carbomer increased proportionally with the content of carbomer in the tablets. Malley et al., [10] described the release of sodium salicylate from a thin sheet of carbomer matrix in gastric liquid as a transient diffusion with concentration-dependent diffusivities. Zhang and Schwartz [11] recently reported that the drug release from carbomer tablets appears to follow a zero order release mechanism in most of the cases studied. Previous experimental results in this laboratory showed that the drug release would follow a zero order process if the content of carbomer was more than 40% of the tablet weight in a tablet formulation. Zhang and Schwartz also observed a change of release mechanism due to the levels of carbomer in the tablet. However, many questions of the release kinetics and mechanism have not been answered completely.

The objectives of this investigation were: (1) to study the drug release mechanisms for a directly compressed carbomer tablet, (2) to describe the release kinetics from the carbomer matrices, and (3) to investigate factors, such as the concentrations of polymer in the dosage form, the use of different types of drugs, and dissolution media at various pH values.

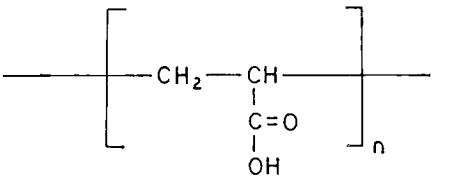

FIGURE 1

Chemical structure of carbomer
(the cross-linkage is not shown here)

MATERIALS AND METHODS

Materials

Three different medicinal compounds were used as model drugs for the present studies (i.e., theophylline, anhydrous USP, sodium salicylate USP, and chlorpheniramine maleate USP).The polymer, carbomer NF (trade name Carbopol 934P from B. F.Goodrich Company) was used in the tablet formulation.

Preparation of Tablets

Both drug and carbomer in powder forms were mixed with various ratios. The powder mixtures were directly compressed into tablets using a laboratory Carver press (Fred S. Carver,Inc., Menomonee Falls, WI). Tablets were round, flat faced and 0.9525 cm in diameter. The target tablet hardness ranged from 7 to 9 Kp.

Dissolution Testing

Drug release studies were carried out using the USP dissolution apparatus I with a 50 rpm basket rotational speed. Three different dissolution media (i.e., 0.1 N HCl, distilled water, and a pH 7.2 phosphate buffer solution) were used. Samples of liquids were taken at predetermined time intervals for an UV analysis at 272, 300, and 264 nm wavelenth for theophylline, sodium salicylate, and chlorpheniramine maleate respectively. Calibration curves were constructed prior to each sample analysis.

Swelling Experiments

Swelling of carbomer tablets in three different dissolution media (i.e., 0.1 N HCl, distilled water, and a pH 7.2 phosphate buffer solution) were conducted using a swelling determination apparatus as shown in Figure 2. A tablet sample placed inside the glass tube was situated at the bottom of a dissolution flask. The rotating speed of the stirring paddle was set at 50 rpm. The tablet sample was taken at predetermined time intervals in order to measure hydration of carbomer tablets.
The weight gain was measured by a calibrated analytical balance. The experiment was completed in five replicates.

Theophylline Solubility Determination

Three dissolution media (i.e., 0.1 N HCl, distilled water and pH 7.2 phosphate buffer solution) were used for the solubility studies. Solubility determinations were conducted at ambient temperature and at 37°C using Distek dissolution apparatus equipped with temperature control system, TCS 0200 (Distek, Inc., Monmouth Junction, NJ). Dissolution medium, 500 mL of each, was placed into separate dissolution flasks equipped with stirring paddles. Theophylline was added in excess to each flask.The samples were stirred at 100 rpm for twenty hours. The mixture was allowed to settle for sixty minutes while the samples were maintained at the specified temperatures. The supernatant was filtered through a 0.45 micrometer filter (Gelman Science, Ann Arbor, MI). Five milliliters (mL) of the filtrate were immediately diluted with the appropriate dissolution medium for quantitative analysis. A Shimadzu UV-160 spectrophotometer was used for UV absorbance measurements at wavelength 272 nm for the determination of theophylline concentration in each of the three different dissolution media.

