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CONTROLLED RELEASE THEOPHYLLINE TABLET WITH ACRYLIC POLYMERS PREPARED BY SPRAY-DRYING TECHNIQUE IN AQUEOUS SYSTEM

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ABSTRACT

Sustained release and enteric theophylline tablets were prepared by directly compressing spray-dried microsphers with Eudragits L30D, L100-55 and E30D. The spray-drying process was free from using organic solvent. Drug dissolution of the enteric tablet in an acidic solution (pH 1.2) was highly dependent on the polymer content of the microsphere. Completely enteric function was observed with drug-to-polymer ratio of 1:3 using Eudragit L30D or L100-55. Tablet with Eudragit E30D formulated at the 2-40% level showed good sustained drug release which was throughly independent of the pH of dissolution media. The dissolution pattern was similar to that of Theo-dur and gave a straight line in Higuchi plot. In each tablet, the

controlled drug release was attributed to continuous and well-dispersed polymer matrix formed by spray-drying and subsequent compressing process.

INTRODUCTION

Various dosage forms with controlled drug release characteristics have been developed to improve patient compliance and to obtain sufficient therapeutic effects with minimum dose. Polymer coating is one of the popular methods in manufacturing the controlled release tablets or granules. Recently, an ambitious shift has been made from the use of organic solvents to the use of aqueous film-forming polymers because of avoiding explosion hazard and toxicity associated with solvent system and several water dispersing polymers have become commercially available for enteric and sustained release coating. Lehmann and Dreher (1) investigated the coating of tablets and small particles with acrylic resins, including the aqueous dispersing one, by means of fluid bed technique. Mehta and Jones (2) have evaluated the morphology of coated pellests, concluding that the physicochemical properties of films are highly dependent on the processing techniques used in manufacturilng them. Matrix type tablet as well as coated tablets and particles has been reported as an

useful controlled release dosage form with coating polymers. It can be prepared by directly compressing the powdered mixture of drug and polymers (3) or tableting microcapsules(4) or solid dispersed particles (5) prepared with the polymers. The latter method impart the more precisely controlled and predictable drug release rate to the resultant tablet, because the active ingredients are coated with or embedded in various polymers with characteristic permiability and solubility properties, such as retarded and enteric properties.

In the present study, theophylline microspheres for matrix tablet were prepared in various aqueous polymer systems using spray-drying technique. The drug release characteristics of the tablets prepared by compressing them were evaluated in vitro dissolution test. The physicochemical properties of the spray-dried microspheres were investigated relating to the drug dissolution.

EXPERIMENTAL

Material

Eudragits L30D, E30D and L100-55 were obtained from Rohm Pharma. Eudragit L100-55 has been commercially prepared by freeze-drying Eudragit L30D, and therefore it has the same chemical structure as that of Eudragit

L30D. Colloidal silica (Aerosil 200) was given from Aerosil Japan. Theophylline was purchased from Nakarai Chemical.

Spray-drying technique

A laboratory spray-dryer, with a drying chamber 1.2m in diameter and equipped with a centrifugal wheel atomizer (Okawara, L12 type) was used. When aqueous dispersing type Eudragit E30D or L30D was formulated, the aqueous drug suspension containing colloidal silica and plasticizer (PEG 6000) if necessary and a diluted Eudragit dispersion with distilled water (2.5 - 150 times) were fed separately to the spray-dryer, where they were mixed on the centrifugal wheel prior to being atomized. In using powdered Eudragit L100-55, the polymer, PEG 6000 and the drug were dissolved in 2% ammonia water. After adding the colloidal silica to the ammonia solution, it was fed to the spray-dryer. Representative formulae were listed in Chart 1. The spray-drying conditions were: the temperatures at the inlet and outlet, 150-170 C and 105-110 C, respectively; the flow rate of the solution, 1000mLh^{-1}; and the rotation speed of atomizer, 16500 rev min^{-1}.

