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CONTROLLED-RELEASE THEOPHYLLINE TABLET FORMULATIONS CONTAINING ACRYLIC RESINS. I. DISSOLUTION PROPERTIES OF TABLETS

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ABSTRACT

The dissolution properties of controlled-release theophylline tablets containing acrylic resins are presented. Four different resins (Eudragit RSPM, RLPM, S100 and L100) were incorporated into theophylline tablets by direct compression techniques and the properties of the resulting dosage form were evaluated in dilute acid, buffer media pH 4.0 and simulated intestinal media pH 7.5. Tablets (500 mg) containing 300 mg of theophylline were prepared with each of the four resins and compressed to a hardness level of 6.5 to 7.5 kg. Excellent flow properties, weight uniformity and drug content uniformity were observed with all tablet formulations. Preliminary data suggest that three of the four resins tested showed great promise as a retardant in a matrix controlled drug delivery system. The dissolution properties of three commercially available sustained-release theophylline tablets were also determined. A comparison of profiles from Theodur^{R} (300 mg) in acid and simulated

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intestinal media showed a similarity in release properties to those of theophylline in tablets containing the RLPM resin.

INTRODUCTION

With the current worldwide decline in the numbers of new drug entities reaching the market place, there has been a resurgence of interest in the development of novel drug delivery systems for the presently available pharmaceutical agents. Numerous articles have been published to point out the variations in drug bioavailability due to formulation factors and physico-chemical properties of the active ingredient in controlled-release dosage forms.

For drugs formulated into long-acting dosage forms, the release of drug from the delivery system ideally should be at a controlled and predictable rate. The return of interest in theophylline as a major asthma drug has lead to a considerable increase in the number of controlled-release theophylline dosage forms marketed. Upton et al, (1,2) have evaluated the absorption of some commercial enteric-coated theophylline products (1) and commercial sustained-release theophylline products (2). Two of the three sustained-release products showed a statistically indistinguishable bioavailability from that of the standard uncoated tablet. Differences in peak concentrations and rates of absorption were however, observed with some of these products. In vitro dissolution tests of the enteric-coated tablets in simulated gastric juice showed that less than 1% of the drug was released after one hour. In an earlier report, these authors stated that the rationale that enteric-release preparations might protect theophylline from degradation by gastric

acid has little merit, since uncoated tablets and solutions usually yield 100% bioavailability when compared to intravenous solutions (3). Significant differences in bioavailability of theophylline were reported by Weinberger et al, (4) for coated tablets, sustained-release bead filled capsules and sustained-release tablets.

The present report is the first in a series of papers on the development and evaluation of controlled-release theophylline tablets prepared by direct compression techniques. Various acrylic resins have been evaluated for their retardant effects on drug release from the dosage form. The use of acrylic coatings in the manufacture of controlled-release tablets has been the subject of numerous papers by Lehmann (5-7). Sustained-release tablet formulations of propranolol and acrylic resins were prepared by Jayaswal et al, (8) by employing wet granulation techniques.

The dissolution properties of controlled-release theophylline tablets containing four types of acrylic resins will be studied and compared with three commercially available controlled-release theophylline tablets.

EXPERIMENTAL

Materials - The following materials were used: acrylic resins[1] including Eudragit RSPM®; Eudragit RLPM®; Eudragit S100® and Eudragit L100®; fumed silicon dioxide[2], dextrose[3], magnesium

[1] Rohm Pharma, Darmstadt, West Germany
[2] Cabosil®, Cabot Corp., Boston, MA
[3] Emdex®, Edward Mendell Co., Carmel, NY

stearate[4] and talc[5]. All other chemicals and solvents were reagent grade and were used as received.

Methods - From preliminary screening evaluations of controlled-released theophylline tablets containing acrylic resins, the following prototype formulation was developed.

Theophylline	60%
Acrylic resin	15%
Dextrose	23%
Talc	1.5%
Magnesium stearate	0.5%

The acrylic resin and theophylline were blended for 10 minutes in a twin shell blender. Dextrose was then added and the mixture was blended for 5 minutes. The granulation was blended for an additional 5 minutes following the addition of the glidant and the lubricant.