A standard curve of theophylline was constructed for each solvent system (i.e., 0.1 N HCl, distilled water and pH 7.2 phosphate buffer solution) prior to sample analysis.

RESULTS AND DISCUSSION

During the dissolution testing, two general trends were observed: (1) the polymer swelled; the more polymer in the sample, the more the sample swelled, (2) the swelling of the drug/carbomer tablets occurred in all dissolution media studied (i.e., 0.1 N HCl, distilled water, and pH 7.2

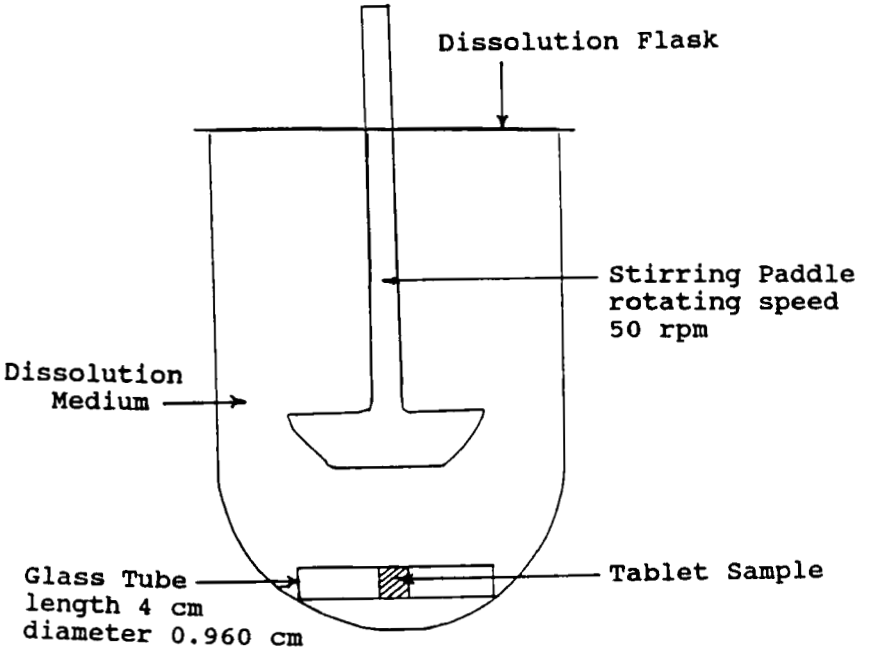

FIGURE 2

Swelling determination apparatus

phosphate buffer); but tablets did not swell equally in each dissolution medium.

Solubility of Theophylline

Theophylline is a weakly acidic compound with the proton on the nitrogen at position 7 being dissociable. The reported pK_a of theophylline is 8.6 in aqueous solution [12]. Because of its relatively high pK_a, theophylline is largely unionized at the pH range 1.0 to 7.5 which includes the changes in pH seen in the gastrointestinal tract. The absorption of theophylline should be independent of pH over this range.

The solubility of theophylline is 8.3 mg/mL at 25°C in water [13]. Theophylline solubility data relevant to 0.1 N HCl, distilled water, and pH 7.2 phosphate buffer solution at ambient temperature and 37°C have not been completely documented in the literature. To investigate the drug release mechanisms and to enhance understanding the factors influencing

TABLE 1

Solubility of theophylline in various dissolution media

		Concentration of Theophylline (mg/mL)		
		0.1 N HCl	Water	pH 7.2 Buffer
ambient	Mean±SD	6.8±0.1	5.4±0.1	5.6±0.1
	RSD (%)	1.5	1.8	1.8
37°C	Mean±SD	14.5±0.1	11.1±0.4	12.1±0.1
	RSD (%)	0.6	3.3	0.9

