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RESEARCH PAPER

Release Characteristics of the Matrices Prepared from Co-spray-Dried Powders of Theophylline and Ethylcellulose

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ABSTRACT

Co-spray-dried powders of theophylline and ethylcellulose were prepared using aqueous ethylcellulose dispersion. Co-spray-dried powders were directly compressed into the matrices and the release characteristics of the prepared matrices were investigated. The co-spray-dried powders exhibited good matrix formations with high hardness at rather low compression force. The concentration of ethylcellulose in the matrices was, as expected, the rate-determining factor in controlling the release rate of the drug. Increasing the weight fractions of ethylcellulose resulted in a corresponding decrease in the drug release rates in both 0.1 N HCl and phosphate buffer pH 6.8. However, at the same level of ethylcellulose content, the drug release in acidic conditions was higher than in alkaline medium. To modify release characteristics of the matrices, PVP K30 and lactose were employed as channeling agents. At concentrations of 5 and 10%, PVP K30 was found to slow the drug release when incorporated into the co-spray-dried powder formulations containing 5% ethylcellulose. Lactose at a concentration of 15% provided an increasing effect on drug release when added in the formulations. But an increase in lactose quantity from 15 to 25% did not exert much more influence on release characteristics. Higuchi plots were found to be best applicable to all release data. Scanning electron

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microscopic examinations on the surface and cross-section of the matrices before and after subjection to release testing revealed the formation of porous networks within the matrices by the ethylcellulose fibers. Such polymeric networks would account for the controlled diffusion of the drug from the matrices.

Key Words: *Co-spray drying; Ethylcellulose; Matrices; Release characteristics; Theophylline*

INTRODUCTION

The spray drying process has been applied extensively in pharmaceutical systems to modify pharmaceutical powders having various desired properties. This process has also been investigated for its potential application in the manufacture of modified release products (1–7). In this process, the mixed solution of the drug and polymeric material was spray dried to produce the powder which could be directly compressed into matrices with sustained release properties. Various polymeric materials, e.g., hydroxypropyl methylcellulose, hydroxypropyl methylcellulose phthalate, cellulose acetate phthalate, polymethacrylates, have been evaluated for their controlled release properties when employed to prepare co-spray-dried powders (1–8). The development of aqueous-based polymeric dispersions facilitates the application of more polymeric materials in the spray drying process as the risk of explosive hazard and environmental impacts associated with the use of organic solvents could be eliminated. Takeuchi et al. (4) reported the preparation of theophylline and polymethacrylate co-spray-dried powders using aqueous dispersions of polymethacrylate polymers. The resultant co-spray-dried matrices exhibited good sustained drug release properties.

Ethylcellulose (EC) has also been formulated in aqueous polymeric dispersions, with the potential application in spray drying for the manufacture of sustained release matrices. Therefore, in this present study, an attempt has been made to produce the co-spray-dried powders of theophylline with ethylcellulose, and the drug release characteristics of the matrices prepared from co-spray-dried powders were investigated. The incorporation of channeling agents, water-soluble materials employed to alter the release rate of the drug from the matrices, into the co-spray-dried formulations was also studied.

EXPERIMENTAL

Materials

The following materials obtained from commercial sources were used as received: theophylline anhydrous, BP (supplied by Asia Drug & Chemical Ltd., Bangkok, Thailand), ethylcellulose aqueous dispersion (Surelease®, Colorcon Inc., USA), polyvinylpyrrolidone (PVP K30, Kollidon® 30, BASF, Germany), lactose monohydrate (Wyndale, New Zealand), colloidal silica (Aerosil® 200, Degussa, Germany), 25% ammonium hydroxide (AR grade, E. Merck, Germany). All other chemicals were analytical grade.

Preparation of Co-spray-Dried Powders

The feed liquids for spray drying were prepared in compositions such that the co-spray-dried powders obtained would contain the various percentage amounts of ethylcellulose and channeling agent (lactose or PVP K30) as presented in Table 1.

The feed solutions of Formulations I–IV were prepared by adding theophylline into ethylcellulose aqueous dispersion and then adjusted with water to have a solid content of 20%. The feed solutions of Formulations V–IX were prepared by mixing theophylline and channeling agent in 2% ammonia solution, then ethylcellulose aqueous dispersion was added. Colloidal silica (Aerosil 200) in the amount of 1% w/w was also incorporated into the formulation as anti-adherent. The solids content of Formulations V–IX was 12%.

