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Different Types of Direct Compressible Excipients Affecting the Release Behavior of Theophylline Controlled-release Tablets Containing Eudragit Resins

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ABSTRACT

Theophylline released from direct-compressed tablets containing Eudragit RSPM/RLPM and different types of direct compressible excipients was investigated. The influences of the type of dissolution medium and stirring speed on the release behavior of theophylline were also studied. The results showed that the type of direct compressible excipients, dissolution medium and stirring conditions significantly influenced the dissolution rate. The tablet made by dicalcium phosphate or microcrystalline cellulose exhibited the most controlled-release behavior. Almost all the release kinetics of tablets followed a Fickian-transport model.

INTRODUCTION

Direct compression as a means of tablet manufacture gains increasing acceptance because of it has many merits (1-4). Since the process of direct compression involves only blending and compression, many types of direct compressible excipients with better flowability and compressibility have been used in pharmaceutical tabletting. Thus, direct compression technique gives the formulators an opportunity to design and manufacture solid dosage forms.

Many acrylic resin polymers have been used to act as a film-coating or slow-release coating membrane for granules or tablets (5-7), but only few reports have focused on the preparation of matrix tablets containing acrylic resins (8-10). Lin et al. have found that the direct compressible controlled-release (CR) theophylline tablets can be prepared by monitoring the combined ratios of Eudragit RSPM and RSPM, and the addition of dicalcium phosphate (DCPA). The release behavior of theophylline from these tablets without DCPA showed a pH-independent property but CR tablets with DCPA had pH-dependent release behavior, suggesting that excipient also played an important factor (11). In this study, different types of direct compressible excipients were used to replace DCPA. Their influence on the release behavior of theophylline from the acrylic resin matrix tablets produced by direct compression was studied. The release kinetic of theophylline from these tablets was also examined.

MATERIALS AND METHODS

Materials:

Theophylline anhydrous (100-150 mesh, Delta Synthetic Co. Ltd., ROC), Eudragit RSPM and RLPM (Rohm Pharma., Germany) were used. Direct compressible excipients: dibasic calcium phosphate anhydrous (DCPA)[1], Neocel[2], Pure-Flo starch[3], Mobile starch[4], Avicel PH-101[5], Di-Tab[6], LG[7] and LSD[7] were used. The other materials used were pharmaceutical grade.

Preparation of direct compressible tablets:

Table I shows the tablet formulation for direct compression. All the ingredients were first mixed in vinyl bags for 10 minutes, then tableted by a rotary tablet machine. The die and punches (flat-face) were 10.0 mm in diameter. The hardness of tablets was controlled between 13-18 kg.

Dissolution rate analysis of tablets

A USP dissolution paddle assembly (NRT-VS3, Toyama San Gyo Co. Ltd., Japan) containing 900 ml of pH 1.2 dissolution medium was used. The temperature of dissolution medium was controlled at 37±0.5°C and stirring speeds were maintained at 50 or 100 rpm, respectively. The concentration of theophylline was determined spectrophotometrically at 270 nm (UV-650, Jasco Co. Ltd., Japan). The pH changed method was also carried out (11-12). Each data point represents the mean of measurements from three tablets.

RESULTS AND DISCUSSION

Fig. 1 shows the effect of the amount of DCPA on the dissolution of theophylline released from the matrix- tablets

TABLE I
Tablet Formulations for Direct Compression

Ingredients	Formulations (%)									
	I	II	III	IV	V	VI	VII	VIII	IX	X
Theophylline	60	60	60	60	60	60	60	60	60	60
Eudragit RLPM	15	12.5	7	7	7	7	7	7	7	7
Eudragit RSPM	15	12.5	7	7	7	7	7	7	7	7
Aerosil	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
Talc	1	1	1	1	1	1	1	1	1	1
Magnesium stearate	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5	1.5
DCPA[1]	6	12	22	-	-	-	-	-	-	-
Neocel[2]	-	-	-	22	-	-	-	-	-	-
Pure-Flo starch[3]	-	-	-	-	22	-	-	-	-	-
Mobile starch[4]	-	-	-	-	-	22	-	-	-	-
Avicel PH-101[5]	-	-	-	-	-	-	22	-	-	-
Di-Tab[6]	-	-	-	-	-	-	-	22	-	-
LG[7]	-	-	-	-	-	-	-	-	22	-
LSG[7]	-	-	-	-	-	-	-	-	-	22

