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CONTROLLED-RELEASE THEOPHYLLINE TABLET FORMULATIONS CONTAINING ACRYLIC RESINS, III. INFLUENCE OF FILLER EXCIPIENT.

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ABSTRACT

The selection of a filler excipient was demonstrated to have a dramatic effect on the release properties of theophylline from matrix tablets containing an acrylic resin polymer as the retardant substance. Theophylline tablets were formulated to contain 60 percent drug, 28 percent filler excipient, 10 percent Eudragit S100, 1.5 percent fumed silica and 0.5 percent magnesium stearate. Release rates were most rapid when microcrystalline cellulose was the filler excipient and the slowest when calcium sulfate was used as the diluent. Dissolution rates decreased in acidic medium as the level of Eudragit S100 increased from zero to fifteen percent. In pH 7.4 phosphate buffer, USP, the converse held true because of the high solubility of the resin at this pH

value. There was no difference between dissolution rates at pH 1.1 and pH 4.0. Tablet porosity was influenced significantly by the filler excipient. Higher porosity usually resulted in greater theophylline dissolution rates. When sucrose was employed as the filler excipient, tablet porosity was inversely related to tablet hardness.

INTRODUCTION

The development of pharmaceutical methodology used in the production of controlled-released dosage forms has concentrated on methods to reduce the rate at which the active moiety is released from the dosage form for absorption by the body. In earlier reports, McGinity and co-workers[1,2] examined the retardant properties of acrylic resin polymers in controlled-release theophylline tablets. In addition, Khanna and Speiser studied the release properties of chloramphenicol from methacrylic acid and methylmethacrylate polymeric beads. Swelling and diffusion were the major factors influencing drug release. Increasing the pH and ionic strenth of the dissolution media were found to accelerate diffusion from the beads.[3]

Carli and co-workers reported that Eudragit RS and Eudragit RL copolymers had poor surface wettability.[4] These polymers, however, were reported to have good liquid transport properties. Drug release was controlled by diffusion through the matrix pores, and copolymers containing a higher percentage of hydrophilic

groups produced the fastest drug release rates. El-Fattah and coworkers[5] found that compact hardness had a pronounced influence on the release rate of theophylline from tablets prepared from coprecipitates containing different Eudragit resins. The resulting dissolution patterns were found to be described best by the Higuchi equation.[6] In an earlier report, McGinity and coworkers reported that tablet hardness influenced drug release over the hardness range between 4 to 7 kg, but no significant differences were seen in the hardness range from 7 to 15 kg.[2] Yoshida and coworkers[7] achieved controlled drug dissolution from tablets by radiation-induced polymerization in the presence of acrylic resins. Using wet granulation techniques, controlled-release tablets containing propranolol and acrylic resins were prepared successfully.[8] However, most reported applications for the acrylic resin polymers have been concerned with the coating of tablets and beads to control drug release from the dosage forms.[9-14] The objective of the present study was to examine the influence of filler excipients on the dissolution properties and porosity of controlled-release theophylline tablets containing the acrylic resin, Eudragit S100.

EXPERIMENTAL

The filler excipients investigated included microcrystalline cellulose,[15] lactose,[16] dextrose,[17] sucrose,[18] and calcium sulfate.[19] Tablets (500mg), compressed to a hardness level between nine and fifteen kg, were formulated to contain 60 percent

theophylline, 28 percent filler excipient, 10 percent Eudragit S100, 1.5 percent fumed silica, and 0.5 percent magnesium stearate. Other materials and the methods used were the same as those reported earlier.[1]

Porosity measurements were conducted in duplicate using mercury intrusion porosimetry.[20] These determinations were conducted on tablets containing the Eudragit S100 resin and the following filler excipients; sucrose, dextrose, spray-dried lactose, microcrystalline cellulose, and calcium sulfate. Tablets were evacuated of air for a period of thirty minutes before being subjected to porosity measurements.

The total porosity of the tablets was determined from the volume of mercury forced into the tablets. Percentages of individual pore size ranges relative to the total porosity, were determined using a cylindrical pore model, by measuring the changes in volume of mercury forced into the tablets with incremental increases in pressure. Porosity was measured as a function of the tablet hardness as well as a function of the filler excipient.

