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CONTROLLED-RELEASE THEOPHYLLINE TABLET FORMULATIONS CONTAINING ACRYLIC RESINS, II. COMBINATION RESIN FORMULATIONS

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ABSTRACT

Theophylline tablet formulations containing a combination of cationic and anionic acrylic resins were prepared and evaluated. Equal amounts of Eudragit RSPM (cationic resin) and Eudragit L100 (anionic resin) were included at the 15% level (total polymer content) into the tablet formulations. Pressure-hardness profiles with theophylline-resin compacts (4:1) demonstrated that compacts containing the RSPM resin were the most compressible. The dissolution profiles for theophylline in acidic media showed slower release rates from tablets containing the combined resins than from those containing each of the single resins. It was proposed that this decrease in drug release rate was a result of a solid state interaction between the oppositely charged polymers.

As the amount of retardant in the matrix increased, the release rates in acidic media decreased. In pH 7.4 phosphate buffer, much faster release was seen due to the higher solubility of the Eudragit L-100 resin at this pH level. Tablet hardness between the range of 6.8 kg to 15 kg showed minimal influences on the dissolution rate. Recompression and relubrication of the tablet formulation containing both polymers, produced a decrease in release rates of theophylline from the tablet matrix.

INTRODUCTION

The resurgence of research and development of controlled-release dosage forms during the past ten years was discussed in depth in a recent article by Amsel, et al.[1] The present emphasis has not been restricted to oral delivery systems, since extensive research is also being conducted with transdermal, ocular, nasal, rectal, and parenteral dosage forms. Applications of biodegradable polymers in targeted drug delivery systems have also been reported in the literature.

Among the methods used to formulate oral controlled-release products, the retardation of drug release by the use of barriers to dissolution, continues to be the most widespread method. These barriers have been utilized in tablets, granules, beads, matrix systems and ion-exchange systems.[2,3,4] The matrix systems appear to be a most attractive approach, from an economic as well as from the process development and scale-up points of view. A multitude of retardant polymers including waxes, cellulose derivatives, high

molecular weight alcohols, glycols, and hydrogels have been reviewed by Lee and Robinson.[5] Solid dispersion techniques that in the past have been employed to accelerate dissolution rates have also been successfully employed to retard drug release for up to 11 hours.[6]

In an earlier report,[7] the authors discussed the retardant properties of four acrylic resins (Eudragits) in theophylline slow release tablets. The physicochemical properties of these resins had been previously described by Lehmann.[8] The present investigation is concerned with the properties of tablets containing a combination of an anionic and a cationic resin, Eudragit L100 and Eudragit RSPM, respectively.

EXPERIMENTAL

With the exception of the glidant used, fumed silicon dioxide,[9] the materials and methods used in this study were the same as previously reported.[7] Sucrose[10] was used as the filler excipient in the tablet formulations. Combination resin tablets were prepared to contain a 1:1 ratio of Eudragit RSPM[11] and Eudragit L100.[11] These polymers were present at the 15% level (total resin content), unless otherwise stated. With the exception of the dissolution studies conducted in phosphate buffer pH 7.4, the remaining studies were conducted in 900 ml of 0.1N hydrochloric acid containing 0.02% Tween 80, maintained at 37°C and agitated at 50 rpm, and employing the USP method I apparatus.

A comparison of method I and II was conducted and the influence of agitation intensity was studied with both test methods.

Compaction pressure-hardness profiles of drug and resin were developed using 500 mg compacts containing 98% theophylline and single resins at different ratios, with 1% fumed silicon dioxide and 1% magnesium stearate. For comparison purposes, Eudragit RLPM and Eudragit S100 were included in these studies. The powdered mixture was blended for five minutes in a twin-shell blender before compaction. These compacts were produced on a Stokes Model F single station tablet press, fitted with an Enerpac hydraulic load cell to record the pressure delivered to the lower punch during the compaction process. The granulation for the recompression studies was obtained by milling tablets that had been previously prepared by directly compressing the powder blend to 3-5kg. Seventy-five percent of the resultant granulation was in the 20 to 80 mesh size.

RESULTS AND DISCUSSION

A wide variety of theophylline-acrylic resin compacts containing different ratios of drug and polymer were evaluated for their compaction properties. A four to one ratio of drug to resin is reported in the compact formulations since drug and resin were present in this ratio in the tablet formulations. The compaction profiles for this formulation for the four resins are shown in Figure 1. Each data point represents the mean of ten determinations. Linear relationships were observed with all the