Tablets (500 mg) of the above formulation were compressed using direct compression techniques with a Stokes Model F single punch tablet machine using 7/16" flat face bevel edge punches. The dissolution properties of the controlled-release theophylline tablets containing the acrylic resins were compared to those of the commercially available products in dilute acid, buffer pH 4.0 and simulated intestinal media pH 7.5. The experimental conditions for the in vitro dissolution tests were the same as those previously described by McGinity and Harris (9).

[4] Alfa Division, Ventron Corp., Danver, MA
[5] Matheson Coleman and Bell, Norwood, OH

RESULTS AND DISCUSSION

The structures, solubilities and other physical properties of the four acrylic resins employed in the tablet formulations, have been previously described by Lehmann (6). The RSPM and RLPM types of Eudragit are insoluble in water and their swelling and permeability properties are independent of the pH conditions in the gastrointestinal tract. The L100 and S100 grades of Eudragit are soluble above pH 6 and 7 respectively.

Tablets (500 mg) containing 300 mg of theophylline were prepared with each of the four resins. Excellent flow properties, weight

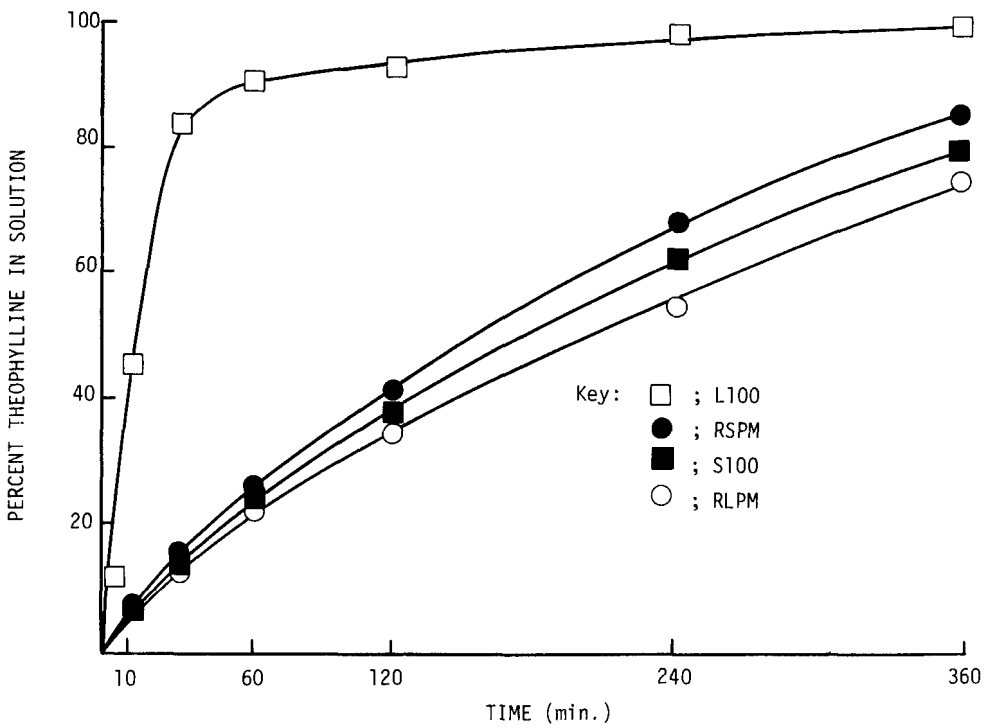

Figure 1—Influence of resin type on the dissolution rate of theophylline (300 mg) from tablets in 0.1N hydrochloric acid containing 0.02% Tween 80, at 37° and stirred at 50 r p m.