Measurement of physicochemical properties of spray-dried particles

The particle size of the spray-dried particles was measured by a photographic counting method using a

CHART 1

Rp.1	Eudragit L30D	100ml	Rp.2	Eudragit E30D	50ml
	PEG 6000	3.0g		Water	950ml
	Water	900ml			
				Theophylline[1)]	100g
	Theophylline[1)]	40.0g		Aerosil	5.0g
	Aerosil	5.0g		Water (add to)	1000ml
	Water (add to)	1000ml			

Rp.3	Eudragit L100-55	15.5g
	PEG 6000	1.5g
	2%Ammonia water	1000ml
	Theophylline[2)]	15.0g
	Aerosil	2.0g

1) Theophylline was dispersed in the solution.
2) Theophylline was dissolved in the solution.

particle size analyzer (Karl Ziess, TGZ-3). The shape and surface topograph of the particle were observed with a scanning electron microscopy (Nihon Densi, JSM-T20, -T330). The crystallinity of theophylline in the spay-dried particles was examined by X-ray diffractometry (Nihon Densi, JDX).

Dissolution test

Matrix type tablets were prepared by directly compressing the spray-dried particles with a single-punch macine. The dissolution test of the tablet was undertaken using a dissolution test apparatus with a paddle stirrer and disintegration test solutions No.1 (pH 1.2) and No.2 (pH 6.8), all of which are specified in Japanease Pharmacopoeia XI. Theophylline released

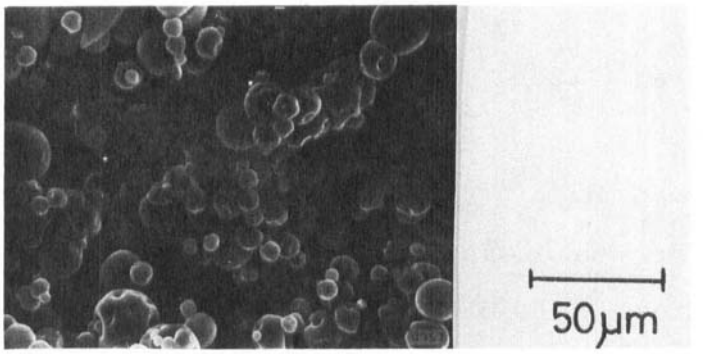

FIGURE 1

Scanning electron photomicrographs of spray-dried Eudragit L100-55

in the dissolution medium was measured spectrophotometrically at 270 nm.

RESULTS

Spray-dried particles

An ammonia solution of Eudragit L100-55 and PEG 6000 was spray-dried to form spherical particles as shown in the scanning electron photomicrographs (Fig.1), but they were hardly recovered in a reservor because of their adhering to the walls of drying chamber and cyclone collector. When the drug was formulated with the polymer, the resultant spray-dried particles were less adhesive than the spray-dried Eudragit, but the recovery was not good. The usages of Eudragit L30D and

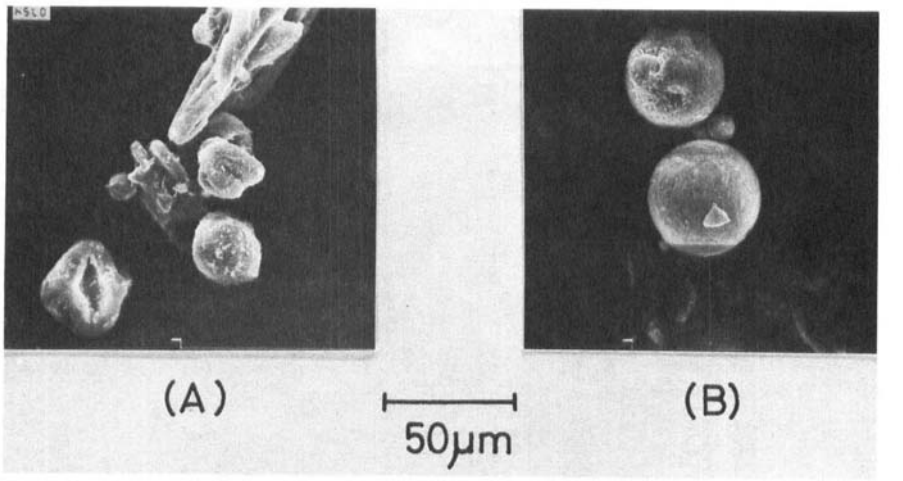

FIGURE 2

Scanning electron photomicrographs of spray-dried theophylline with Eudragit L100-55