Note: Mean= Average of three determinations

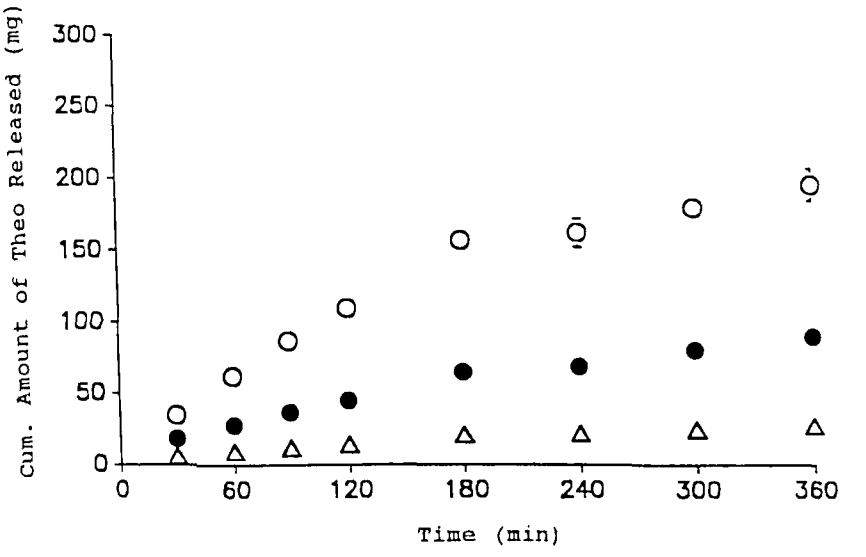

FIGURE 3

Cumulative amount of theophylline (Theo) released as a function of time in the 0.1 N HCl solution. (theoretical compression weight is 300 mg per tablet. carbomer = CBM) Key : (○) Theo/CBM (90/10), (●) Theo/CBM (60/40), (△) Theo/CBM (15/85).

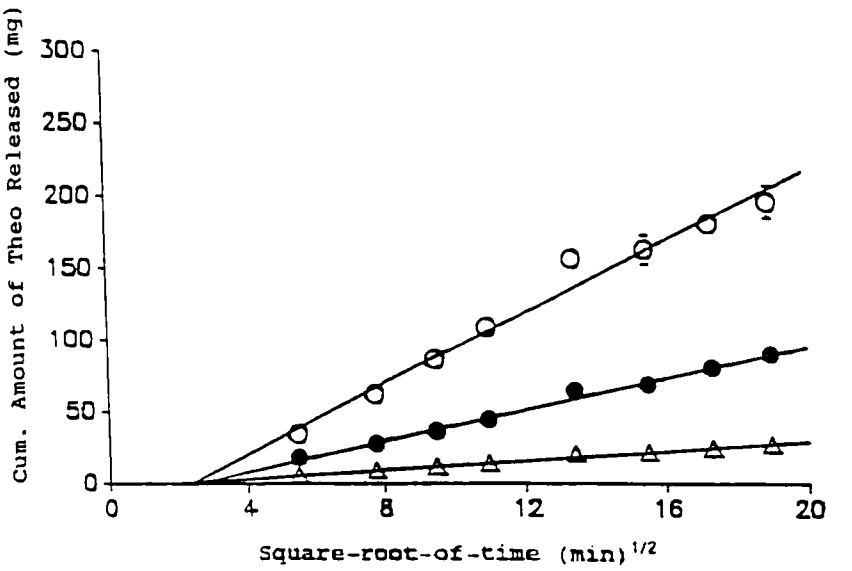

FIGURE 4

Cumulative amount of theophylline (Theo) released versus square-root-of-time (minutes)$^{1/2}$ in the 0.1 N HCl solution. (theoretical compression weight is 300 mg per tablet. carbomer = CBM) Key: (○) Theo/CBM (90/10), (●) Theo/CBM (60/40), (△) Theo/CBM (15/85), (——) linear regression line.

the release kinetics, the solubilities of theophylline in the above-mentioned solvent systems at ambient temperature and 37°C were determined.

In Table 1, the solubility of theophylline increases as the temperature rises from ambient temperature to 37°C. The difference of the solubility of theophylline in distilled water and pH 7.2 phosphate buffer solution at 37°C was determined to be statistically significant. The trend shows that theophylline is relatively more soluble in 0.1 N HCl than in pH 7.2 phosphate buffer solution or in distilled water at ambient temperature and 37°C.