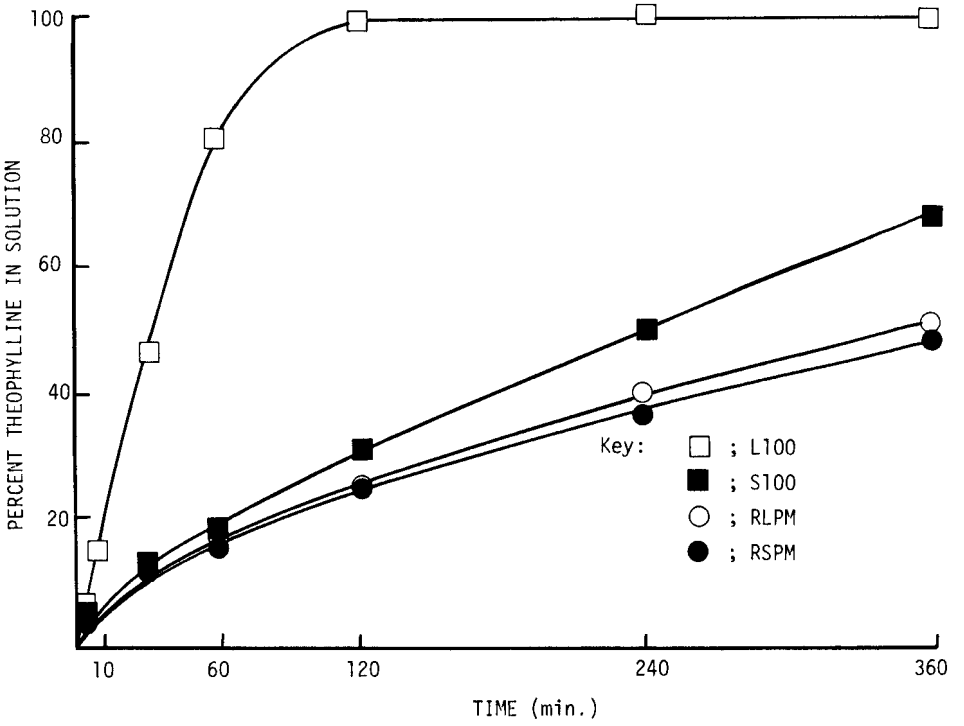

Figure 2—Influence of resin type on the dissolution rate of theophylline (300 mg) from tablets in buffer media, pH 4.0 at 37° and stirred at 50 r p m.

uniformity and drug content uniformity were observed with all tablet formulations. The tablet hardness levels were in the range of 6.5 to 7.5 kg. The dissolution profiles from tablets containing the acrylic resins in dilute acid, buffer pH 4.0 and simulated intestinal fluid pH 7.5, are shown in Figures 1, 2 and 3 respectively.

The Eudragit resins RLPM and RSPM are copolymers synthesized from acrylic and methacrylic acid esters with a low content of quaternary ammonium groups. Slow dissolution rates of theophylline tablets containing resins RLPM and RSPM, were found in all media