Drug:polymer : (A)8:3, (B)1:3

E30D brought the same problems espescially with high polymer content. The adhesive property of the particles was much decreased by adding a small amount of colloidal silica to the formulation and product was recovered in a reservior throughout the cyclone collector.

The shape and surface topography of the spray-dried particles were found to be affected by the drug-to-polymer ratio in the formulation. When Eudragit L100-55 was formulated with the drug-to-polymer ratio of 8:3 a lot of agglomerated crystals of theophylline were observed in the spray-dried particles, while with

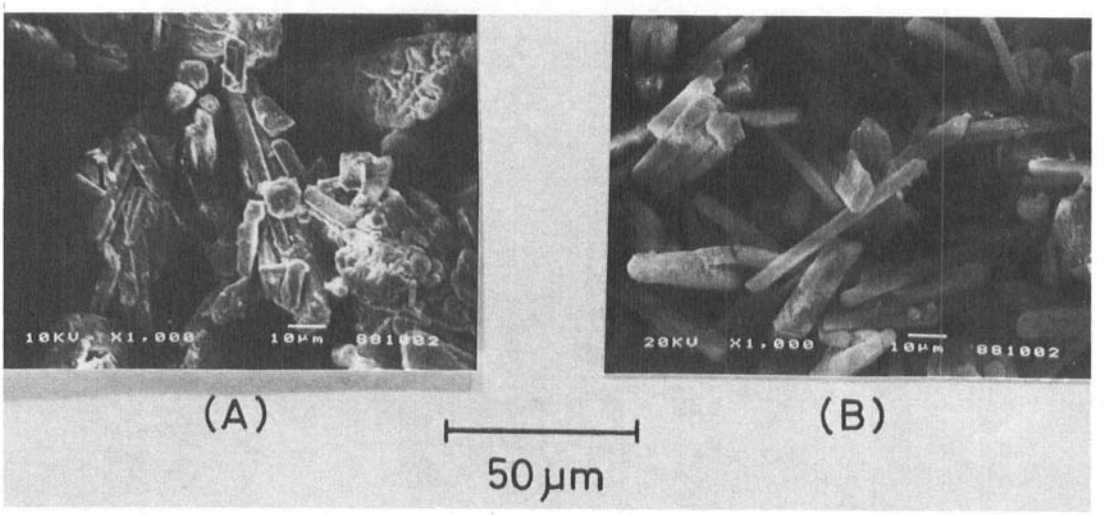

FIGURE 3

Scanning electron photomicrographs of spray-dried theophylline with Eudragit E30D

Drug:polymer : (A)20:3, (B)50:1

the ratio of 1:1 or 1:3, most paricles were microspheres with smooth surface (Fig.2). Their particle size distributions were represented by a log-normal form having various mean particle diameters (10 - 30 μm). Relatively large mean particle diameter of the particle with low polymer content was attributed to the presence of the agglomerated crystals of theophylline.

Nearly the same change in shape of spary-dried particle due to the change in the polymer content was observed when Eudragit L30D and E30D were formulated.

There were many un-agglomerated drug crystals besides of agglomerated ones when the Eudragit was formulated with very low content (Fig.3).