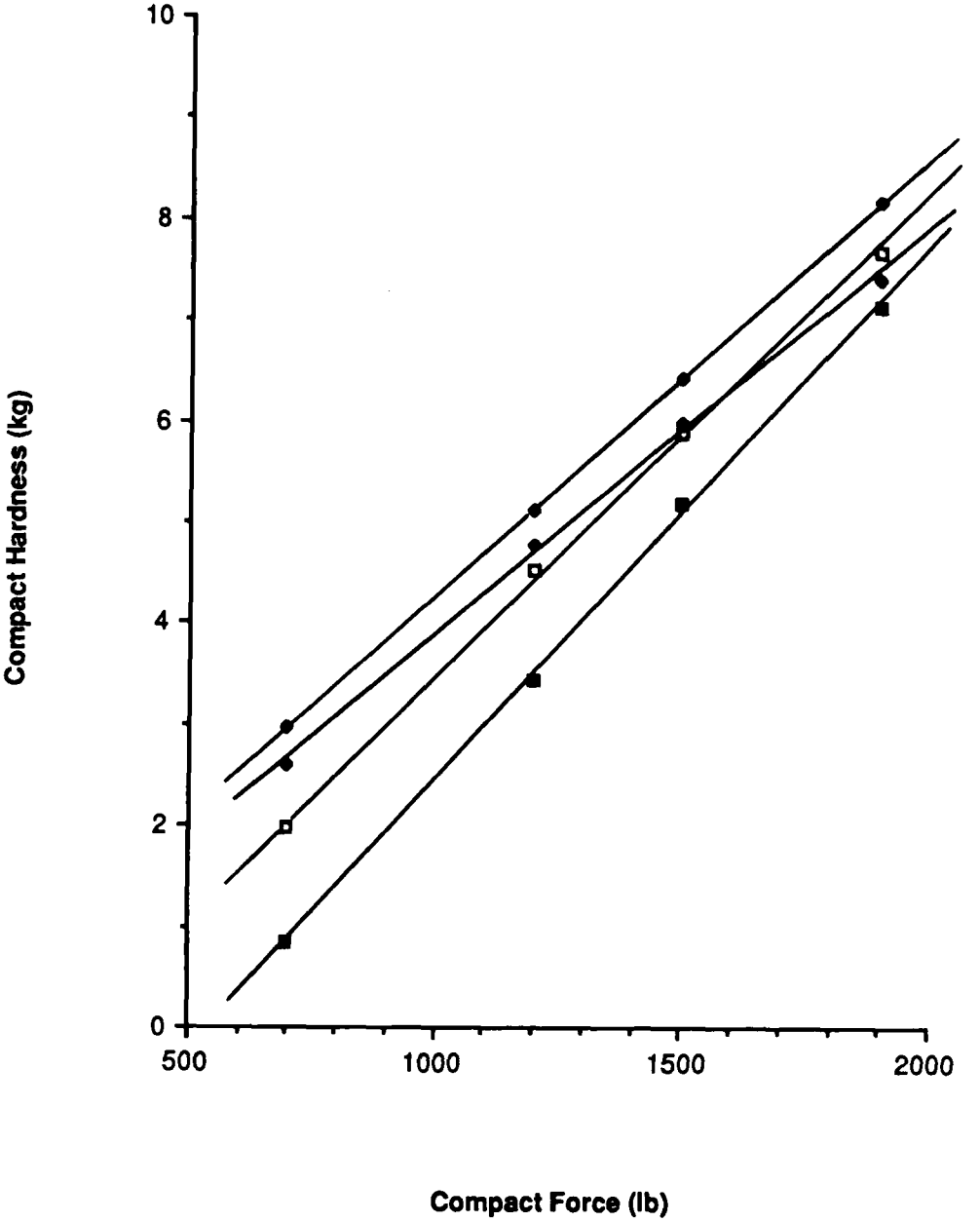

FIGURE 1.

Hardness-pressure profiles of theophylline and Eudragit-containing compacts (drug to resin 4:1) blended with the lubricant for five minutes. Each point represents the mean of ten measurements. Key: ◆ - Eudragit RSPM; ◇ - Eudragit RLPM; □ - Eudragit L100; ■ - Eudragit S100. All points, when comparing different copolymers, all points were significantly different at $p > 99.9\%$

polymers studied. The Eudragit RSPM polymer appeared to be the most compactable and the Eudragit S100, the least compactable. Over the pressure range investigated, no lamination was seen in any of the compacts.

In an earlier report,[7] dissolution studies with controlled release theophylline tablets demonstrated that the Eudragit RSPM resin, with quaternary ammonium groups, showed excellent retardant properties. The Eudragit L100 resin, an anionic polymer, demonstrated little ability in retarding drug dissolution. A combination of both resins in a 1:1 ratio was utilized at the 15% (total resin content) level, and the release profiles are illustrated in Figure 2. A greater retardant effect was seen with the combination resin than with either single resin formulation. It is proposed that the slower erosion of the matrix was caused by a solid-state interaction between the positive and negative charges on the solid resins. This could account for the slower erosion rate of the tablet matrix containing the combination resins. The substitution of fumed silicon dioxide for talc as the glidant in the tablet formulation was necessary because of the poor flow properties of the combination resin tablet formulation. Although talc was used successfully with single resin formulations,[7] this was not the case when the combination polymers were employed. Fumed silicon dioxide that often has been reported in the literature to overcome flow problems due to static charge, was very effective in overcoming problems caused by the oppositely