Drug Release Studies from the Carbomer Matrix Tablets

As shown in Figure 3, the amount of theophylline released from the carbomer tablet matrix in the 0.1 N HCl dissolution medium was plotted

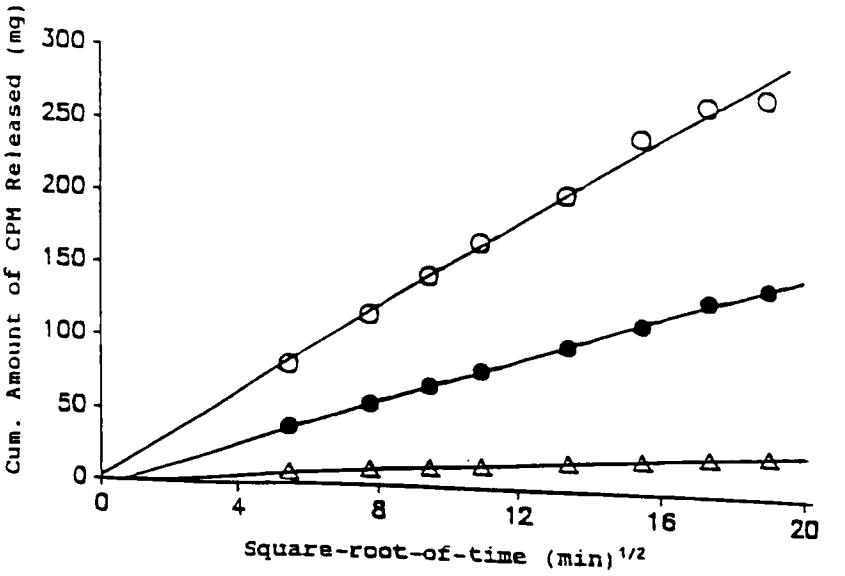

FIGURE 5

Cumulative amount of chlorpheniramine maleate (CPM) released versus square-root-of-time (minutes)$^{1/2}$ in the 0.1 N HCl solution. (theoretical compression weight is 300 mg per tablet. carbomer =CBM) Key: (o) CPM/CBM (90/10), (●) CPM/CBM (60/40), (△) CPM/CBM (15/85), (—) linear regression line.

against time. The release of theophylline appeared to decrease with increasing polymer levels, i.e., the more polymer, the less release. The experimental results follow the predicted trend that the more polymer included in the formulation, the greater the degree of the tablet swelling. As seen in Figure 4, a straight line relationship between the amount of theophylline released and the square-root-of-time was observed at least over the first 60% of the initial drug concentration as predicted by theory, for all polymer concentrations (10-85%).

To investigate drugs with different solubilities on release kinetics, a very water soluble drug, chlorpheniramine maleate and a highly water soluble drug, sodium salicylate were used in the tablet formulation. The release behaviors of chlorpheniramine maleate and sodium salicylate as shown in

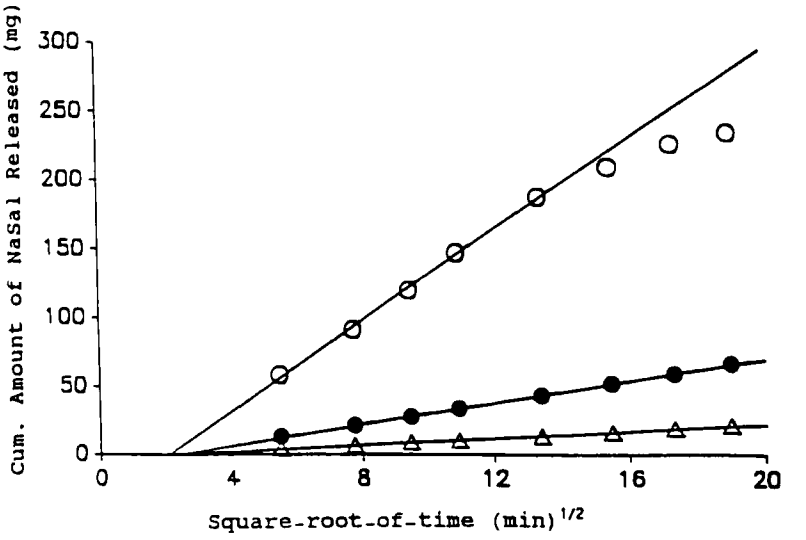

FIGURE 6

Cumulative amount of sodium salicylate (NaSal) released versus square-root-of-time (minutes)$^{1/2}$ in the 0.1 N HCl solution. (theoretical compression weight is 300 mg per tablet. carbomer = CBM) Key: (○) NaSal/CBM (90/10), (●) NaSal/CBM (60/40), (△) NaSal/CBM (15/85), (——) linear regression line

