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# EFFECT OF EUDRAGIT RESINS AND DIBASIC CALCIUM PHOSPHATE ON THE COMPACTION AND DISSOLUTION BEHAVIOR OF DIRECTLY COMPRESSIBLE CONTROLLED-RELEASE THEOPHYLLINE TABLET

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## ABSTRACT

The compaction behavior and release property of tablets made by the combined formulations of Eudragit RLPM and RSPM with or without dibasic calcium phosphate anhydrous (DCPA) using direct compaction were examined. The larger the amount of Eudragit RSPM or DCPA the higher the value of the tensile strength. A linear relationship was found in the logarithm of tensile strength plotted against the porosity of the compacts. The Heckel plot was also used to evaluate the compaction behavior of tablets. The results indicate that Eudargit RSPM and DCPA are responsible for the good compressibility of compacts. The contact angle of tablets without DCPA became smaller with an increase in the Eudragit RSPM, but exhibited a higher contact angle than tablets with DCPA. The controlled release

behavior of theophylline from tablets without DCPA was found and showed a pH-independent property, whereas tablets with DCPA were pH-dependent and exhibited a faster dissolution than tablets without DCPA. The result suggests that controlled-release and better compressible tablets can be prepared by adjusting the combination ratios of Eudragit RLPM and RSPM with or without DCPA by direct compression.

## INTRODUCTION

Eudragits are a variety of acrylic resins and are widely used for the pharmaceutical industry as a coating material to prepare film-coated, enteric-coated and sustained-release granules or tablets (1-3). Some Eudragits e.g. Eudragit RSPM or RLPM, have been applied by direct compression to the preparation of sustained release dosage forms (4-6). Eudragit RS and RL show a pH independent and distinct permeability, but RS is poorly permeable and RL is highly permeable to an aqueous solution. The combination of Eudragit RSPM and RLPM as a release retardant by direct tableting has not been studied, although combinations of these substances have been applied to the film coating formulations of tablets and granules by using the organic solvent method (7).

Controlled-release theophylline preparations taken once or twice per day are widely used for the

treatment of chronic airway obstruction. In order to maintain plasma theophylline concentrations within the therapeutic range with minimal variation between peak and trough values, various methods are used to produce controlled-release theophylline preparations (8-10). From the economic point of view, direct compression is one of the most convenient method, since it requires no drying step and permits a great reduction in handling and simplifying steps.

The aim of this investigation is to study the tablet strength and compaction behavior of the combined formulations of Eudragit RSPM and RLPM by direct compression, and to evaluate the release behavior of these tablets. The influence of dibasic calcium phosphate anhydrous as an excipient on the compression and release properties of tablets made from different combinations of Eudragit RSPM and RLPM direct-tableting formula is also examined.

## MATERIALS AND METHODS

Materials- Theophylline anhydrous was obtained from Delta Synthetic Co. Ltd. Taiwan, ROC. The Eudragit RSPM and RLPM were kindly supplied by Rohm Pharma., Darmstadt, West Germany. Dibasic calcium phosphate anhydrous (DCPA, GS grade) was a gift from Kyowa Chem. Ind. Co. Ltd., Japan. The fumed silicon dioxide was purchased from Japan Aerosil Co. Ltd., Japan. The other materials were reagent grade purchased in the market.

Compression of compacts- Formulations for compression are listed in Table I. Compacts (10 mm in diameter) were made with or without DCPA by compressing 500 mg of mixed powder. Compression was achieved by using an IR spectrophotometric tableting machine (Riken Seiki Co., Japan) under the four respective pressures of 60 kg, 100kg, 260 kg and 400 kg/cm$^2$ for 30 seconds and then rapidly removing the pressure.

Tensile strength of compacts- The tensile strength of the compact was determined from the force required to facture compacts by diametral compression in a universal testing machine (Model: UPL 2000, Lohmann-V. Tarnogrodci, West Germanny). At least 24 hours elapsed between compact compression and measurement of compact strength to allow for any stress relaxation. Tensile strength (T), was determined by the formula $T = 2F/\pi D\ell$, where F is the applied force, D is the diameter of compact and $\ell$ is the compact thickness (11). The diameter and thickness were determined by a digimatic caliper ( Mitustoyo, Japan). For each determination, ten compacts were tested and the mean and standard deviation were calculated.