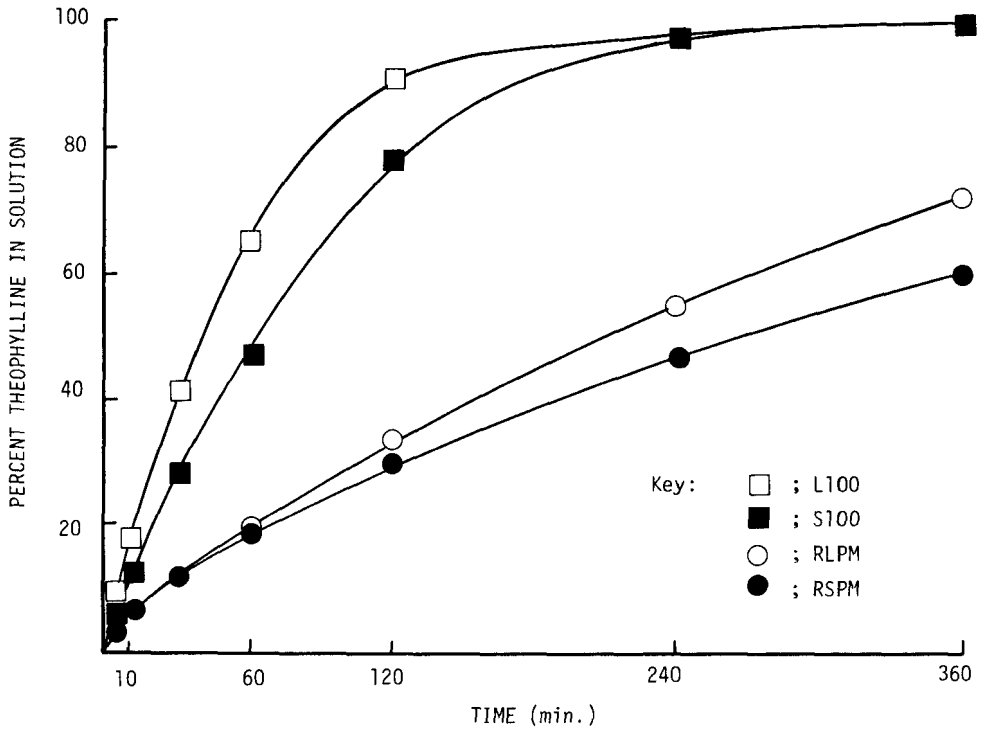

Figure 3—Influence of resin type on the dissolution rate of theophylline (300 mg) from tablets in simulated intestinal media, pH 7.5 at 37° and stirred at 50 rpm.

studied (Figures 1-3). The RLPM resin has been reported to be more permeable in digestive juices than the RSPM polymer (6). The Eudragit L100 resin, being an anionic polymer synthesized from methacrylic acid and methacrylic acid methyl ester, is insoluble in both acid and purified water and soluble in media above pH 6. Poor retardant properties were found however, in all media for tablets containing Eudragit L100. These profiles suggest that the tablets were quite permeable to the dissolution media.

The Eudragit S100 resin has similar structural and solubility properties to those of the L100 resin. The solubility is also pH

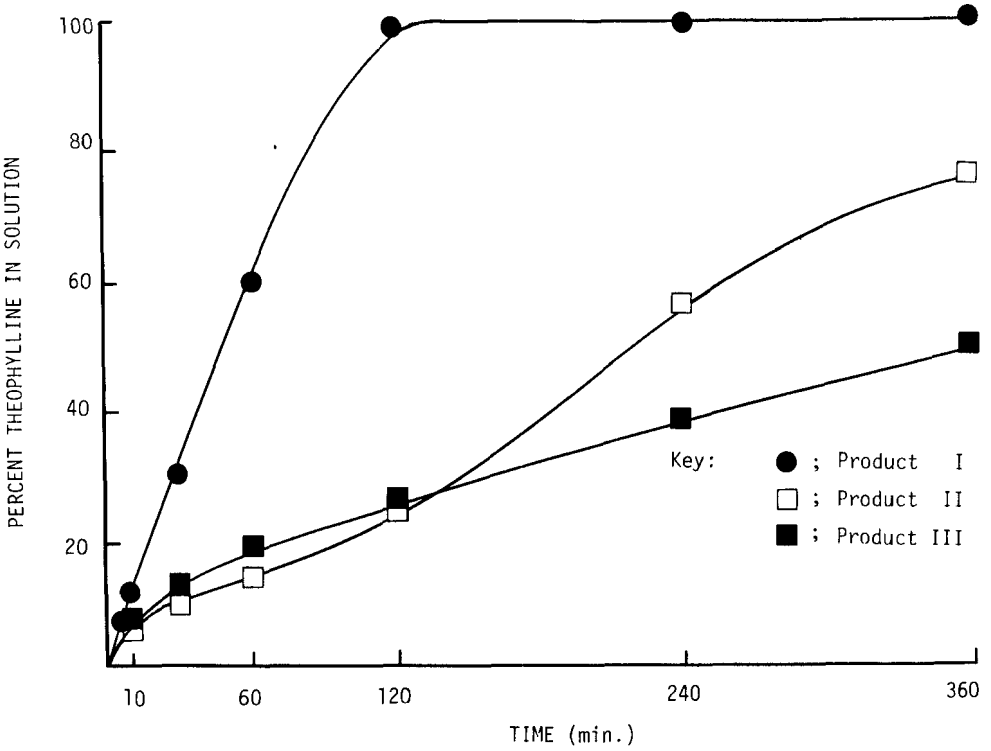

Figure 4—Dissolution profiles of theophylline (300 mg) from three commercial controlled-release tablets in 0.1N hydrochloric acid containing 0.02% Tween 80, at 37° and 50 r p m.