Figures 5 and 6, appeared to exhibit a square-root-of-time dependence under acidic environment. This pattern suggests that all dissolution results in the 0.1 N HCl dissolution medium appear to obey Fick's law of diffusion, and display a squqre-root-of-time dependence for all the drug/polymer ratios, and for all the water soluble drugs studied.

As indicated in Figure 7, the release of theophylline in the pH 7.2 phosphate buffer solution appeared to display a nearly zero-order process which could be either the polymer acting as a physical barrier or polymer relaxation slowing the rate. Case II transport, defined as very rapid diffusion compared with the relaxation process, is a special case of anomalous diffusion when the glassy/rubbery front moves at a constant velocity. The Case II transport mechanism did not seem likely to be a major contributor because a constant weight gain as a function of time was not obtained from the results of the hydration of the carbomer tablets in the three

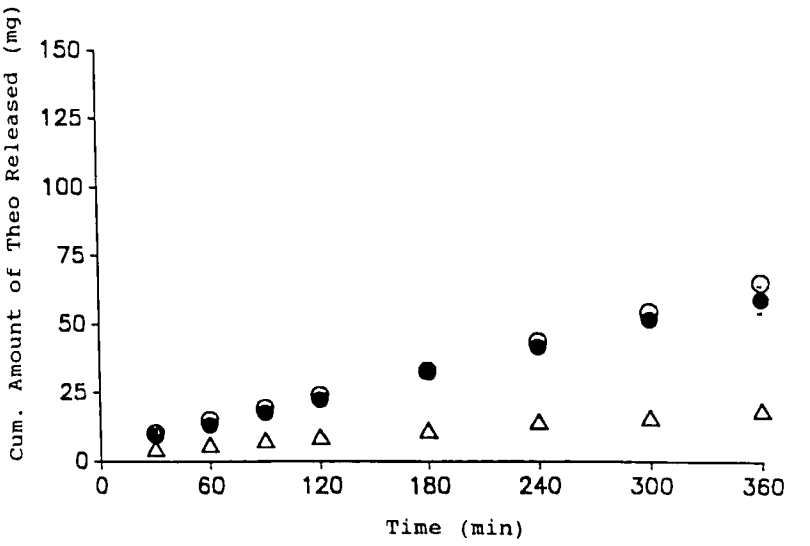

FIGURE 7

Cumulative amount of theophylline (Theo) released as a function of time in the pH 7.2 buffer solution. (theoreticalcompression weight is 300 mg per tablet. carbomer = CBM) Key: (○) Theo/CBM (90/10), (●) Theo/CBM (60/40), (△) Theo/CBM (15/85).