RESULTS AND DISCUSSION

Several filler excipients were evaluated for their influence on the release rate and physical properties of theophylline tablets. An earlier publication[2] reported that the Eudragit S100 resin was the least compressible of the four resins studied. However, at the 10 percent resin level, the compressibility of the

4:1 drug to resin formulation was sufficient to produce tablets with acceptable physical properties. Variations in tablet hardness were minimal and the friability values varied from 0.1 percent for microcrystalline cellulose to 0.58 percent for sucrose. Excellent content uniformities were seen with tablets for all excipients studied.

The dissolution profiles in acidic medium are shown in Figure 1. These profiles demonstrate a dramatic influence of the filler excipient on the drug release characteristics from the tablet matrices. Drug release was most rapid from tablets containing microcrystalline cellulose. Tablets containing calcium sulfate released drugs at the slowest rate, while tablets containing the other remaining excipients, released drug at intermediate rates. Dissolution was uniform in all cases with standard errors of means less than four percent for all formulations tested. When comparing different filler excipients, the quantities of drug released after six hours were found to be significantly different at the 99 percent level. These differences may be attributed to porosity, dissolution, or permeability of these materials. Of particular interest was the dissolution curve for the tablets containing microcrystalline cellulose. Drug release from these tablets was retarded by the acrylic resin, in spite of the inherent disintegrant properties of the microcrystalline cellulose. Although the tablets laminated within one hour of contact with the elution medium, four hours were required to release approximately 85 percent of the active

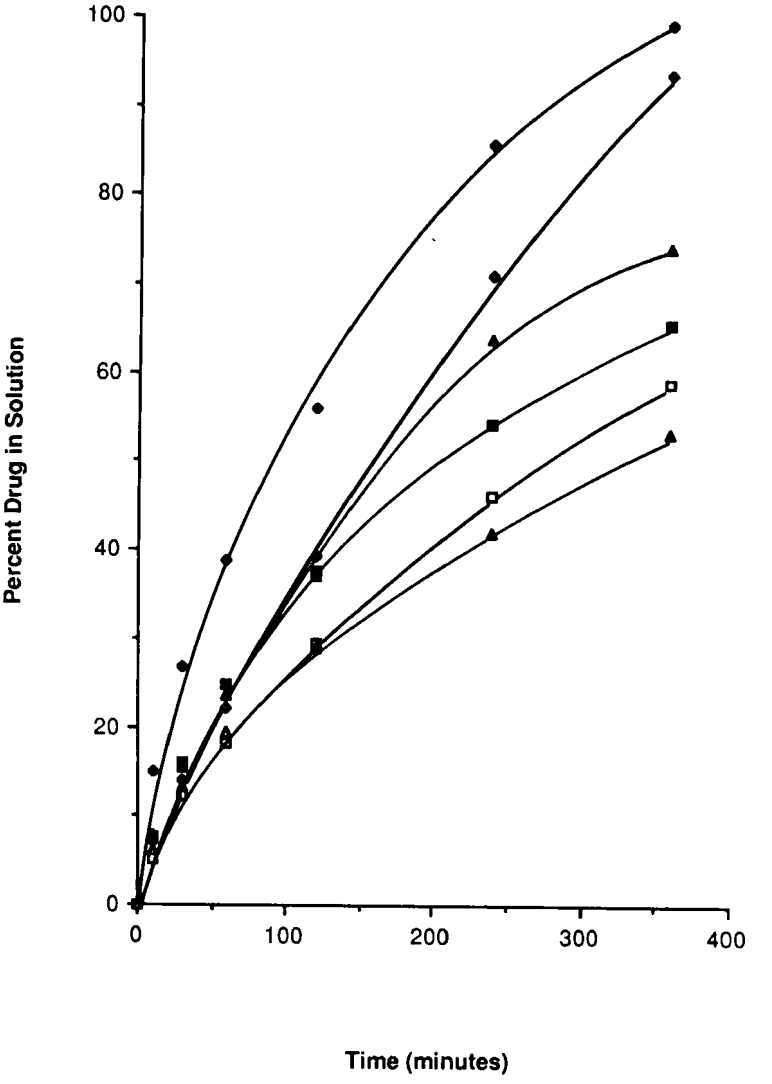

FIGURE 1.

The influence of filler excipients on the release rate of theophylline (300 mg) from tablets containing Eudragit S100 in 900 ml of acidic media (see Experimental for details). Key: ◆ , microcrystalline cellulose; ◇ , lactose; ▲ , sucrose; ■ , calcium sulfate (90/S); □ , dextrose; △ , calcium sulfate (90A/A).

ingredient from the tablet matrix. This lamination was not evident with tablets containing the other excipients which released theophylline by a slow erosion of the tablet matrix.