Key: 1. Kyowa Chem. Ind. Co., Ltd, Japan; 2. Cheng Chyi Co. Ltd, ROC;
3. National Starch & Chem. Co., Ltd, USA; 4. CPC Internal., Australia;
5. Ashahi Kasei Co., Japan; 6. Stauffer Chem. Co., USA;
7. Ming-Tai Chem. Co., Ltd, ROC

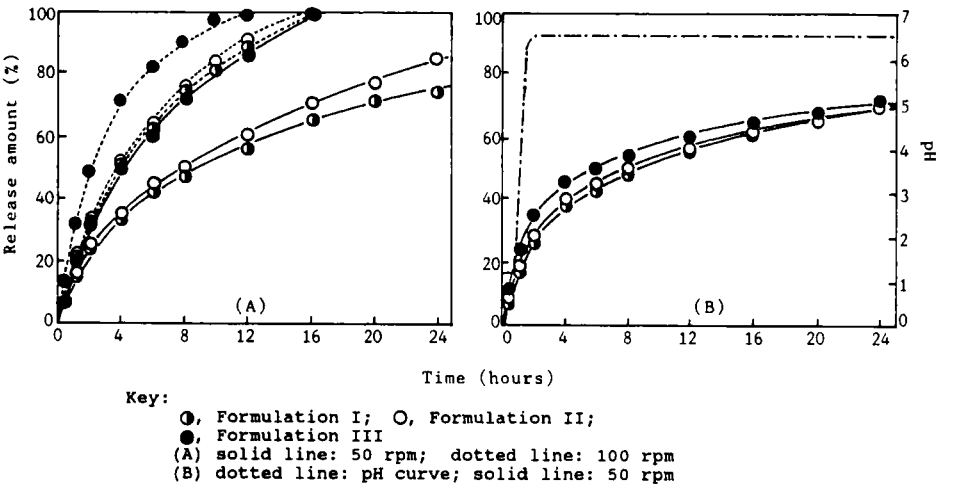
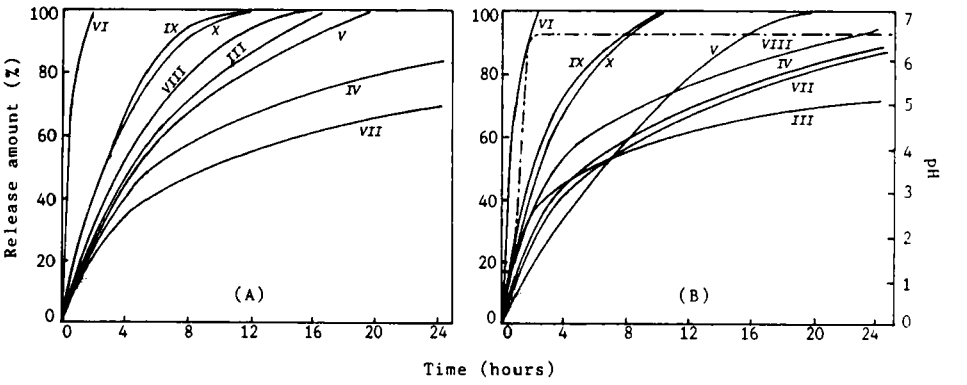