Transformation of drug crystal into amorphous state was confirmed by powder X-ray diffractometory. Crystallinity of drug in the spray-dried particles with Eudragit L100-55 decreased with increase in the polymer content of the spray-dried particles, and the complete transformation into amorphous state was observed for the spray-dried particles with the drug-to-polymer ratio of 1:3 (Fig.4). Although the similar decrease in drug crystallinity with increase in polymer content was observed with the particles with Eudragit L30D, the transformation into amorphism was not complete with the drug-to-polymer ratio of 1:3 because a part of drug remained undissolved in the fed fluid. It was also proved that most drugs were crystallized without amorphisms in the spray-dried particles when the Eudragit E30D was formulated with low content (< 13%).

Dissolution studies

The drug release patterns of tablets prepared from the spay-dried particle with Eudragit L100-55 were measured in the test solutions No.1 (pH 1.2) and No.2 (pH 6.8). Enteric behaviour was observed with the tablet formulated with a sufficient amount of polymer

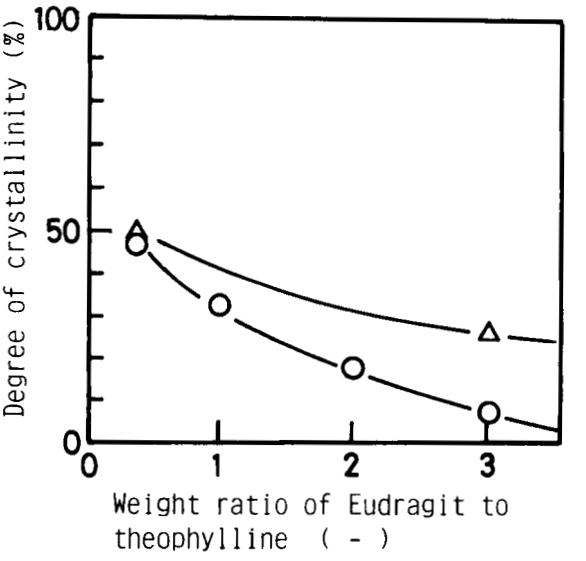

FIGURE 4

Crystallinity of drug dispersed in spray-dried particle as a function of polymer content

○, Spray-dried particle with Eudragit L100-55;
△, spray-dried particle with Eudragit L30D.

(polymer/drug>3), while the release rate increased with decrease in the polymer content (Fig.5). The same enteric function was obtained by formulating Eudragit L30D at the same ratio (Fig.6), although the drug in the spray-dried particle was not perfectly transformed into amorphous state as shown in Fig.4. On the other hand, a corresponding matrix tablet prepared by directly compressing a mixture of powdered Eudragit L100-55 and drug showed 12% drug release in the

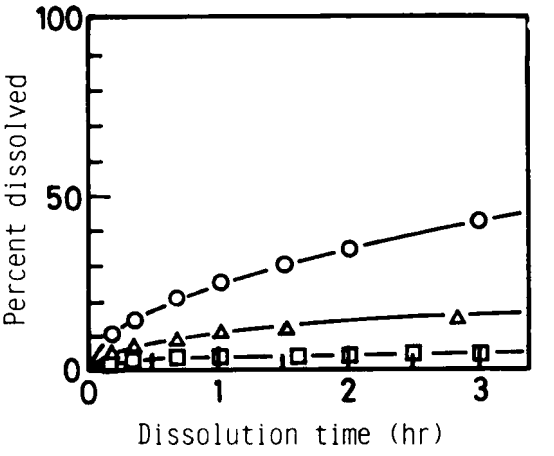

FIGURE 5

Drug release patterns of tablets with various amount of Eudragit L100-55

Drug:polymer : ○,8:3; △,1:1; □,1:3.

dissolution medium No.1 within 2 hours. These results suggested that the depression of drug release in the dissolution medium was colsely related to dispersibility of the enteric polymer matrix in the tablet.