Using sucrose as the filler material, the influence of resin level on the dissolution rate of theophylline from tablets in acidic medium is shown in Figure 2. A significant difference between tablet formulations ($P > 99$ percent) was observed when comparing the influence of the level of acrylic copolymer on the dissolution rates of theophylline. Increasing copolymer content from zero to fifteen percent decreased the amount of drug dissolved after six hours by approximately one third. The release rates were very reproducible as indicated by the small standard errors of means: less than five percent in all cases.

Drug dissolution as a function of resin level in phosphate buffer (pH 7.4, USP) is shown in Figure 3. Whereas drug dissolution decreased with increasing resin level in the acidic medium, the converse held true in this buffer. Since the Eudragit S100 resin was soluble at this pH, the higher resin levels increased erosion of the tablet matrix and promoted the drug release process. Release rates were found to depend significantly upon the amount of resin present within the tablet at pH 7.4. These release rates were significantly higher when compared to those obtained in medium at pH 1.1. The influence of pH on the dissolution properties of theophylline from tablets containing sucrose and 15 percent Eudragit S100 is shown in Figure 4. Drug release in pH 4.0 medium was not significantly different from the

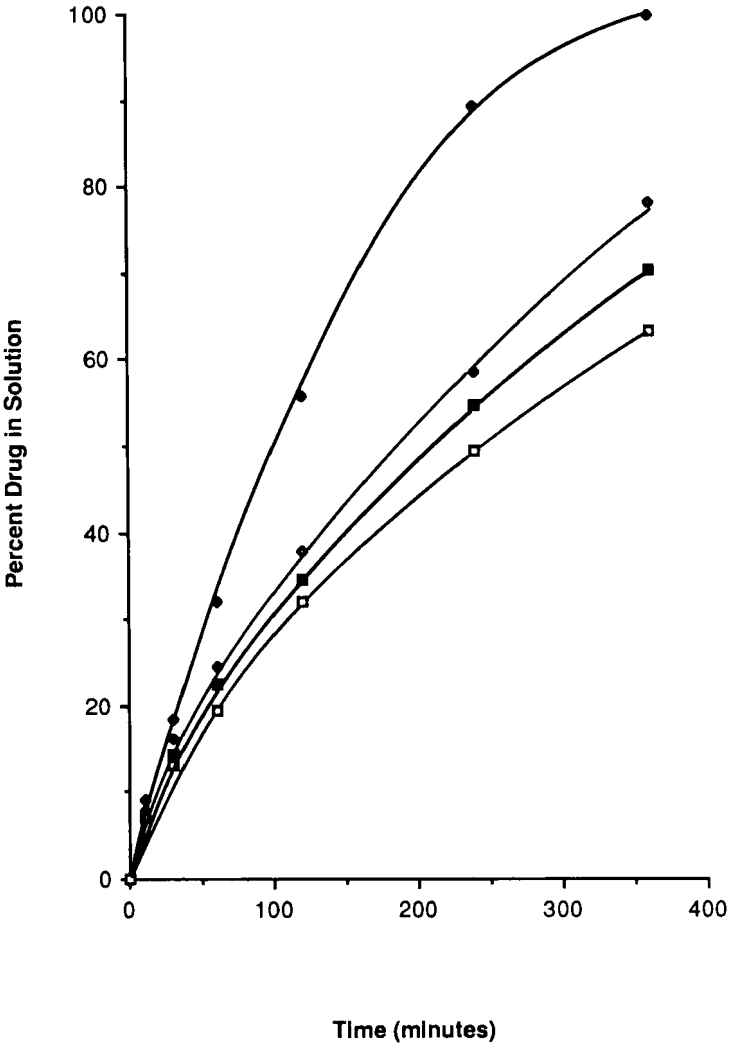

FIGURE 2.

Dissolution profiles of theophylline (300 mg) from tablets containing Eudragit S100, as a function of total resin content, in 900 ml of acidic medium (see Experimental for details). Key: ◆ , 0% S100 ◇ , 5% S100; ■ , 10% S100; □ , 15% S100.