dependent and is freely soluble in simulated intestinal media and buffer media above pH 7.0. Unlike the L100 resin, the release of theophylline from tablets containing the S100 resin was in good agreement with the solubility properties of the resin. Slow release of drug was seen in acidic media and buffer media pH 4.0 (Figures 1 and 2 respectively). Slower release rates of theophylline were seen in buffer media pH 4.0 than in acid or simulated intestinal media for tablets containing S100, RLPM and RSPM resins.

The dissolution properties of three commercially available sustained-release theophylline tablets containing 300 mg drug

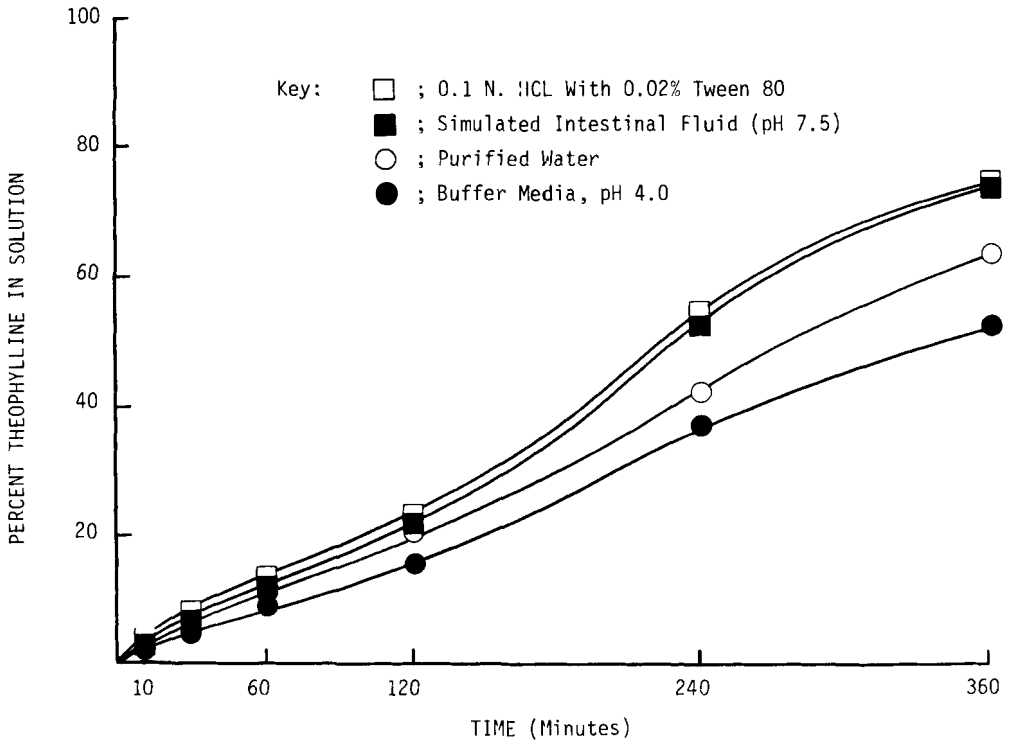

Figure 5—Influence of media on the dissolution properties of theophylline from Theodur^{R} (300 mg) tablets at 37° and 50 r p m.