The resultant feed materials were spray dried on a laboratory spray dryer (Niro Atomizer Mobile Minor Unit, Soeborg, Denmark) having a drying chamber of 80 cm in diameter, 60 cm in cylindrical height, and conical base with cone angle of 60°. The feed liquids were atomized using a rotating centrifugal wheel atomizer. The conditions of the spray

Table 1

The Compositions of Co-spray-Dried Powders Prepared to Contain Various Amounts of Ethylcellulose and Channeling Agent

Formulation	Ethylcellulose[a] (%)	PVP K30 (%)	Lactose (%)	Drug to Total Excipient Ratio (%)
I	5	—	—	92.7:7.3
II	10	—	—	85.7:14.3
III	15	—	—	78.6:21.4
IV	20	—	—	71.4:28.6
V	5	5	—	86.9:13.1
VI	5	10	—	81.9:18.1
VII	5	—	15	76.9:23.1
VIII	5	—	25	66.9:33.1
IX	3	—	25	69.7:30.3

[a]Ethylcellulose aqueous dispersion (Surelease®) had solids content of 25.1%, 70% of which was ethylcellulose.

Table 2

Spray Drying Conditions Employed to Prepare Co-spray-Dried Powders

Condition	Formulation I–IV	Formulation V–IX
Inlet air temperature (°C)	140	130
Feed rate (mL/min)	23.8	23.8
Atomizing air pressure (bar)	4	4

drying process adopted after preliminary investigations are presented in Table 2.

Preparation of Co-spray-Dried Matrices

Co-spray-dried powders containing 300 mg of theophylline were weighted and compressed into the tablet matrices. The powders were compressed at a force of 500 lb on a hydraulic press (Carver Laboratory Press, Model C, Fred & Carver Inc., Menomonec Falls, USA) using a 0.95-cm flat-faced, circular punch–die assembly.

Physical Properties of the Matrices

The thickness of 10 matrices was measured using a micrometer (Telclock Co., Tokyo, Japan). The hardness of 10 matrices was determined using a hardness tester (Schleuniger-2E, Dr. K. Schleuniger Co., Solothurn, Switzerland). Disintegration times of six matrices were measured in water using a USP disintegration tester with disk (Model QC-21, Hanson Research Corporation, USA).

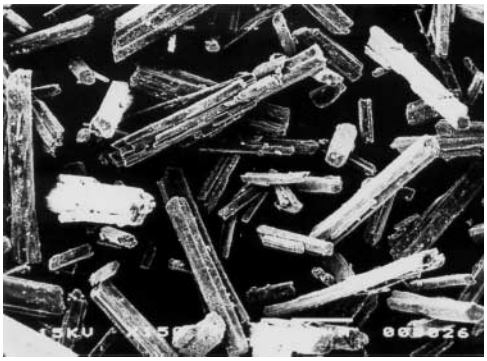
Drug Release Studies

The dissolution testing of the matrices was carried out in two media, 0.1 N HCl and phosphate buffer pH 6.8, using USP dissolution testing apparatus type II (Model SR-2, Hanson Research Corporation, Chatsworth, USA). Three matrices of each formulation were evaluated. The volume of dissolution medium was 900 mL and the paddle was operated at 50 rpm. The proper amounts of dissolution media were withdrawn at various time intervals over a period of 12 hr or until the drug was completely released. The amount of drug dissolved was assayed spectrophotometrically at 268.5 nm and 270.3 nm for 0.1 N HCl and phosphate buffer pH 6.8 as the media, respectively (Spectronic 2000, Bausch & Lomb Ltd., New York, USA).

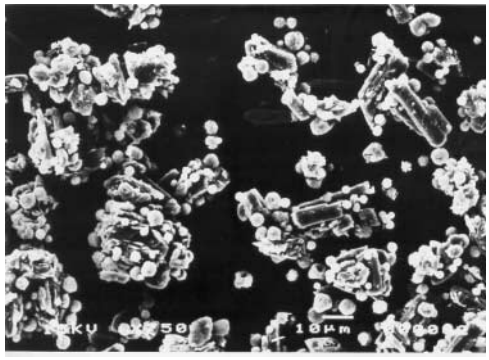
In this work, Formulation IX was also tested in a pH change model according to the method described by Jonkman et al. (9) in comparison with two standard commercially available products. This dissolution test was carried out in 0.1 N HCl for 2 hr, then the pH was increased to 6.8 by adding 4.4 g of NaOH followed by 6.1 g of KH_2PO_4 which was dissolved in a few milliliters of 0.1 N HCl. The dissolution test was continued at pH 6.8 for 10 hr. Other operating conditions of the dissolution test apparatus and determinations of the drug release at various time intervals were as described previously.