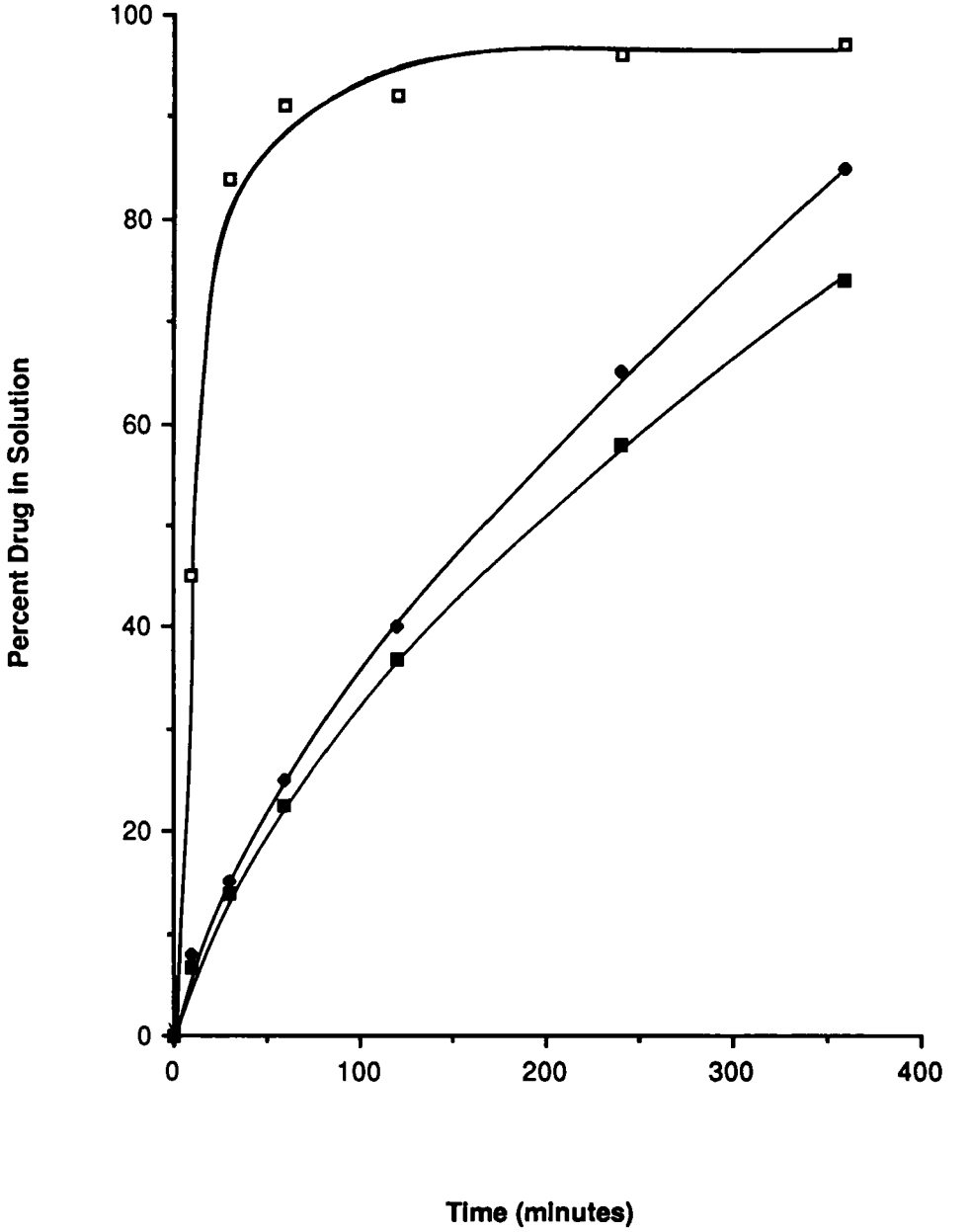

FIGURE 2.

Influence of resin type on the dissolution properties of theophylline (300 mg) from tablets in 900ml of acidic medium (see Experimental for details). Key: □- Eudragit L100; ◆- Eudragit RSPM; ■- Eudragit RSPM/L100 combination.

charged polymers. The inclusion of sucrose, a non-hygroscopic filler excipient, was found to produce superior dosage forms compared to tablets reported earlier containing dextrose.[7]

The influence of agitation conditions on drug release and tablet erosion was investigated using the basket method. The dissolution profiles appear in Figure 3. Similar results were found with the paddle method, and a comparison of the results from both methods are shown in Figure 4. When agitation conditions were increased from 50 RPM to 125 RPM, faster erosion of the tablet matrix was evident and the release rate of theophylline was approximately doubled.

The influence of tablet hardness on the dissolution process is shown in Figures 5 and 6. Drug release from the tablet with a hardness of 4 kg was quite rapid. The friability value of three percent for this tablet formulation verified that it had limited potential for future development. It was interesting to note that the drug release profiles from tablets with hardness values between 6.8 and 15 kg were very similar. The tablet friability for these tablets varied from 0.45 percent to 0.25 percent, respectively. As suggested by the plateau in the profiles of Figure 6, the influence of tablet hardness on the theophylline release rate was minimal in this hardness range.

The influence of medium pH and resin levels on the dissolution of theophylline from Eudragit-containing tablets is shown in Figures 7 and 8. There was an obvious effect in acidic

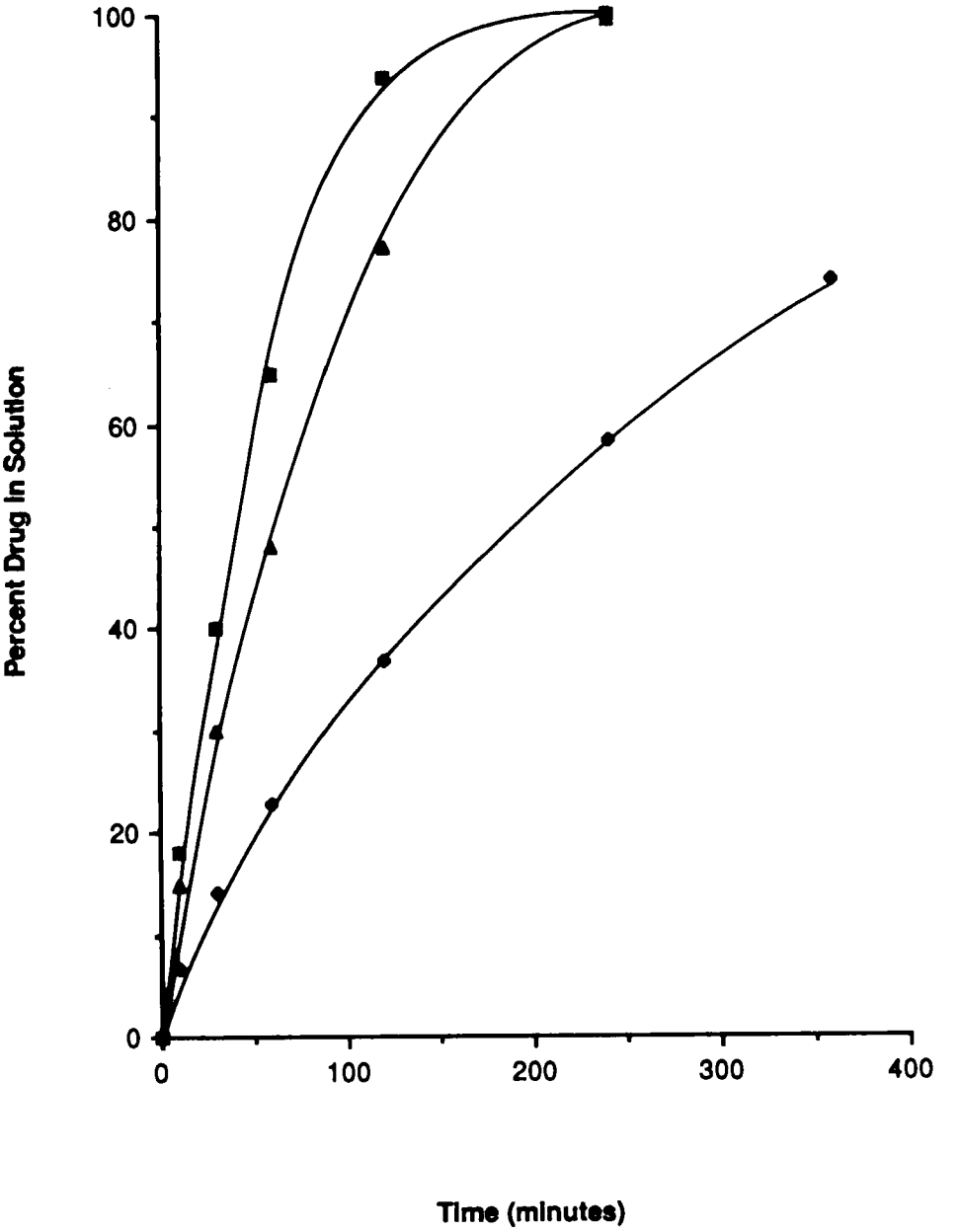

FIGURE 3.