Preparation of tablets- Tablets (500 mg), made by the direct compression method, were prepared by a rotary tablet machine. All formulations used in the study are shown in Table I. The die and punches were 10.00 mm

TABLE I
Formulations for direct preparation of tablets made by different combination ratios of Eudragit RLPM and RSPM with or without DCPA

| | Formulation | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|
| Content % | I | II | III | IV | V | VI | VII | VIII | IX | X |
| Theophylline | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 | 60 |
| Eudragit RLPM | 36 | 26 | 18 | 10 | 0 | 25 | 0 | 15 | 12.5 | 7 |
| Eudragit RSPM | 0 | 10 | 18 | 26 | 36 | 0 | 25 | 15 | 12.5 | 7 |
| Silicon dioxide | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| Mg. Stearate | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 | 1 |
| Talc | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 | 1.5 |
| DCPA | 0 | 0 | 0 | 0 | 0 | 11 | 11 | 6 | 11 | 22 |

in diameter, and the punches were flat-faced. The hardness of the tablets was determined by a tablet hardness tester (Toyama SanGyo Co., Ltd., Japan) and controlled between 13 and 18 kg.

Measurement of contact angle- The contact angle of the tablet was measured by a contact anglemeter with distilled water (Kyowa Kaimenkagaku Co., Ltd., Japan). Measurement was repeated 5 times for each kind of tablet, and the mean value and standard deviation were determined.

Determination of dissolution behavior- A USP dissolution paddle assembly (NRT-VS3, Toyama SanGyo Co., Ltd., Japan) containing 900 ml of pH 1.2 and pH 6.8 dissolution medium was used. The dissolution medium was controlled at 37±0.5°C and stirred constantly at 50 rpm. The concentration of theophylline was determined spectrophotometrically at 270 nm (UV-650, Jasco Co., Ltd., Japan). Results were reported as the mean of three tablets. The pH change method was also used. During the first 1.5 hours, the test was carried out at a pH 1.2 medium, and then the pH was increased to pH 6.5±0.2 by adding 14.5 gm of tribasic sodium phosphate powder.

## RESULTS AND DISCUSSION

When external mechanical forces are applied to a powder bed, there are several stages in the compression

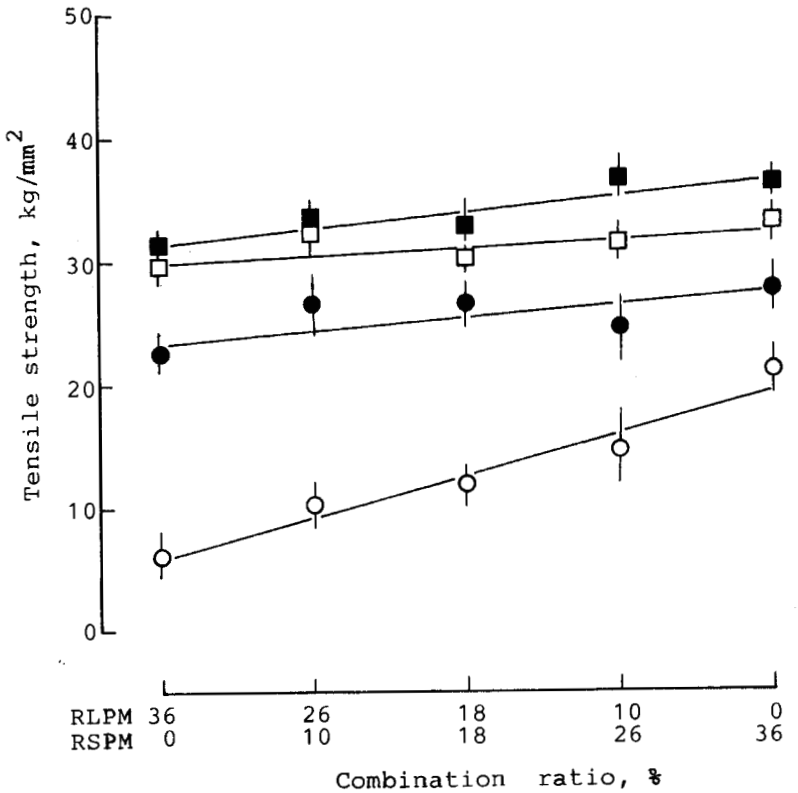


FIGURE 1
Effect of combination ratios of Eudragit RLPM and RSPM on the tensile strength of tablets without DCPA at different compression forces
Key:

Compression forces:
○, 60 kg/cm²; ●, 100 kg/cm²;
□, 260 kg/cm²; ■, 400 kg/cm²

The bars indicate the standard deviation (n=10)

(12). Closer repacking occurs first in the interparticular rearrangement due to pressure loading, and results in an initial volume reduction. Further compression in deformation (elastic or plastic) of the particles due to brittle rearrangement. Eventually, an increase in force no longer reduces the relative volume of the compacts.

Fig. 1 indicates that the tensile strength of compacts without DCPA under four applied pressures, was dependent on the compressional force and the combination ratio of Eudragit RLPM and RSPM. The more the compressional force, the higher the tensile strength. The consolidation to the closest packing might be responsible for their intensive compact. Moreover, the larger the amount of Eudragit RSPM, the higher the value of the tensile strength. This might be attributed to the fact that Eudragit RSPM was more compactable than Eudragit RLPM (5), since Eudragit RLPM also showed a more elastic deformation and relaxed behavior than Eudragit RSPM, leading to a lower tensile strength of compacts.

Compacts containing DCPA as an excipient showed an increase of tensile strength with an increase of compressional force as shown in Fig. 2. The larger the amount of DCPA used, the higher the value of the tensile strength. Fig. 2 also indicates that DCPA more

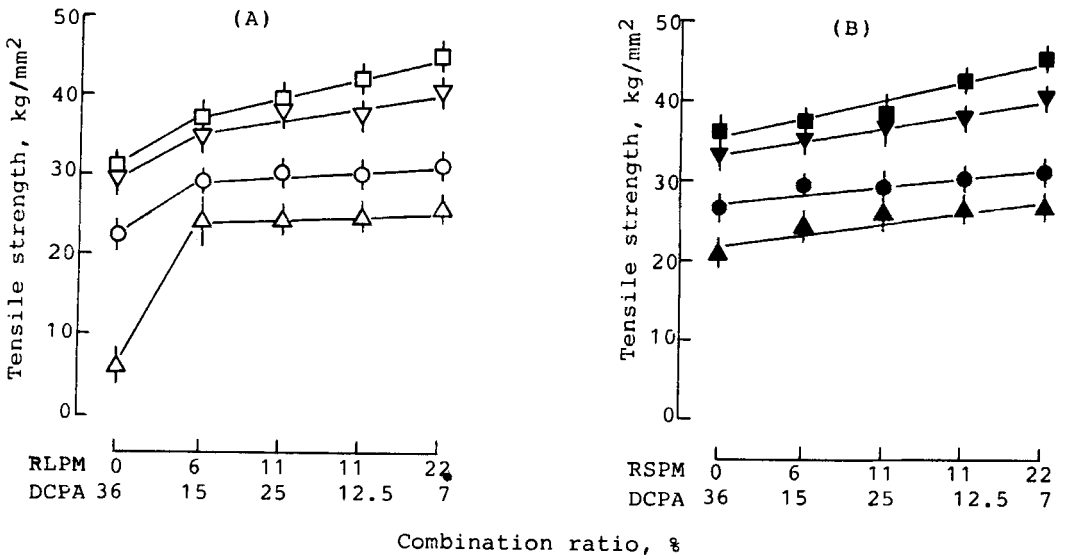


FIGURE 2
Effect of DCPA amounts on the tensile strength of tablets made by different combination ratios of Eudragit RLPM and RSPM
Key:
Compression forces:
△, ▲: 60 kg/cm²; ○, ●: 100 kg/cm²;
▽, ▼: 260 kg/cm²; □, ■: 400 kg/cm²

The bars indicate the standard deviation (n=10)

influenced the compact of Eudragit RLPM than the compact of Eudragit RSPM, when the DCPA concentration in the compact was lower. This might be due to the spontaneously reversible deformation of Eudragit RLPM. However, a DCPA amount above a certain level (>6%) resulted in a consolidated compact, indicating that DCPA is suitable for use as an excipient for direct compression of the tablet.