RESULTS AND DISCUSSION

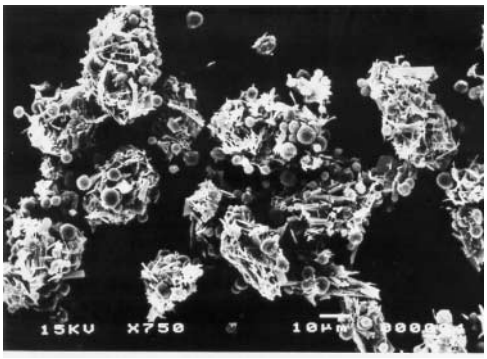
The shape and surface topography of co-spray-dried powders were found to be affected by the formulation of feeding liquids. The photomicrographs of co-spray-dried powders of Formulations I–IV are displayed in Fig. 1. They consist of irregularly shaped agglomerates formed by the cohesion of microspherical particles (largely less than 5 μm) together with rod-shaped particles which might be the crystals of theophylline. But for Formulations II–IV, needle-shaped particles were seen deposited



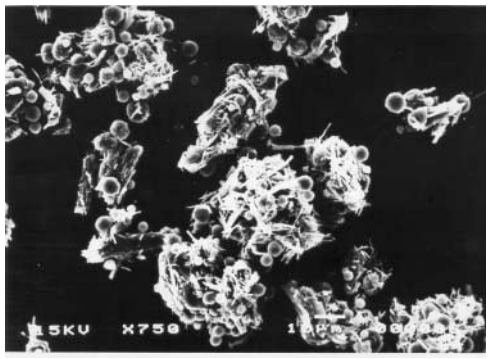
Theophylline



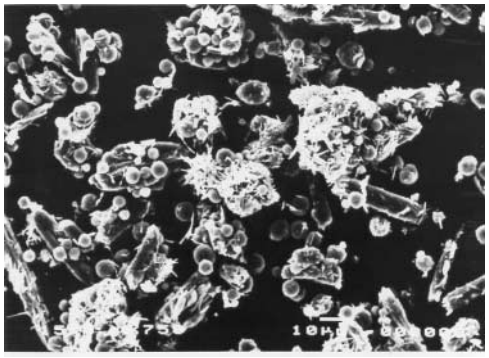
Formulation I



Formulation II



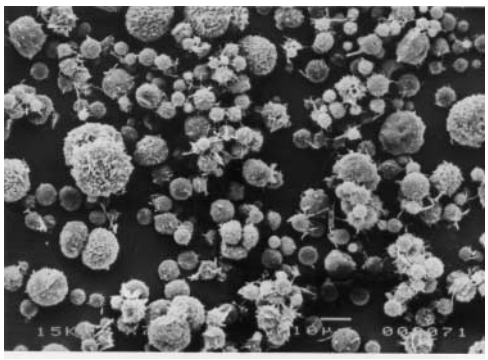
Formulation III



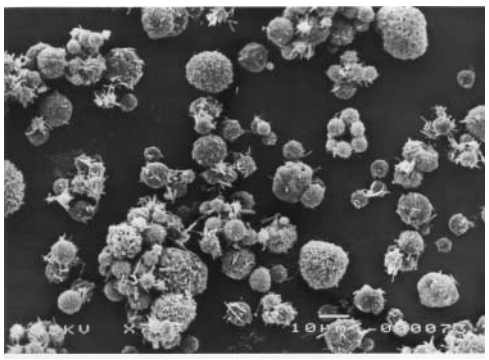
Formulation IV

Figure 1. Photomicrographs of original theophylline crystals and co-spray-dried powders of Formulations I–IV (×750).

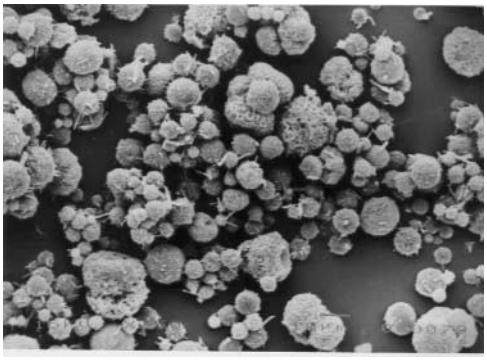
on the surface of agglomerates. The feed liquids of these formulations contained increasing amounts of ethylcellulose aqueous dispersion, which was composed of other additives besides ethylcellulose polymer, e.g., plasticizer, stabilizer, anti-adherent. Therefore, such needle-shaped particles might be formed by the precipitation of these components. Co-spray-dried powders of Formulations V–IX were in spherical particles of various sizes (from about 5 μm to 20 μm) with a needle-shaped microcrystal crust covering on the surfaces (Fig. 2). The formation of agglomerates was also observed, but to a lesser extent in comparison with Formulations I–IV. As water was employed to prepare the feed liquids of Formulations I–IV, a high quantity of rod-shaped crystals of theophylline was observed in