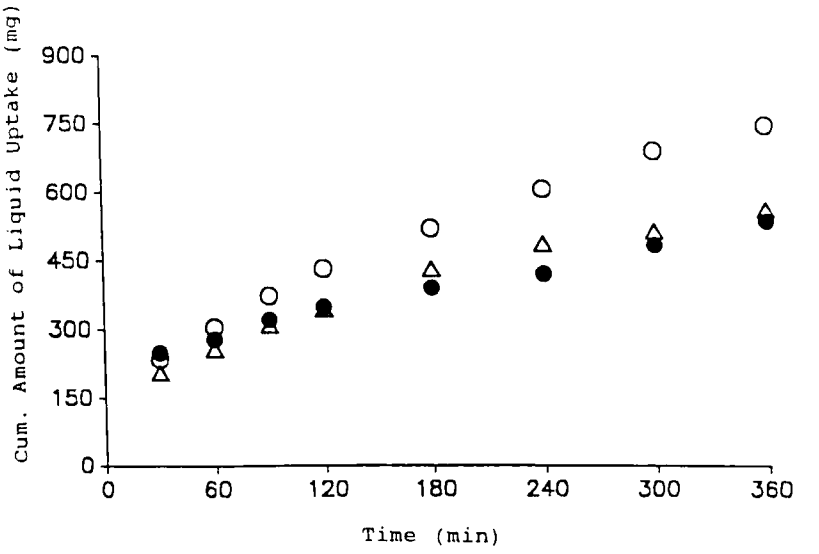

FIGURE 8

Cumulative amount of liquid uptake by 100% carbomer (CBM) tablets as a function of time. (theoretical compression weight is 300 mg per tablet) Each data point represents the average of five determinations. Key: (○) pH 7.2 phosphate buffer, (△) 0.1 N HCl, (●) H_2O.

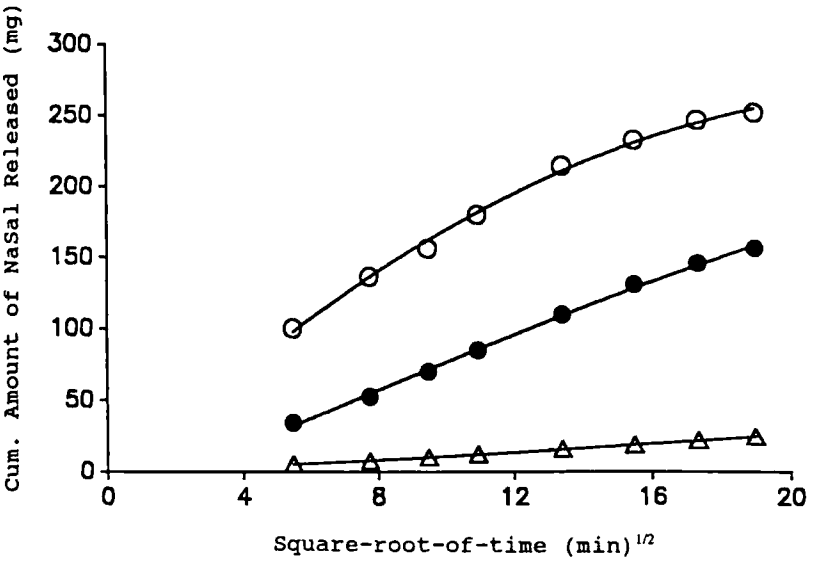

FIGURE 9

Cumulative amount of sodium salicylate (NaSal) released versus square-root-of-time (minutes)$^{1/2}$ in the pH 7.2 phosphate buffer solution. (theoretical compression weight is 300 mg per tablet. carbomer = CBM) Key: (○) Theo/CBM (90/10), (●) Theo/CBM (60/40), (△) Theo/CBM (15/85), (—) predicted curve with equation (1).

solvents (Figure 8). Alfrey [14] reported that for a polymeric matrix system, a Case II transport was characterized by a constant velocity of the moving solvent front and a linear weight gain with time.

When the theophylline in the tablet formulation was substituted with an ionic species and a highly water soluble drug such as sodium salicylate, the release kinetics, as shown in Figure 9, in the pH 7.2 phosphate buffer solution appear to have contributions from the matrix and barrier-controlled mechanisms. It was believed that the viscosity of the diffusion layer and the organization, orderliness and the structure of water melecules within the gel layer may have been modified in the presence of the highly water soluble drug.