Fig. 1 Dissolution profiles of theophylline released from direct-compressed tablets in pH 1.2 solution (A) and pH changed medium (B)

containing different combined ratios of Eudragit RSPM and RLPM (Formulations I-III). Obviously, in the pH 1.2 dissolution medium, the rate of theophylline released from the matrix tablets increased with DCPA amount. The less acrylic resins, higher porosity and disintegration phenomenon to the tablets might be responsible for this higher dissolution rate (11). The soluble of DCPA and theophylline in pH 1.2 acidic medium might facilitate the disintegration phenomenon (13). The release behavior was also affected by stirring speed. The higher the stirring speeds the more the release amount. At lower stirring speed (50 rpm), the tablet produced by Formulation III only was gradually decreased and disintegrated with the dissolution time but tablets prepared by Formu-

lation I and II did not change its size and shape. At higher stirring speed (100 rpm), however, all tablets made from Formulations I-III gradually decreased and disintegrated, leading to higher dissolution rate. On the other hand, the dissolution of tablets in pH changed medium showed a different dissolution behavior from that in pH 1.2 medium. A rapid release rate of theophylline was found in the initial phase of dissolution and then maintained constant with time. The faster-release phenomenon might be due to the free soluble of DCPA in pH 1.2 acidic medium (13). As the tribasic sodium phosphate was added, the systemic pH of medium changed to pH 6.5±0.2 to slow down the solubility of DCPA and theophylline to cause a sustained release behavior again.

The effect of different types of direct compressible excipients on the dissolution rate of theophylline released from the tablets in pH 1.2 medium is shown in Fig. 2-A. The tablet containing mobile starch had the fastest dissolution rate, since the mobile starch exhibitd its better disintegrating property. However, the tablet made by pure-flo starch eroded gradually to release theophylline, because pure-flo starch was made of starch by pregelatinization (14). Although free water-soluble lactose was the main composition of LG or LSG, the tablet containing LG or LSG also showed a somewhat delayed dissolution rate. This might be due to the LG or LSG was granulated with PVP binder, the viscous barrier of PVP which might delay the release behavior. The tablet



Key:
(A) in pH 1.2 solution; (B) in pH changed medium

Fig. 2 Dissolution profiles of theophylline released from direct-compressed tablets containing different types of direct compressible excipients

produced by Formulation III or VIII exhibited similar release behavior, since DCPA or Di-Tab was soluble in pH 1.2 medium. However, the tablet made by Neocel or Avicel possessed the most controlled-release function. The water-insoluble property and compact characteristics of microcrystalline cellulose that resulted in a non-disintegrated matrix tablet, thus played an important role in dissolution behavior. When the tablets were carried out in pH changed medium, its release behavior was similar to that in pH 1.2 medium in spite of tablets prepared by DCPA or Di-tab (Fig. 2- B). The initial release rate of theophylline from tablets produced by DCPA or Di-tab was rapid, then slowed down after pH changed. The dicalcium phosphate dissolved in pH 1.2 acidic medium might interpret this faster-release phenomenon.

In order to determine the mechanism of drug release from these direct-compressed tablets, a simple relationship ($Mt/M_\infty = Kt^n$) was used (15-17). Mt/M_∞ is the fractional release of drug, t is the release time, K is a constant and n is the release exponent indicative of the mechanism of release. The value of n for different modes of drug transport indicated as follows: n=0.5 for Fickian or case-I transport, n=1.0 for zero order or case-II transport, and 0.5 <n<1.0 for non-Fickian or anomalous transport. The n values for all tablets (except Formulation III by 100 rpm) were closer to 0.5, suggesting release mechanism was closer to Fickian transport, i.e., Higuchi diffusion model. In contrast, the tablet made by Formulation III with higher stirring speed expressed non-Fickian release behavior. This also implies that stirring speed could improve the disintegrating of tablet to change its release kinetic. The results of this study indicate that the dissolution rate of matrix-tablets containing acrylic resins was significantly influenced by the amount of acrylic resins, stirring speeds, dissolution medium and the types of direct compressible excipients added. Almost all the release kinetics of tablets followed the Fickian-transport model.

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