Influence of stirring speed on the dissolution rate of theophylline (300 mg) from tablets containing Eudragit resins (RSPM and L100) in 900ml of acidic medium (see Experimental for details). Key: ■- 200 RPM; ▲- 125 RPM; ◆- 50 RPM.

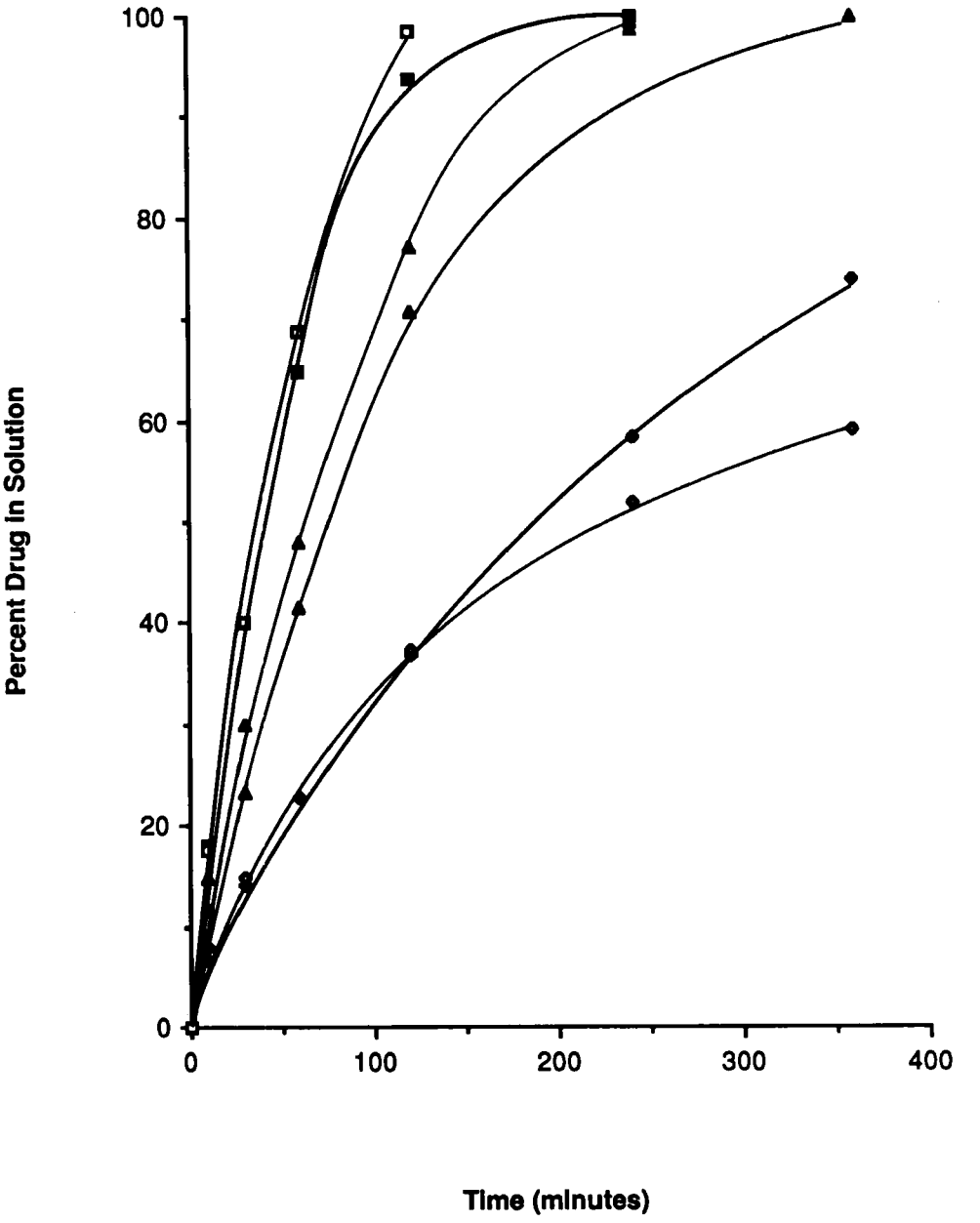

FIGURE 4.

Comparison of dissolution test method and the effect of stirring speed on the dissolution rate of theophylline (300 mg) from tablets containing Eudragit copolymers (RSPM and L100) in 900ml of acidic medium. Key: ■ - 200 RPM Method I; □ - 200 RPM Method II; ▲ - 125 RPM Method I; △ - 125 RPM Method II; ◇ - 50 RPM Method I; ◆ - 50 RPM Method II.