were studied in dilute acid. The profiles of these products appear in Figure 4. The wave-like appearance from product II (Theodur^{R}, 300 mg) is in good agreement with previously reported data of Jonkman et al., (10). It is interesting to note in Figure 5, where the influence of dissolution media on drug release from Theodur tablets is reported, that the data for the acidic media and simulated intestinal fluid are superimposable as is the case for the theophylline tablets containing the RLPM resin. The dissolution rate of drug from Theodur^{R} tablets was also slower in buffer pH 4.0 as was experienced with the acrylic resins (S100, RLPM and RSPM). A comparison of the dissolution profiles

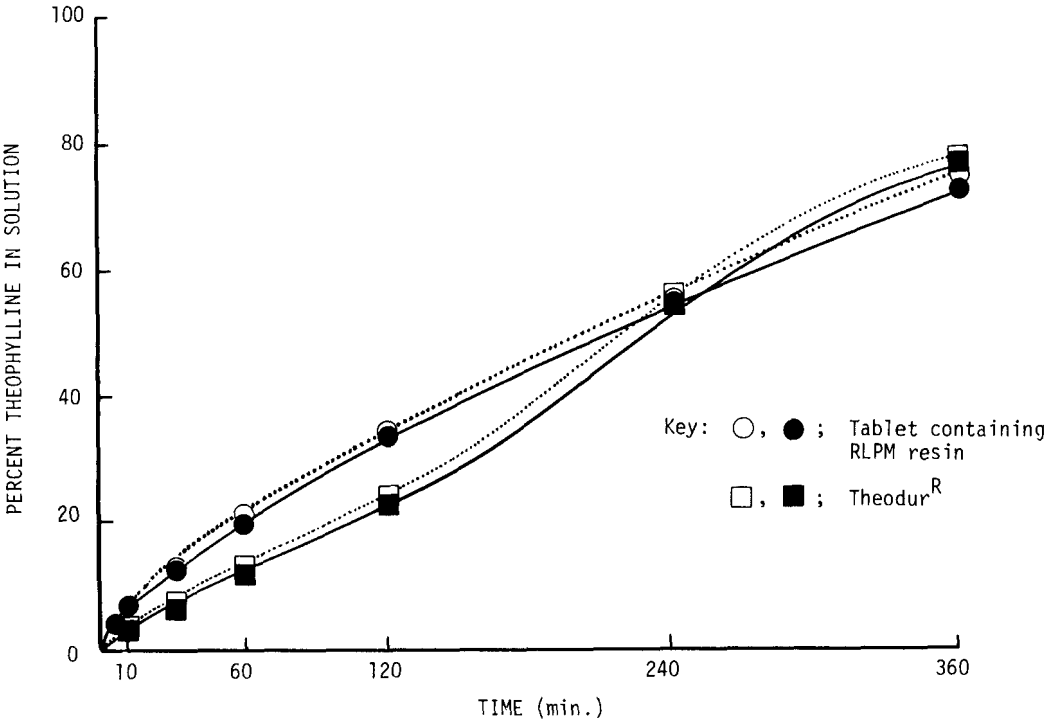

Figure 6—Comparison of dissolution profiles of theophylline from Theodur^{R} (300 mg), and theophylline tablets containing the Eudragit RLPM resin, in 0.1N hydrochloric acid containing 0.02% Tween 80 (open symbols) and simulated intestinal media, pH 7.5 (closed symbols).

of Theodur^{R} tablets with the controlled-release theophylline tablets containing the RLPM resin in dilute acid and simulated intestinal juice is shown is Figure 6.

By altering the ratio of acrylic resin : dextrose, it was possible to increase or decrease the rate of drug dissolution. Slower release rates were seen as the content of resin was increased. The compressibility of each resin was also found to be quite different and a 1:1 ratio of drug and resin was found to have optimal compression characteristics for all resins. These topics will be addressed in detail in future reports.

In summary, preliminary data on the application of acrylic resins in controlled-release theophylline tablets have been presented. Tablets containing the acrylic resin were easily prepared by direct compression of the drug and excipient blends. No problems were experienced with flow, weight uniformity and compression characteristics of the granulation. Dissolution properties of three commercially available sustained-release theophylline tablets were examined and the profiles for Theodur^R were found to be very similar to those from theophylline tablets containing the RLPM resin.

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