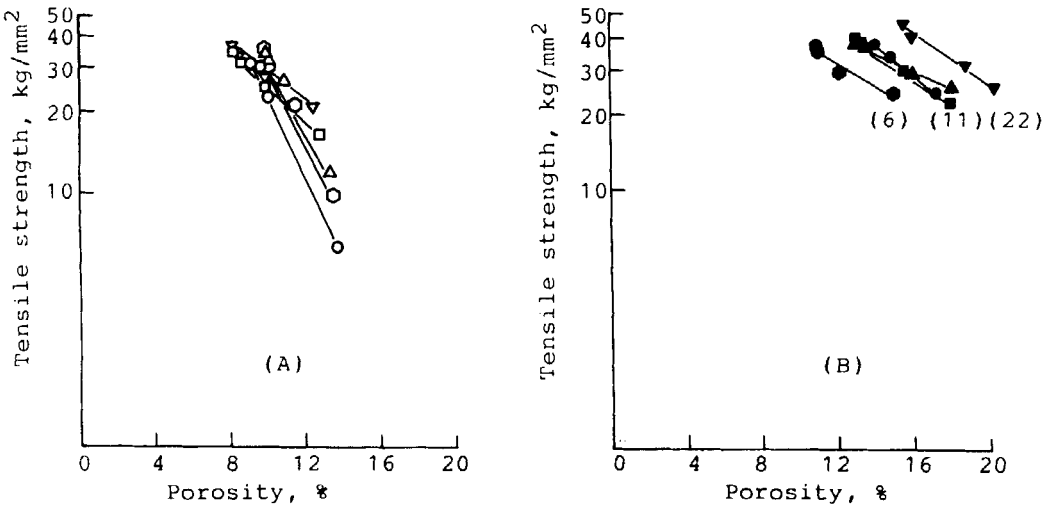


FIGURE 3
Logarithm of tensile strength-porosity relationship of Ryshkewitch equation for tablet made by different combination ratios of Eudragit RLPM and RSPM with or without DCPA
Key:
Formulations:
○, I; △, II; ⬡, III; □, IV; ▽, V
●, VI; ▲, VII; ⬢, VIII; ■, IX; ▼, X
( ): amount of DCPA

Ryshkewitch (13) has observed the relationship between the logarithm of tensile strength and the porosity of the compact, indicated in the following equation (14):

$$\text{Log } T = -b\,\varepsilon + a$$

where T is the tensile strength of the compact, $\varepsilon$ is the porosity of compact, a and b are the constants. The logarithm of the tensile strength plotted against the porosity of the compact is shown in Fig. 3. A linear relationship was found in all formulations. In compacts without DCPA, the increase in Eudragit RSPM

decreases the porosity of compacts, resulting in an increase in tensile strength (Fig. 3-A). The more compactable property of Eudragit RSPM might be responsible for this result. However, the compact with DCPA behaved differently. Fig. 3-B shows that the tensile strength increased as the DCPA increased, but the porosity also increased. This might be due to the lower bulk density (1.20 mL/g) and good compressibility of DCPA, using a greater amount of DCPA resulted in a higher value to the tensile strength. The higher porosity of compacts made by the larger amount of DCPA used, was due to the fact that the DCPA contained many smaller particles (>350 mesh, 51%). As the compressional force was increased and the interparticular distance was shortened, a stronger adhesive force a lower porosity of the compacts was obtained, resulting in the preparation of a tablet with the desired strength.

The Heckel equation was also used to evaluate the relationship between the relative density of compacts and the compressional forces (15).

$$\ln \left( \frac{1}{1 - D} \right) = KP + A$$

where D is the relative density of the compact and is obtained by dividing the apparent density of the compact by the true density and P is the compressional force. The constants K and A are determined from the