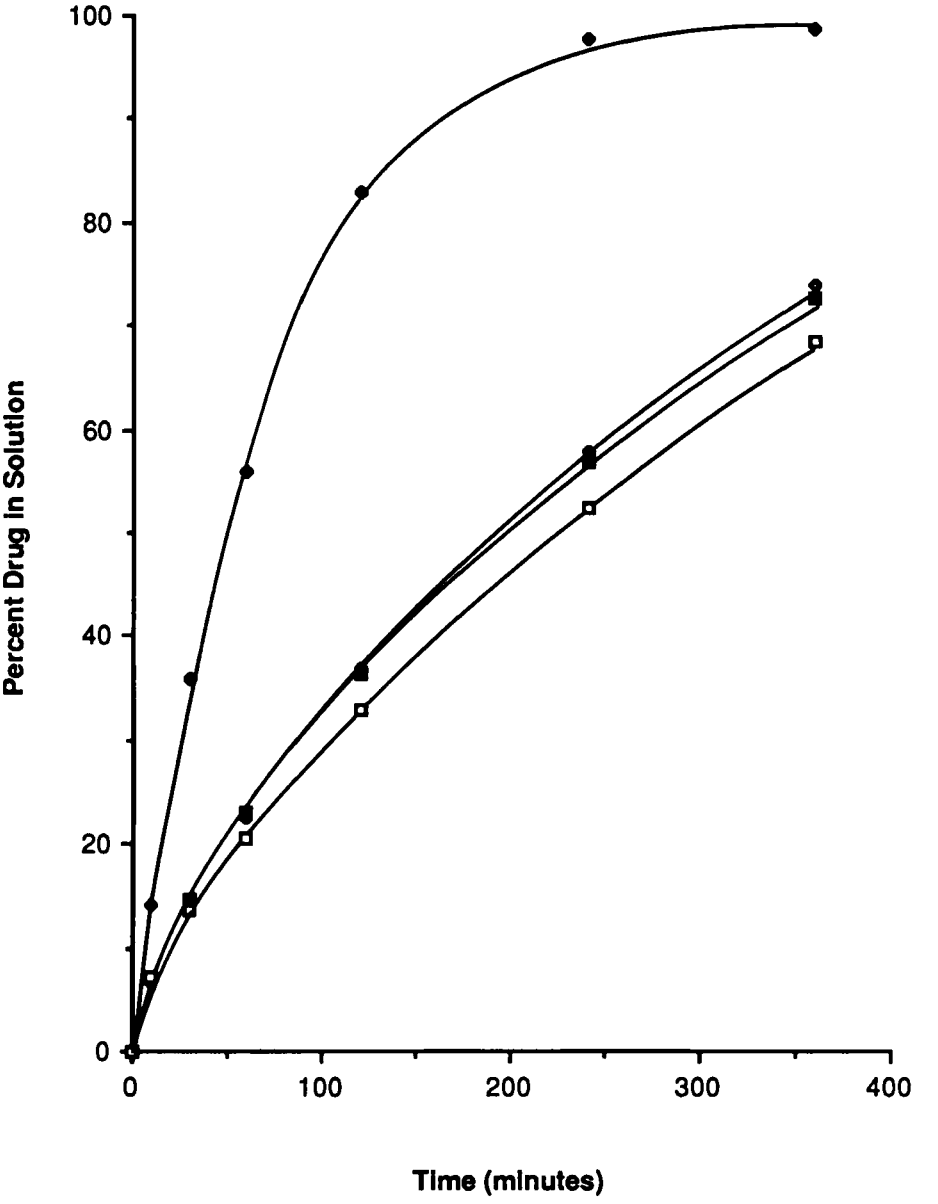

FIGURE 5.

Influence of tablet hardness on the release rate of theophylline (300 mg) from tablets containing Eudragit resins (RSPM and L100) in 900ml of acidic medium (see Experimental for details).
Key: ◆- 4 kg; ◇- 6.8 kg; ■- 9.8 kg; □- 15 kg.

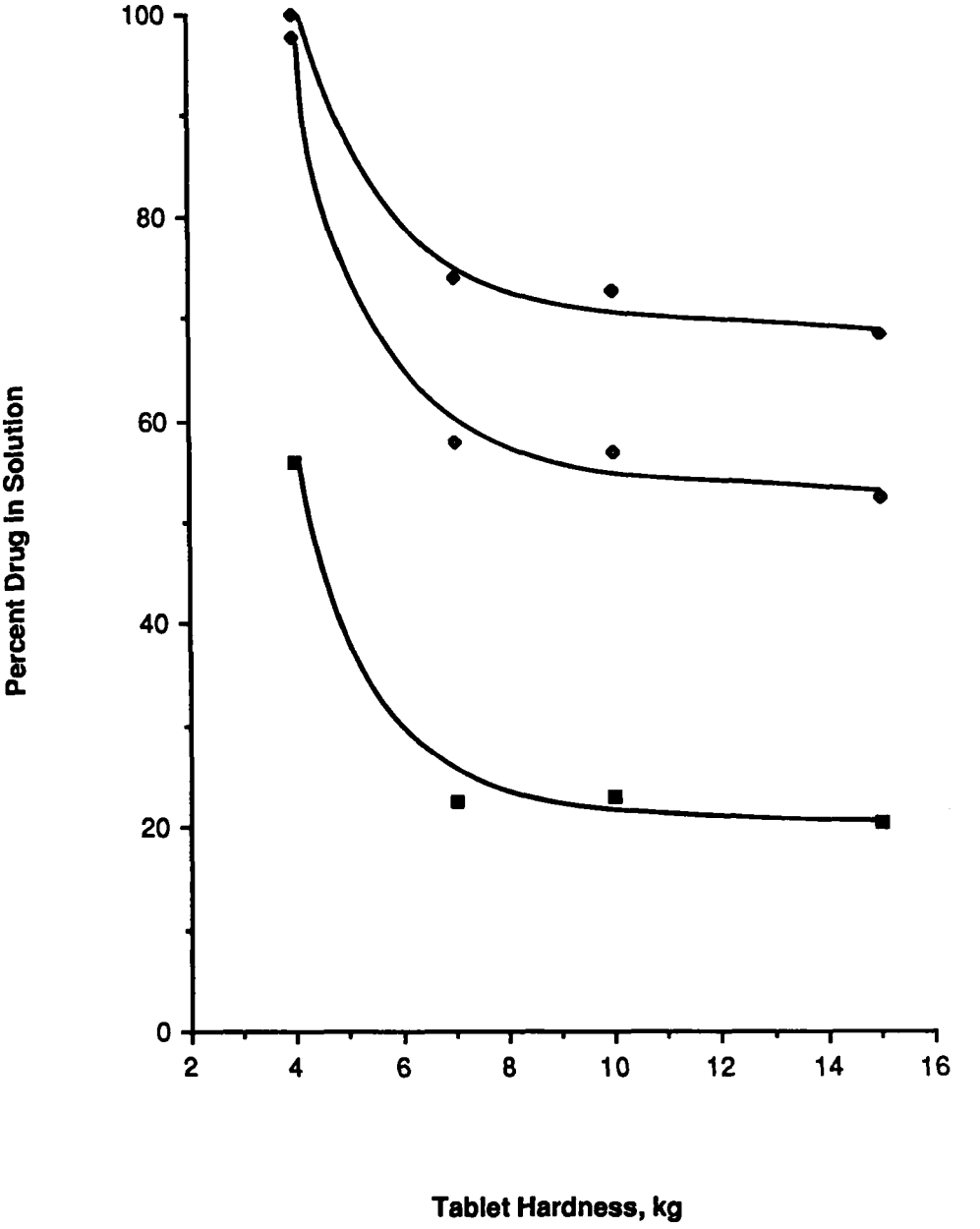

FIGURE 6.