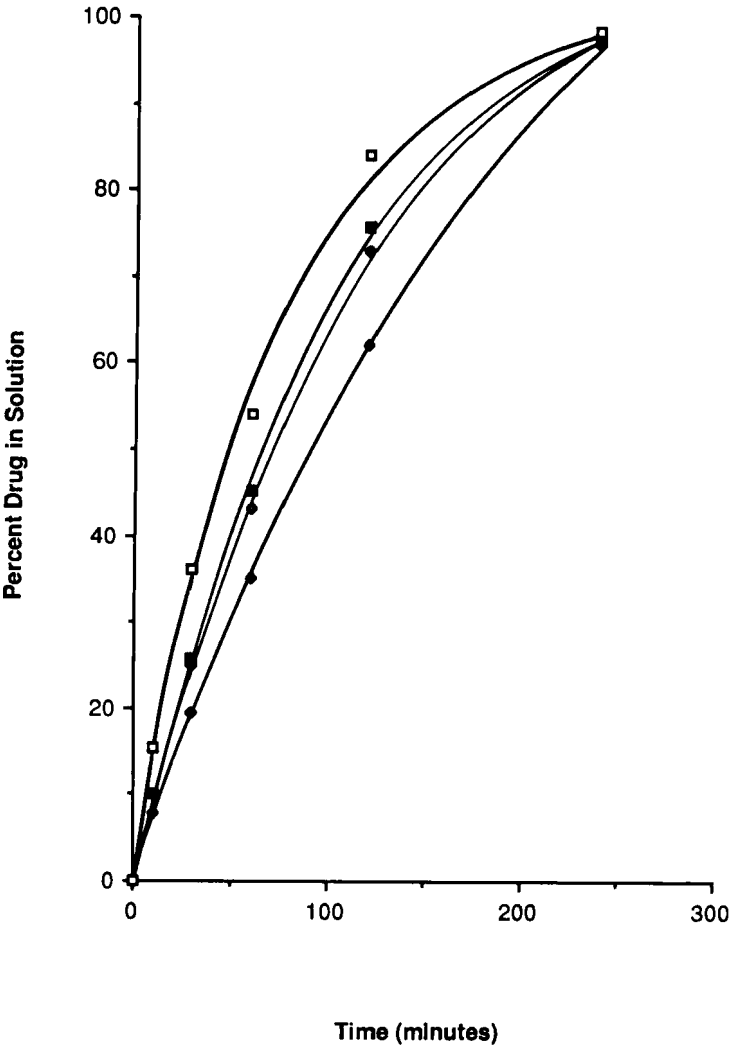

FIGURE 3.

Dissolution profiles of theophylline (300 mg) from tablets containing Eudragit S100 as a function of total resin content, in 900 ml of pH 7.4 phosphate buffer (see Experimental for details). Key: □, 15% S100; ■, 10% S100; ◇, 5% S100; ◆, 0% S100.