Complex macromolecular changes may be taking place in the polymer during the drug release. These changes in turn affect the drug diffusion

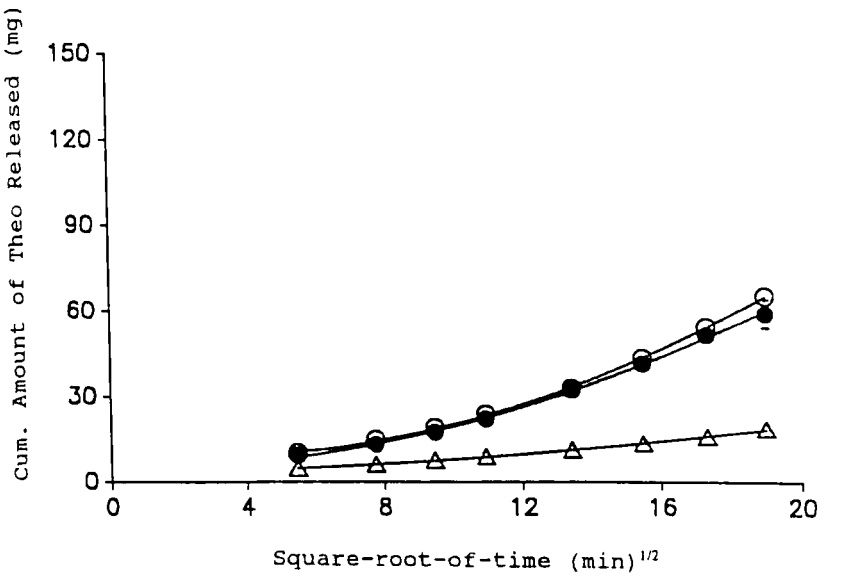

FIGURE 10

Cumulative amount of theophylline (Theo) released versus square-root-of-time (minutes)$^{1/2}$ in the pH 7.2 phosphate buffer solution. (theoretical compression weight is 300 mg per tablet. carbomer = CBM) Key: (○)Theo/CBM (90/10), (●) Theo/CBM (60/40), (△) Theo/CBM (15/85), (——) predicted curve with equation (1).

through the polymer, so that Fickian and non-Fickian diffusion may be observed. The drug diffusion through swollen carbomer matrices is accompanied with macromolecular relaxation and/or barrier-controlled release mechanisms.

Under certain circumstances, Fickian diffusion process may be the predominate drug release mechanism while the magnitude of the other contributions is relatively small. In this case, the application of the Higuchi theory appears to describe the release of model drugs from the carbomer tablet matrices. Conversely, if the barrier-controlled mechanism or polymer relaxation is more important than diffusion, then a zero-order process is the predominate drug release mechanism. In addition, a case may exist where both diffusion and relaxation of polymer chain are important contributors toward the overall drug release process. To include all possible combinations, the proposed methematical model is a simple polynomial

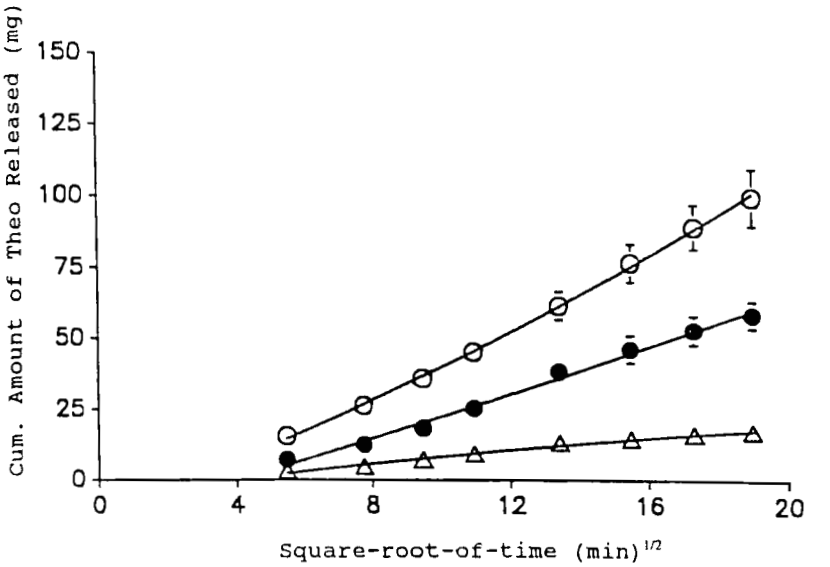

FIGURE 11

Cumulative amount of theophylline (Theo) released versus square-root-of-time (minutes)$^{1/2}$ in water. (theoretical compression weight is 300 mg per tablet. carbomer = CBM) Key: (○) Theo/CBM (90/10), (●) Theo/CBM (60/40), (△) Theo/CBM (15/85), (—) predicted curve with equation (1).