Summary of the influence of tablet hardness on the dissolution of theophylline (300 mg) from tablets containing a combination of Eudragit resins (RSPM and L100) in 900ml of acidic medium (see Experimental for details).
Key: ◆- 360 minutes; ◇- 240 minutes; ■- 60 minutes.

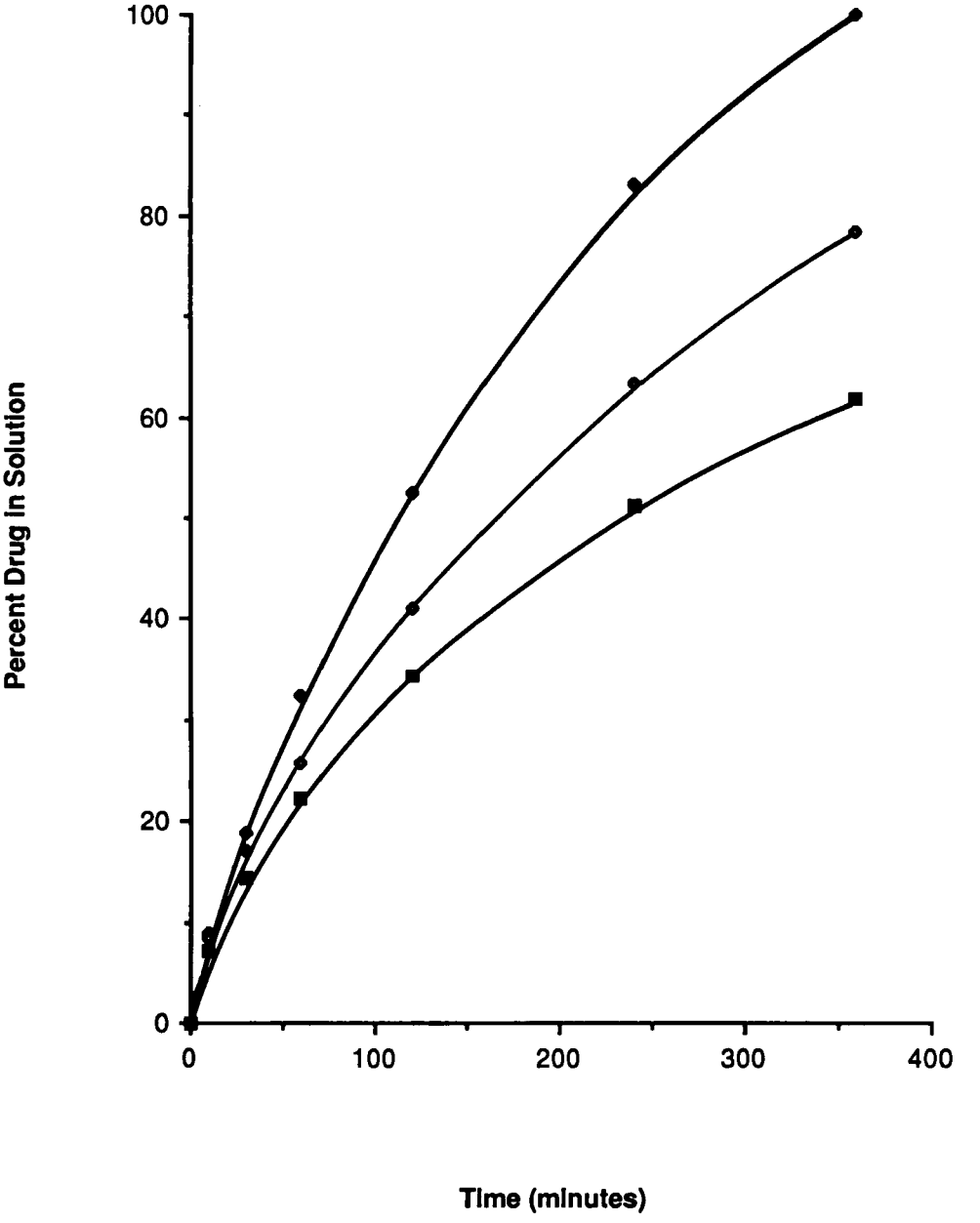

FIGURE 7.

The influence of Eudragit polymer level (RSPM and L100) on the release rate of theophylline (300 mg) from tablets in 900ml of acidic medium (see Experimental for details).
Key: ◆ - 5% resin; ◇ - 10% resin; ■ - 15% resin.