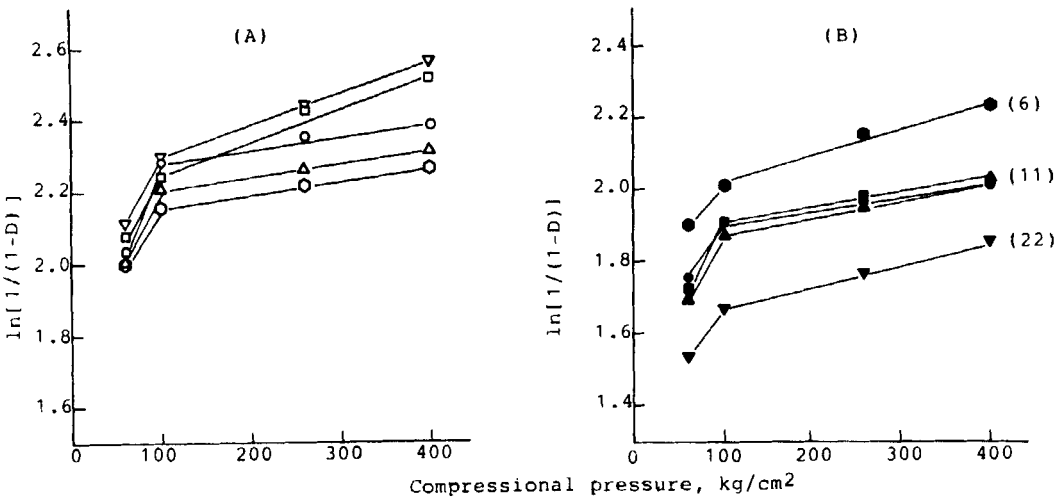


FIGURE 4
Heckel plots for tablets made by different combination ratios of Eudargit RLPM and RSPM with or without DCPA
Key:
see Fig. 3

slope and the intercept, respectively, of the extrapolated linear portion of the plot. The slope of the straight line portion of K, is generally expressed as a reciprocal and is referred to as the yield pressure (Py), K=1/Py. The effect of Eudrgit RSPM and RLPM and the amount of DCPA on the compaction behavior of compacts is shown in Fig. 4. In the absence of DCPA, Fig. 4-A plots the graph of the Heckel equation with the initinal curvature and subsequent linear portion. This initial curvature is attributed to particle slippage and rearrangment (16). The linear portion is attributed to the deformation process after compression. The larger

the amount of Eudragit RSPM, the higher the value of the linear slope. This indicates that a larger amount of Eudragit RSPM resulted in a lower value of yield pressure. A lower value of yield pressure tends to favor plastic deformation during compaction. This suggests that large amounts of Eudragit RSPM result in good compressibility of compacts. In the presence of DCPA, the lines of the Heckel plot are parallel (Fig. 4-B). This shows the compressional behavior for all compacts with DCPA are the same, because the yield pressure has the same value. However, the larger the amount of DCPA used the lower the values of $\ln\frac{1}{1-D}$, since the lower bulk density (1.20 mL/g) of DCPA makes production of small tablets easy, leading to a ranking of linear plots according to the amount of DCPA. The results indicate that Eudragit RSPM and DCPA are responsible for the good compressibility behavior of compacts.

The surface wettability of tablets made by all formulations with a tableting machine was also determined by directly measuring the contact angle of distilled water drops placed on the surface of the tablets. Fig. 5 shows the contact angle of the tablets made by different formulations. It is obvious that the contact angle became smaller with an increase in the Eudragit RSPM (Fig. 5-A). It has been reported that compacts made