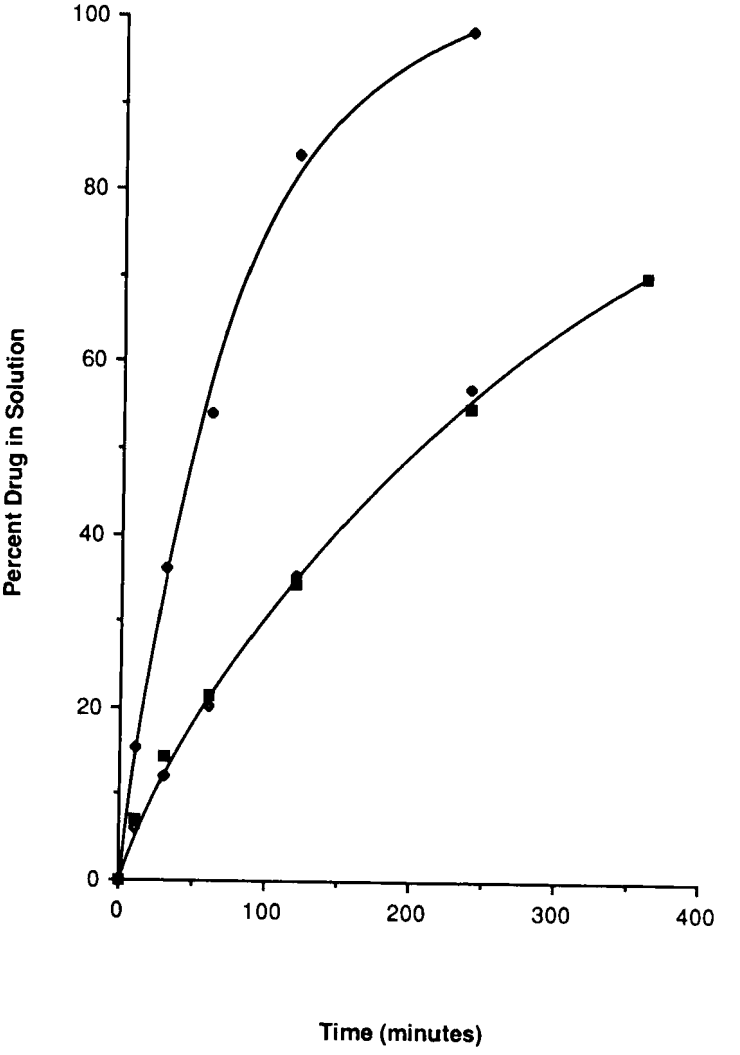

FIGURE 4.

The influence of medium pH on the dissolution of theophylline (300 mg) from tablets containing 15 percent Eudragit S100 resin. Key: ◆ , pH 7.4; ◇ , pH 4.0; ■ , pH 1.1.

dissolution profiles at pH 1.1. Release characteristics were found to be significantly different when comparing results in acidic media with those at pH 7.4.

Tablet pore size distributions as a function of the filler excipient employed are shown in Figure 5. The pore size distributions for the different tablet formulations were similar in shape. However, the pore size distributions for tablets containing different excipients varied in their displacement along the pore diameter axis. Pore size distributions as a function of tablet hardness for sucrose-containing tablets are pictured in Figure 6 which shows that tablet hardness has an inverse relationship with pore size. Additionally, total pore volumes, as well as pore size distributions decrease with increasing tablet hardness. The data in Figure 7 for sucrose containing tablets show that tablet hardness was inversely related to the total pore or void volume.

SUMMARY

The incorporation of Eudragit S100 resin into theophylline tablets containing directly compressible filler excipients, was shown to retard the release of the drug from the tablet matrix. Dissolution of drug from the tablet matrix was found to be dependent upon the type of filler excipient used, the amount of acrylic resin in the tablet and the pH of the dissolution medium employed. In acidic media, release rates decreased as polymer levels increased. The reverse was demonstrated at pH 7.4 in which

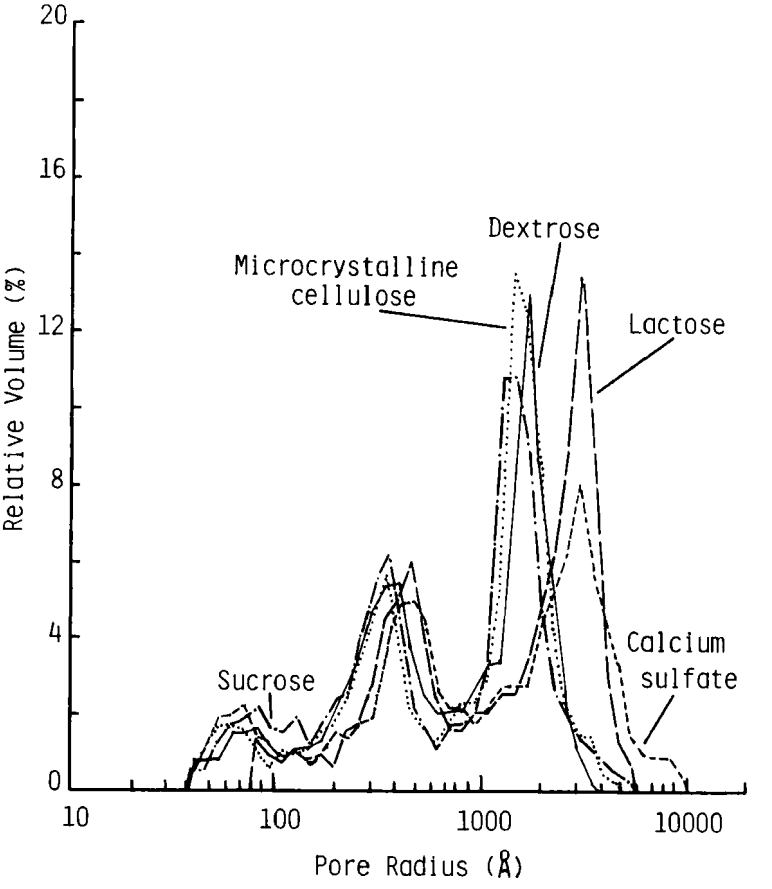

FIGURE 5.