expression as shown in equation (1) to describe the drug release behavior of the tablet dosage form involving a carbomer matrix. A similar expression was reported by Peppas [15], Cattelani [16], Harland [17], Ritger [18], Ford [19], and Colombo [20].

$$M_t = k_1 t^{1/2} + k_2 t \qquad (1)$$

In this equation, M_t is the amount of drug released at time t, k_2 and k_2 are related to kinetic constants, characteristic of the release mechanisms contributing from Fickian diffusion and swelling-controlled or barrier-controlled release, respectively. In the right-hand side of the equation, the first term represents Fickian diffusion and the second term depicts the swelling or barrier-controlled process.

Experimental data were fitted to the equation (1) and are presented in Figures 10 and 11. The proposed model is satisfactory over most of the time interval of the drug release. The deviation between the model predicted and the observed data in the initial period of the drug release may be attributed to the initial film formation of the carbomer at the surface

of the tablets, which acts as a barrier causing a reduction of the flux of water into the carbomer matrix. This is a situation similar to a time lag effect.

CONCLUSIONS

1. The release profiles and release kinetics from tabletted drug/carbomer mixtures are influenced by the drug/carbomer ratios, the drug solubility characteristics, and the dissolution media.
2. The proposed equation appears to adequately describe all of the release data.

ACKNOWLEDGMENTS

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REFERENCES

1. H. P. Brown, US Patent No. 2,798,053 (1957).
2. B. F. Goodrich Bulletin "Sustained release patents using Carbopol resin", B. F. Goodrich Company, Cleveland, OH, 1987.
3. M. H. Hudson, Ph.D. Thesis Abstr., 27, 4461B (1967).
4. H. Lapidus, and N. G. Lordi, J. Pharm. Sci., 57, 1292 (1968).
5. T. Higuchi, J. Pharm. Sci., 50, 874 (1961).
6. T. Higuchi, J. Pharm. Sci., 52, 1145 (1963).
7. N. H. Choulis, and H. Papadopoulos, J. Pharm. Sci., 64, 1033 (1975).
8. N. Salib, S. A. El-Fattah, and M. El-Massik, , Pharm. Ind., 45, 902 (1983).
9. E. Graf, I. Tsaktanis, and A. A. Fawzy, Pharm. Ind., 48, 661 (1986).
10. I. Mally, J. Bardon, M. Rollet, J. R. Taverdet, and J. M. Vergnaud, Drug Dev. Ind. Pharm., 13, 67 (1987).
11. X. Y. Zhang and J. B. Schwartz, M.S. Thesis (1988). Philadelphia College of Pharmacy and Science, Philadelphia, PA.
12. J. L. Cohen, in " Analytical Profiles of Drug Substances," Vol 4, K. Florey, ed., Academic Press Inc., New York, NY, 1975, p. 466.
13. The Merck Index, Tenth Edition, 1328 (1983).

14. T. Alfrey, E. F. Gurnee Jr., and W. G. Lloyd, J. Polym. Sci., C12, 249-261 (1966).
15. N. A. Peppas and J. J. Sahlin, Int. J. Pharm., 57, 169 (1989).
16. P. Catellani, G. Vaona, P. Plazzi, and P. Colombo, Acta Pharm. Technol. 34, 38 (1988).
17. R. S. Harland, A. Gazzaniga, M. E. Sangalli, P. Colombo, and N. A. Peppas, Pharm. Res., 5, 488 (1988).
18. P. L. Ritger, and N. A. Peppas, J. Controlled Release, 5, 37 (1987).
19. J. L. Ford, K. Mitchell, P. Rowe, D. J. Armstrong, P. N. C. Elliot, C. Rostron, and J. E. Hogan, Int. J. Pharm., 71, 93 (1991).
20. P. Colombo, P. L. Catellani, N. A. Peppas, , L. Maggi, and U. Conte, Int. J. Pharm., 88, 99 (1992).