A rapid drug release from tablets with the polymers was observed in the test solution No.2 (Fig.6), since Eudragits L100-55 and L30-D were soluble in the solution. The tablet became gradually smaller with the drug release and disappeared when the drug release was 100 %. The initial release rate from the tablet with Eudragit L100-55 was higher than that from

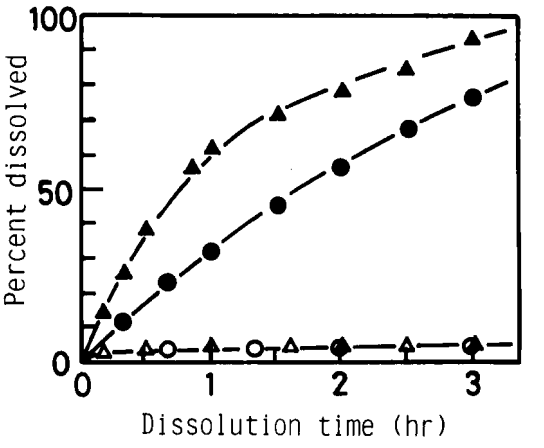

FIGURE 6

Drug release patterns of tablets with Eudragits L30D and L100-55 in test solutions No.1 (open symbols) and No.2 (closed symbols)

○, ●, L30D; △, ▲, L100-55.

the tablet with Eudragit L30D, which was probably attributed to the difference in the drug crystallinity shown in Fig. 4.

Tablets with Eudragit E30D showed the sustained drug release in both dissolution media (pH1.2 and 6.8) and the release pattern was thoroughly independent of pH of dissolution media (Fig.7). Formulating with the drug-to-polymer ratio of 20:3 or 4:3 the release pattern was very similar to that of a commercial sustained release tablet of theophylline (Theo-dur) tested under the same dissolution conditions as shown in Fig.7. The tablet with the ratio of 50:1 showed

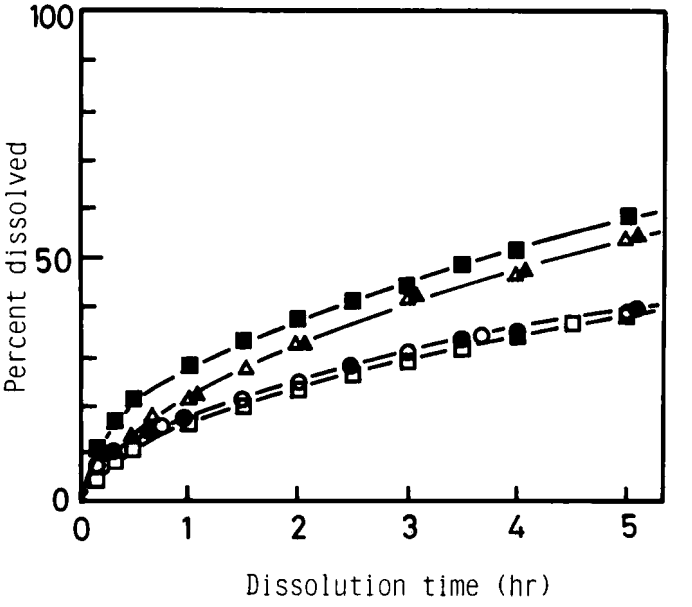

FIGURE 7

Drug release patterns of tablets with Eudragit E30D and those of Theo-dur (100mg) in the test solutions No.1 (open symbols) and No.2 (closed symbol)

Tablet with Eudragit E30D, drug:polymer : ○, ●, 4:3; △, ▲, 20:3. Theo-dur: □, ■.

slightly increased but sufficiently retarded (60% at 5h) release rate. After the drug was completely released, the polymer keeping the original sape of tablet remained undissolved. As Higuchi plot of the data showed the straight lines regardless of the drug-to-polymer ratio, the drug release rates were determined by the diffusion rate of drug through the polymer matrix (6)(Fig.8).