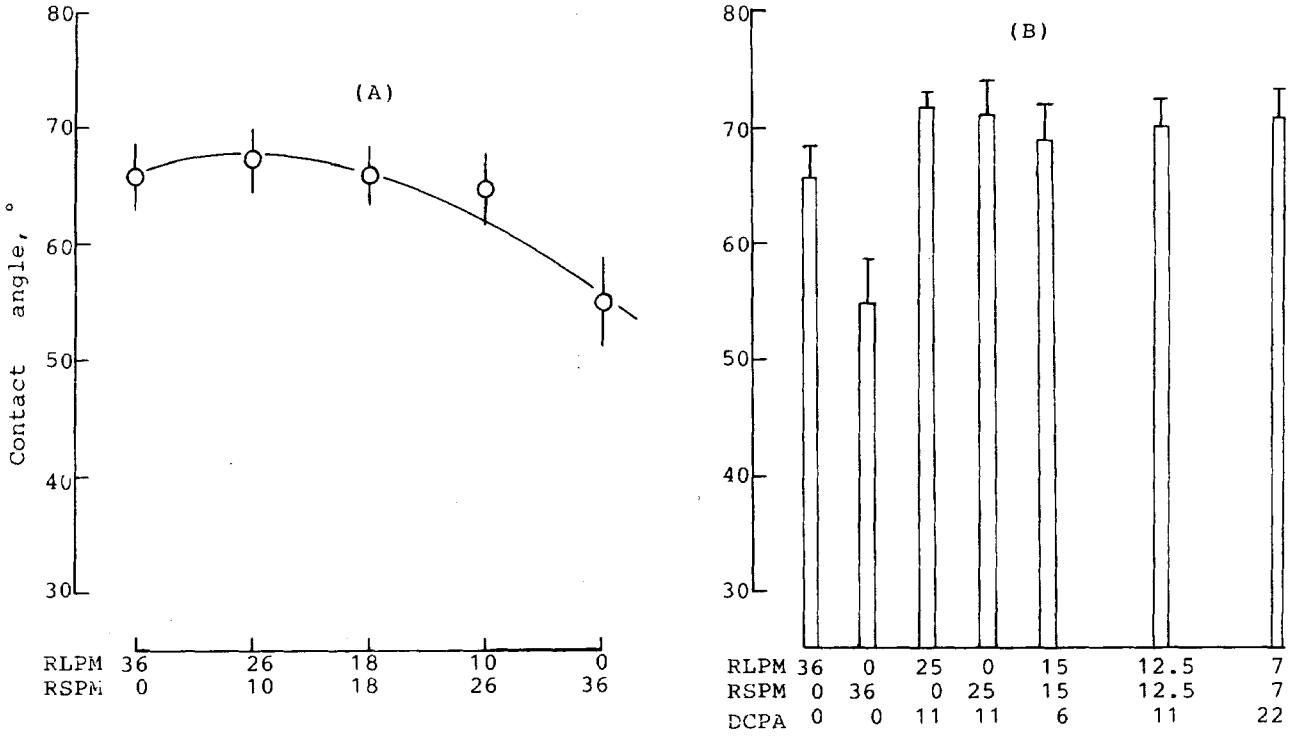


FIGURE 5
Effect of combination ratios of Eudragit RLPM and RSPM on the contact angle of tablets with or without DCPA
Key:
mean±SD (n=5)

by pure Eudragit RSPM or RLPM have no wettable surface, since their contact angle value is higher than 90°, about 98° for both Eugragits (17). Our results differ from these reports. This difference might be due to the fact that the tablets contained other components, e.g. silicon dioxide and theophylline anhydrous. Silicon dioxide possesses hydrophilic silano groups which easily interact with $H_2O$ molecules by hydrogen bonding, leading to a reduction in the surface tension of compacts. The theophylline was an anhydrous form which easily absorbed water and partly transformed into a hydrate form, resulting in a lower contact angle. The water contact angle of the tablets with DCPA was also measured, as shown in Fig. 5-B. Once DCPA was added to the formulations, the tablets exhibited a higher contact angle than tablets without DCPA. There was no significant difference between tablets made by different amounts of DCPA. This can be reasonably attributed to the lower absorption of moisture by DCPA (18).

The dissolution profiles of tablets without DCPA in pH 1.2, pH 6.8 or in pH change dissolution medium are shown in Fig. 6. Each data point represents the mean of three determinations. A controlled release behavior of theophylline from each tablet was found. It is obvious that there was no significant difference for theophylline release from these tablets in these three