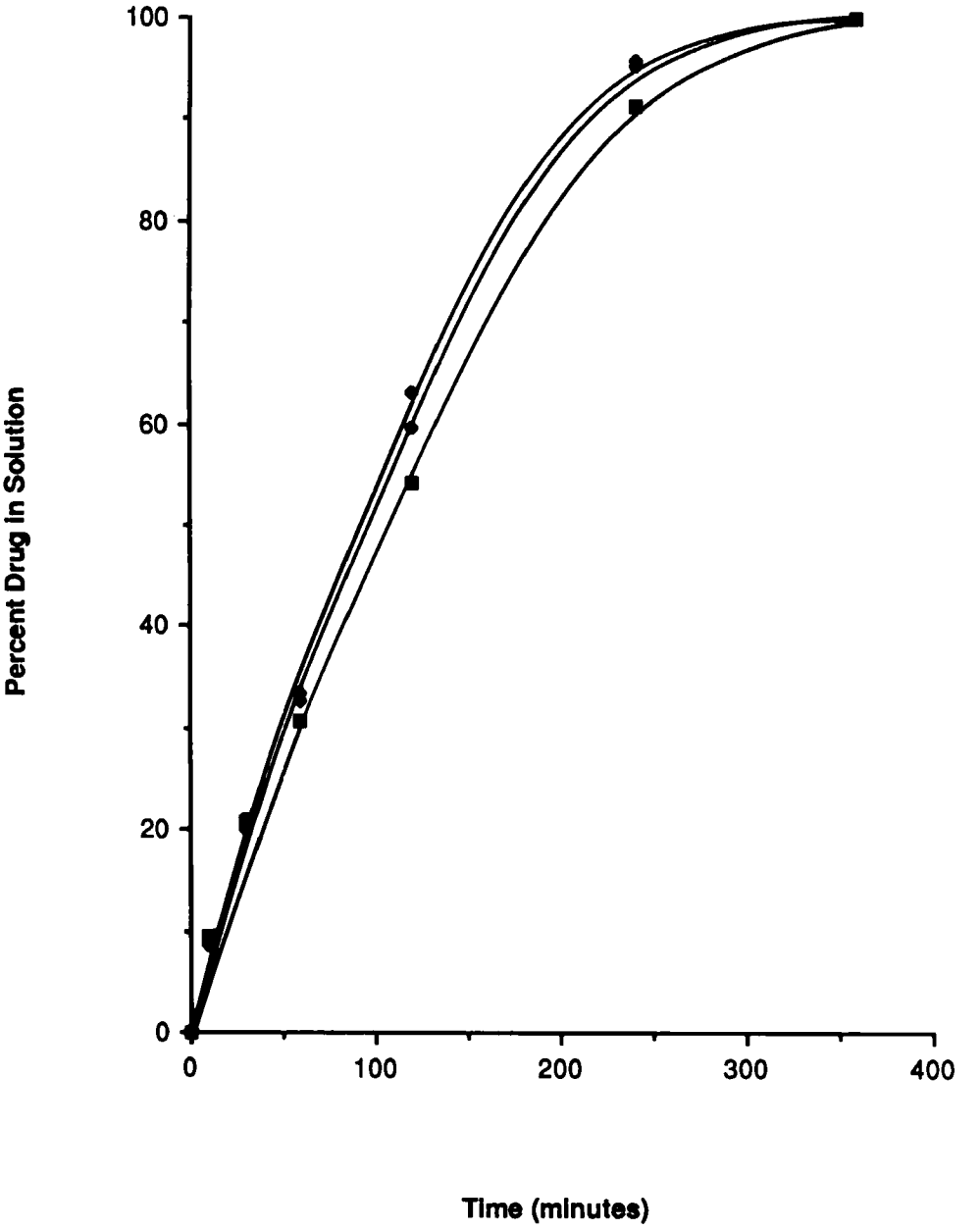

FIGURE 8.

The influence of Eudragit polymer level (RSPM and L100) on the release rate of theophylline (300 mg) from tablets in 900ml of pH 7.4 phosphate buffer (see Experimental for details).
Key: ◆- 5% resin; ◇- 10% resin; ■- 15% resin.

medium. As the total level of polymers in the tablet was increased from 5 to 15 percent, the release rates of theophylline from the tablet matrix decreased. No significant drug dissolution retardation effect was seen with the three combination resin formulations in phosphate buffer at pH 7.4. The retardant effect of the resins was probably absent due to the higher solubility of the Eudragit L100, since it will dissolve above pH 6.0. The dissolution of the Eudragit L100 resin at pH 7.4, resulted in a more porous tablet matrix which broke apart more readily upon agitation. The net result was a faster release of drug into the phosphate buffer.

The profiles in Figures 9 and 10 demonstrate the influence of recompression on the dissolution rate of theophylline from the matrix tablets. Recompression without further addition of a lubricant produced a 30% to 40% reduction in the drug release rate. In this case, stronger bonds were probably formed between the granules resulting in a decrease in the erosion rate of the tablet. Where the granules had been relubricated with magnesium stearate prior to final compaction, a slight increase in drug release was seen (Figure 10). The standard deviations for the drug content and tablet weights for both the recompressed and the relubricated-recompressed tablets were less than one percent. The friability values for all formulations evaluated were less than 0.2 percent.