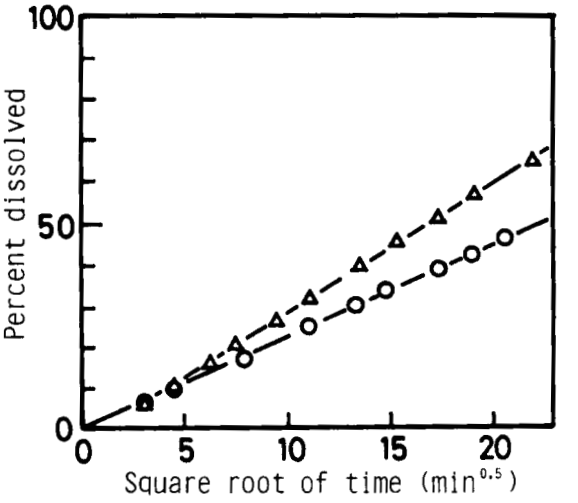

FIGURE 8

A plot of drug released from a tablet with Eudragit E30D as a function of the square root of residence time (Higuchi plot)

Drug:polymer : ○, 4:3; △, 20:3.

Discussion

It was found that the shape of spray-dried particles depended on the drug-to-polymer ratio in the formulation. When the content of the polymer in the formulation was high, spray-dried particles were spherical and the drug in the particle was in amorphous state. The crystallization of drug was assumed to be restricted by a viscous polymer solution formed during the drying process and by the rapid solvent evaporation (7). With low polymer content, the

particles were agglomerated crystals with the polymer. When Eudragit E30D was formulated with very low content (< 13 %) most of resultant particles were discrete drug crystals coated with the polymer. Based on the difference in drug crystallinity the present spray-dried particles can be classified into two types of particles, i.e. solid dispersed particles containing the amorphous drug and microcapsules of the drug with the polymer.

Solid dispersed particles with enteric coating polymers have been investigated as an enteric solid dispersion to obtain a good bioavailability of poorly water soluble drug (8-10). The drug release from the solid dispersion is depressed in gastric juce and is enhanced in intestinal juce. The complete resistance to an acidic solution for the present matrix tablet was achieved by formulating the Eudragit L100-55 and L30D with the drug-to-polymer ratio of 1:3. The polymer matrix in the tablet may be continuous. The well dispersibility of the polymer in the tablet is necessary to get perfect resistence to an acidic solution because it is not achieved by a directly compressed tablet of powdered Eudragit and drug. The drug release from the solid dispersion tablet was rapid in the test solution No.2. It is expected that the spray-dried particle with the enteric Eudragit polymer

is successfully applied to preparing enteric solid dispersion tablets.

While microscopic analysis revealed that many drug crystals were present in the spary-dried particles with Eudragit E30D, effective encapsulation of drug crystals with the polymer was confirmed by the sustained drug release of the resultant tablet. Drug release from the tablet was a thoroughly pH-independent because drug permiability of Eudragit E30D is not affected by pH gradient. The release pattern was similar to that for a commercial tablet, e.g. Theo-dur. Although McGinity et al (3) reported that Theo-dur like release pattern was achieved by direct compression of drug with Eudragit RSPM, it is characteristic for the present matrix tablet to have relatively high drug content ($\sim$ 87%) compared to that of Theo-dur or the directly compressed tablet. It leads to reduction in size of the tablet, which improves the patient compliance.

Aqueous tablet coating with Eudragit E30D for sustained drug release have been reported by several workers as summarized by Lehmann and Dreher (1) and the tackiness problem of the polymer film in the coating process has been pointed out. Recently, Ghebre-Sellassie et al (11) demonstrated the pellet coating with Eudragit E30D in combination with a number of

water insoluble pharmaceutical additives such as kaolin, talc and magnesium trisilicate, which reduce the tackiness of the polymer without affecting the sustained drug release. However, there are few papers claiming that fine drug particles or crystals were coated using Eudragit E30D. In the present method, the tackiness of the polymer film were improved by adding colloidal silica to the formulation. Moreover the spray-drying process prevents the agglomeration of coated drug crystals, since the crystal wetted with the polymer solution is dried up in the drying chamber without contacting each other. Thus, the present spray-drying microencapsulation with aqueous dispersing polymer, Eudragit E30D, is useful and is expected to be applied to drug crystal coating for insulation, taste masking, or O_2-stabilization as well as sustained release of drug.

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