The influence of the filler excipient on the relative volume of pores and pore size distributions for theophylline tablets containing Eudragit S100.

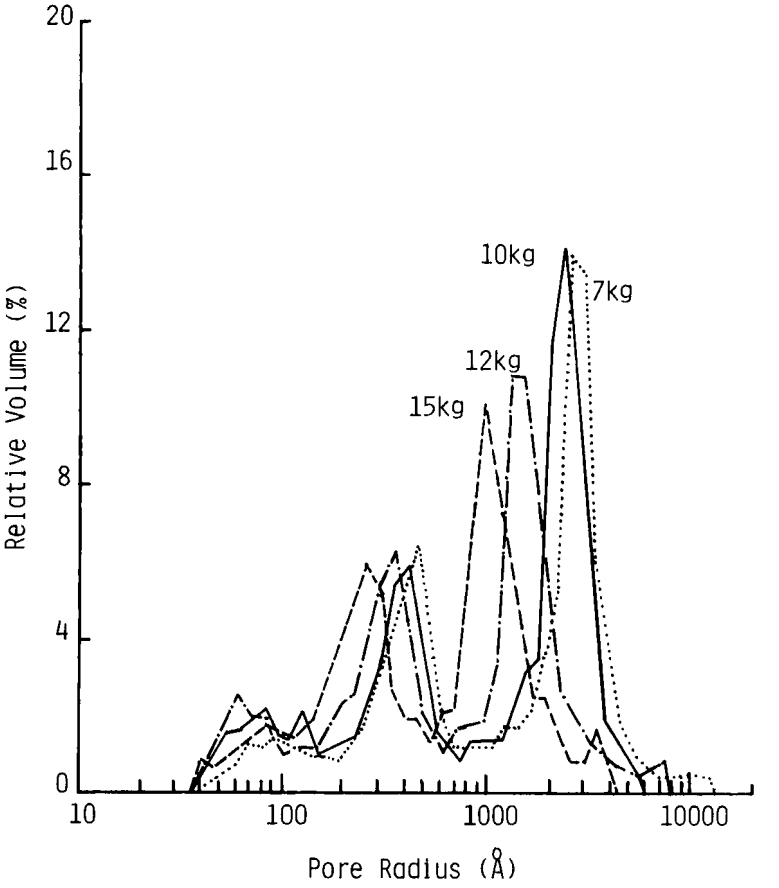

FIGURE 6.

The influence of tablet hardness on the relative volume of pores and pore size distributions for theophylline (300 mg) tablets containing sucrose and Eudragit S100.