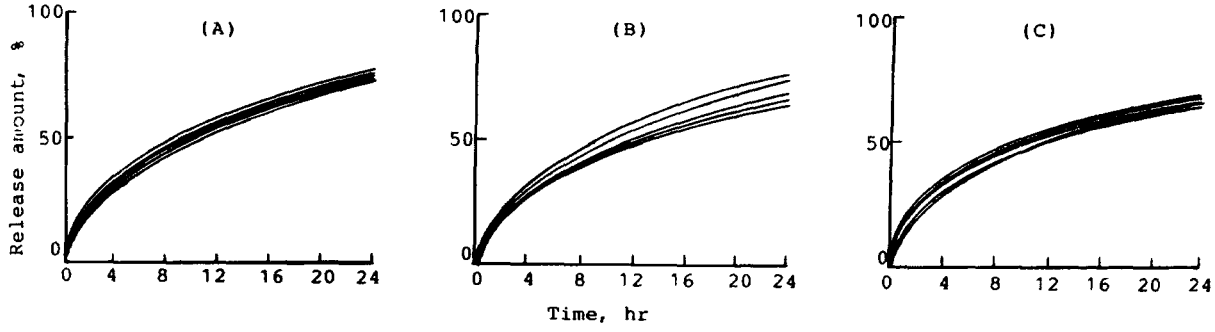


FIGURE 6
Release profiles of tablets made by different combination ratios of Eudragit RLPM and RSPM without DCPA
Key:
(A) pH 1.2 medium
(B) pH 6.8 medium
(C) pH change medium

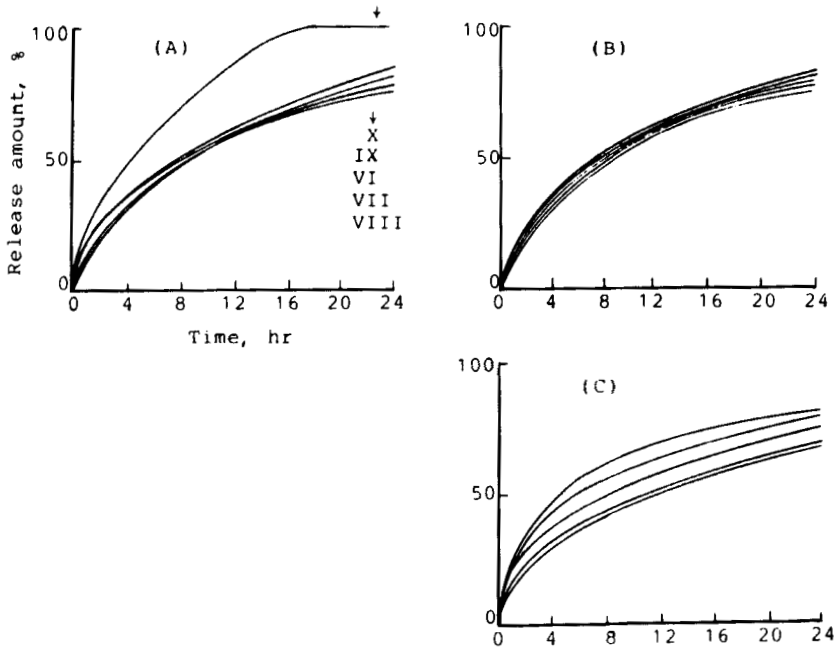


FIGURE 7
Release profiles of tablets made by different combination ratios of Eudrgait RLPM and RSPM with DCPA
Key:
(A) pH 1.2 medium
(B) pH 6.8 medium
(C) pH change medium

different dissolution media. All the tablets belonged to the non-disintegrated matrix and their release behavior was pH independent. The retardation effect of these tablets may be attributed to the fact that Eudragit RSPM or RLPM is a pH-independent polymer, its poor surface wettability and its low swelling property (17). This suggests that different combination ratios of Eudragit RSPM and RLPM can control the release of a drug. On the other hand, tablets with DCPA as an

excipient exhibit a higher dissolution rate than that tablets without DCPA (>10-15%), as shown in Fig. 7. The dissolution rate of theophylline released from the tablets increased with the increase of the amount of DCPA. This may be due to the fact that there was less acrylic resin and higher porosity in the tablet produced by a higher amount of DCPA. It was also found that the dissolution rate of theophylline released from DCPA containing tablets was significantly different from the three dissolution media. The higher solubility of theophylline in pH 1.2 medium may support this result. When the amount of acrylic resin and DCPA were constant (Formulation VI, VII and IX), there was no significant difference in the dissolution rate of these types of tablets ($p>0.05$). The release rate of theophylline from tablets made by Formulation VIII was also the same as the release rate of Formulation VI, VII and IX ($p>0.05$), although the amount of acrylic resin was somewhat higher. However Formulation X exhibited a higher dissolution rate, particularly in pH 1.2 dissolution medium. The higher solubility of theophylline in pH 1.2 medium and disintegration of the tablet during the dissolution process may be responsible for this result.

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