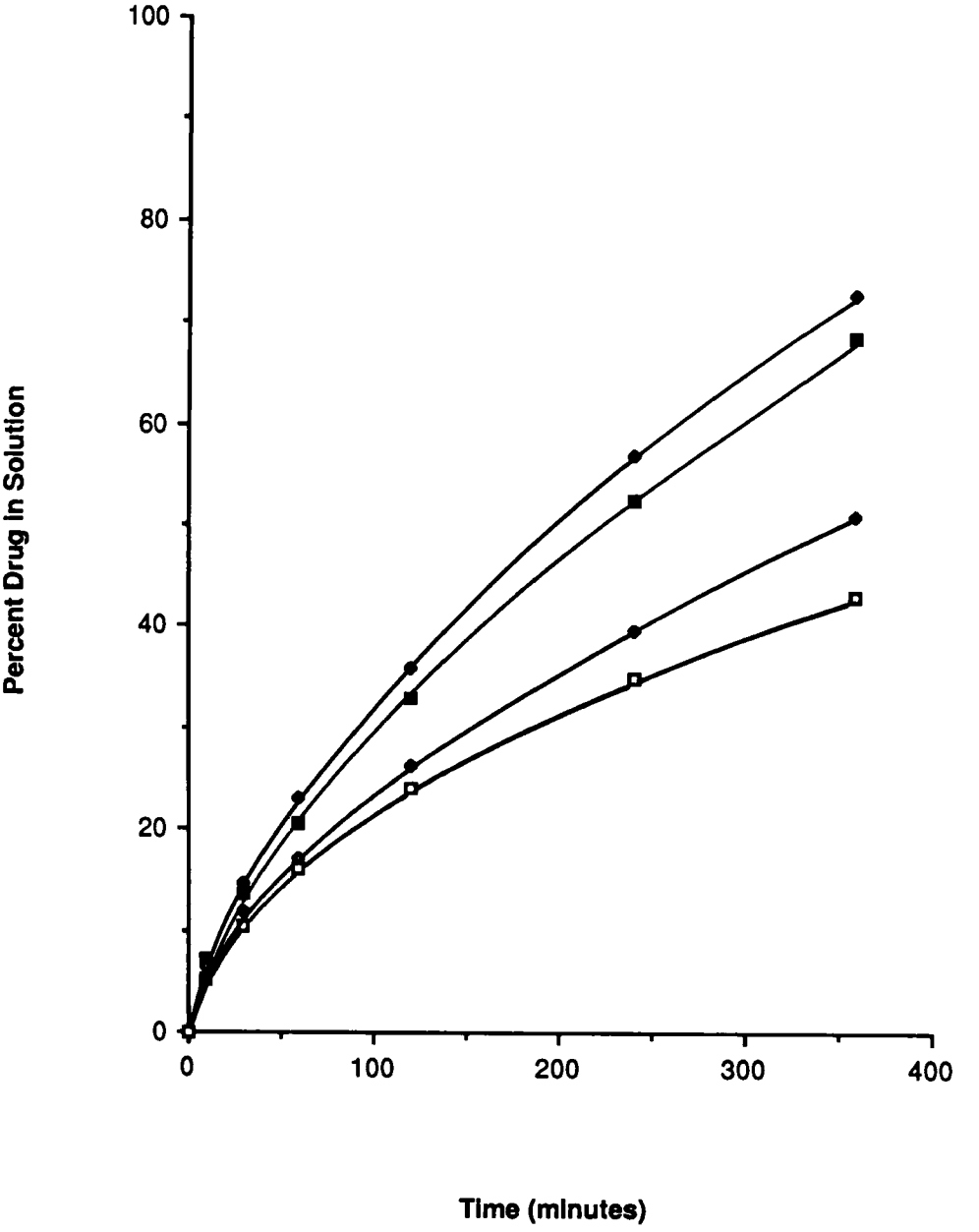

FIGURE 9.

The influence of recompression on the release rate of theophylline (300 mg) from tablets containing Eudragit polymers (RSPM and L100) in 900 ml of acidic medium (see Experimental for details). Key: ◆ - 9.8 kg; ◇ - 15.6 kg; ■ - 9.4 kg (recompressed); □ - 15.3 kg (recompressed).

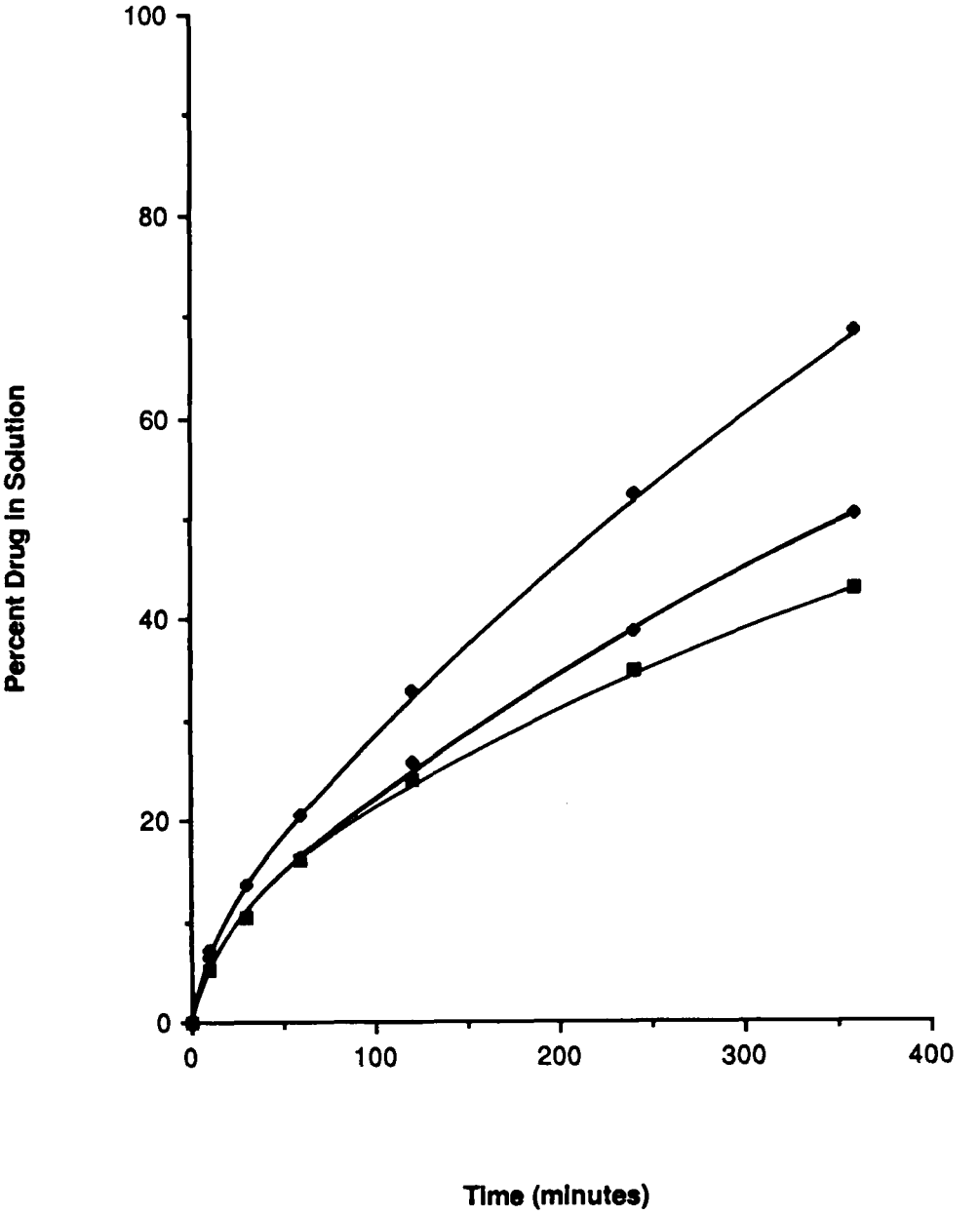

FIGURE 10.

The influence of recompression and relubrication on the dissolution rate of theophylline (300 mg) from tablets containing Eudragit copolymers (RSPM and L100) in 900ml of acidic medium (see Experimental for details). Key: ◆- 15.6 kg (directly compacted); ◇ - 15.1 kg (recompressed and relubricated); ■ - 15.3 kg (recompressed).

SUMMARY

The combination of cationic and anionic resins as a retardant matrix in a theophylline tablet formulation was demonstrated to have good potential in a controlled-release dosage form. The retardant effects in acidic medium were dependent upon the levels of acrylic resin polymer in the dosage form. The more rapid release at pH 7.4 was due to the high solubility of the Eudragit L100 at this pH. The release rates at pH 7.4 were very similar for tablets containing from 5 to 15 percent resin. Compactibility studies showed good compaction properties for theophylline in combination with the Eudragit resins. Although matrix erosion was found to increase as agitation increased, the drug release rate of drug from the tablets was not adversely influenced by tablet hardness in the 6.8-15kg range. Recompression from ground tablets and relubrication of the granulation produced a decrease in dissolution rate when compared to the original tablet formulation.

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