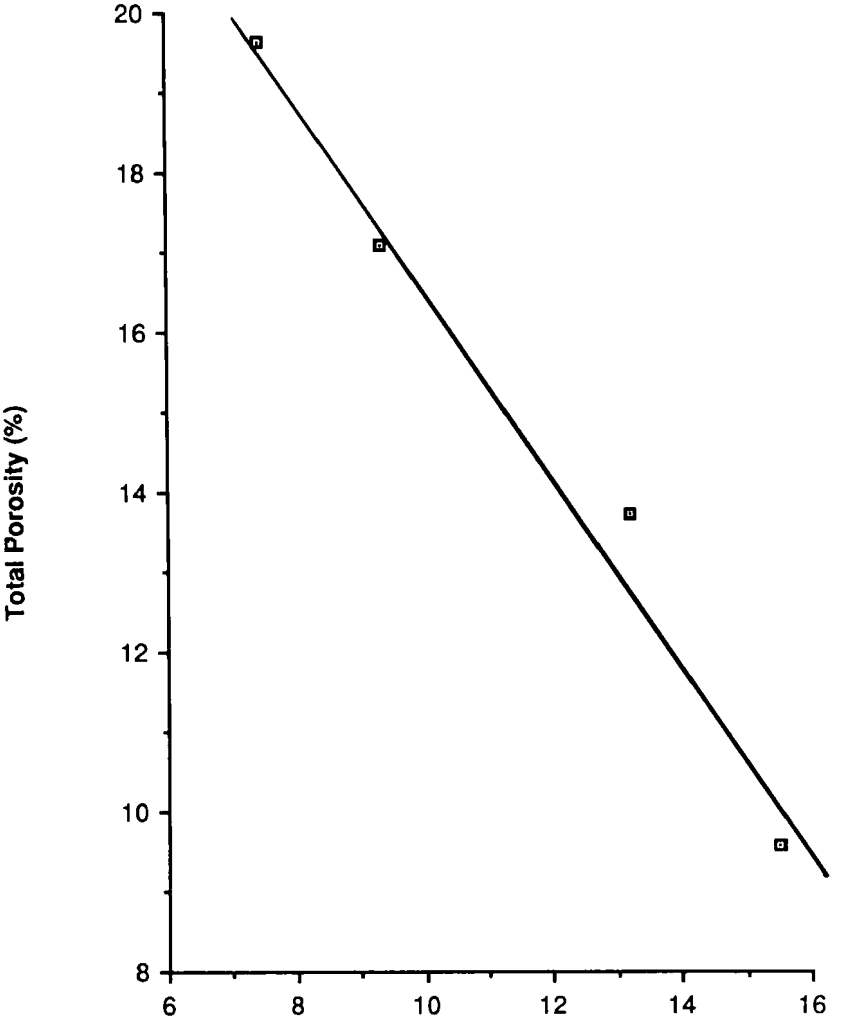

FIGURE 7.

Total porosity as a function of tablet hardness for theophylline tablets containing sucrose and Eudragit S100.

the polymer was freely soluble. The rate of dissolution increased at pH 7.4 as the level of polymer in the tablet was increased. The most rapid release profile was obtained from tablets containing microcrystalline cellulose. Although this excipient promoted the erosion of the dosage forms, the presence of the acrylic resin was sufficient to retard drug dissolution. Calcium sulfate 90 A/A that contained acacia as the binding agent, produced the slowest rate of drug release. Tablets containing the soluble excipients, sucrose and dextrose, and those formulated with calcium sulfate 90S produced release curves between the two extremes. Since the Eudragit S100 is soluble at neutral pH, potential bioavailability problems *in vivo* with drugs formulated into matrix tablets containing the acrylic polymer could possibly be eliminated.

REFERENCES

1. J.W. McGinity, C.G. Cameron, and G.W. Cuff, Drug Dev. Ind. Pharm. 9 (1&2), 57 (1983).
2. C.G. Cameron and J.W. McGinity, Drug Dev. Ind. Pharm. in press, (1986).
3. S.C. Khanna and P. Speiser, J. Pharm. Sci. 59:10, 1398 (1970).
4. F. Carli, G. Capone, I. Colombo, L. Magarotto, and A. Motto, Int. J. Pharm. 21, 317 (1984).
5. S. El-Fattah, M. El-Massik, and N. Salib, Drug Dev. and Ind. Pharm. 10, 809 (1984).
6. T. Higuchi, J. Pharm. Sci, 52, 1145 (1963).
7. M. Yoshida, M. Kumakura, and I. Kaetsu, J. Pharm. Sci. 68, 860 (1979).

8. S.B. Jayaswal, K.D. Gode, and S.K. Khamma, Aust. J. Pharm. Sci. 9, 22 (1980).
9. K. Lehmann, Manufacturing Chemisty and Aerosol News 44, 36 (1973).
10. K. Lehmann, Acta Pharm. Tech. 21, 255 (1975).
11. K. Lehmann, Manufacturing Chemist and Aerosol News 45, 48 (1974).
12. K. Lehmann, Acta Pharm. Fenn. 91, 225 (1982).
13. S.K. Baveja, K.V. Rango Rao, and A. Singh, Intl. J. of Pharmaceut. 19, 229 (1984).
14. K. Lehmann and D. Dreher, Int. J. Pharm. Tech. & Prod. Mfr. 2, 31 (1981).
15. Avicel PH101, FMC Corporation, Philadelphia, PA.
16. Fast Flo Lactose, Formost-McKesson, San Francisco, CA.
17. Emdex, Edward Mendell Co., Carmel, NY.
18. Destab Sugar, Desmo Chemical Co., St. Louis MO.
19. Destab Calcium Sulfate 90 A/A, Desmo Chemical Co., St. Louis, MO.
20. Carlo Erba Strumentazione 2000-1 Mercury Intrusion Porosimeter, Carlo Erba, Italy.