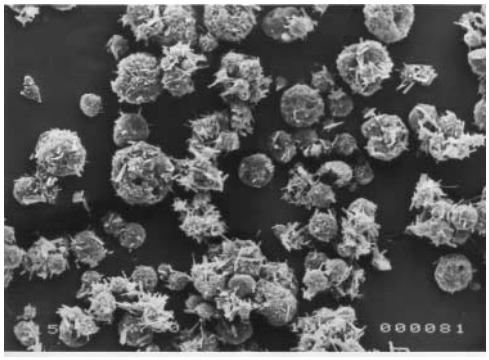
Formulation V



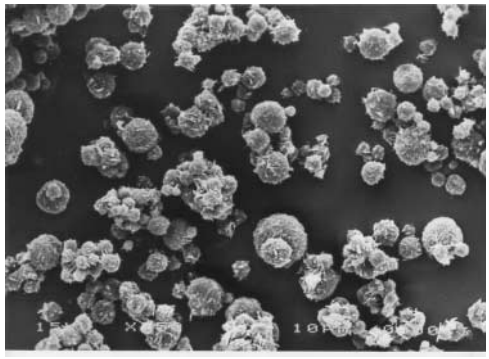
Formulation VI



Formulation VII



Formulation VIII



Formulation IX

Figure 2. Photomicrographs of co-spray-dried powders of Formulations V–IX (×750).

Table 3

Physical Properties of the Matrices Prepared from Co-spray-Dried Powders

Formulation	Weight (mg)	Thickness[a] (mm±SD)	Hardness[a] (kp±SD)	Disintegration Time[b] (hr)
I	312.4	4.14(0.01)	10.7(0.6)	> 2
II	328.8	4.24(0.01)	12.9(0.7)	> 2
III	339.5	4.43(0.01)	15.3(0.5)	> 2
IV	360.3	4.78(0.01)	16.9(0.5)	> 2
V	342.7	4.33(0.01)	10.9(1.0)	> 2
VI	363.1	4.61(0.01)	15.8(2.6)	> 2
VII	390.1	4.97(0.02)	12.6(1.2)	> 2
VIII	429.8	5.45(0.01)	10.4(1.0)	> 2
IX	430.2	5.53(0.01)	9.9(1.2)	> 2

[a]Average of ten determinations.
[b]Average of six determinations.

co-spray-dried powders of Formulations I–IV. This might be due to the drug not being completely dissolved, which left some of the theophylline crystals suspended in the feed solution. While ammonia solution was used to prepare the feed liquids of Formulations V–IX, most of the co-spray-dried powders were in microspherical shapes embedded by a fine needle-like microcrystal crust which might be formed by the precipitation of drug and channeling agent or other components during evaporation of spraying droplets.

The matrices of each formula were prepared by direct compression of spray-dried powders. The resultant physical properties of the matrices are presented in Table 3. The weights of each formulation shown in the table indicate the amounts of co-spray-dried powders employed to prepare the matrices having 300 mg of theophylline (calculated on the basis of drug assay results). All co-spray-dried powders exhibited ease of compression into matrices with high hardness at rather low compression pressure. Compressibility of the co-spray-dried powders was improved with increasing amounts of ethylcellulose in formulations, as shown by the greater hardness of the matrices. Because of the binding action of PVP K30, incorporation of this additive made the matrices harder (Formulation VI). But an increase in the amount of lactose caused a reduction of hardness (Formulations VII and VIII). All matrices remained intact and had no sign of disintegration after 2 hr of testing.

The release profiles of the matrices prepared from co-spray-dried powders of Formulations I–IV in 0.1 N HCl and phosphate buffer pH 6.8 are illustrated in Fig. 3. The concentration of ethylcellulose in the matrices was the rate-determining factor in controlling the release rate of the drug. Increasing the weight fractions of polymer resulted in a corresponding decrease of the release rate in both media. The release rate, therefore, could be modified by alteration of the ethylcellulose content in the matrices.

However, at the same level of ethylcellulose content, the drug release in acidic medium was faster than in alkali medium. This might be due to the higher solubility of theophylline in acidic medium. Figure 4 displays the dissolution of theophylline tablets with no additive in both dissolution media when prepared by direct compression of the pure drug. The dissolution of theophylline from compacted tablets in 0.1 N HCl was faster than in phosphate buffer pH 6.8. The entire tablet was completely dissolved within approximately 5 hr and 6 hr in 0.1 N HCl and phosphate buffer, respectively. This observation was in agreement with the study by Shaikh et al. (10) where the release rate of theophylline from the solid dispersion of theophylline–ethylcellulose in buffer solution pH 7.4 was slower than in 0.1 N HCl.

The different release models (zero-order, first-order, and Higuchi plot) were applied to elucidate the release data of Formulations I–IV. The release characteristics of Formulations I–IV were found to be best fitted to the Higuchi model (Fig. 5). The relationships of Higuchian release rates (the slopes of the plots) in both media as a function of

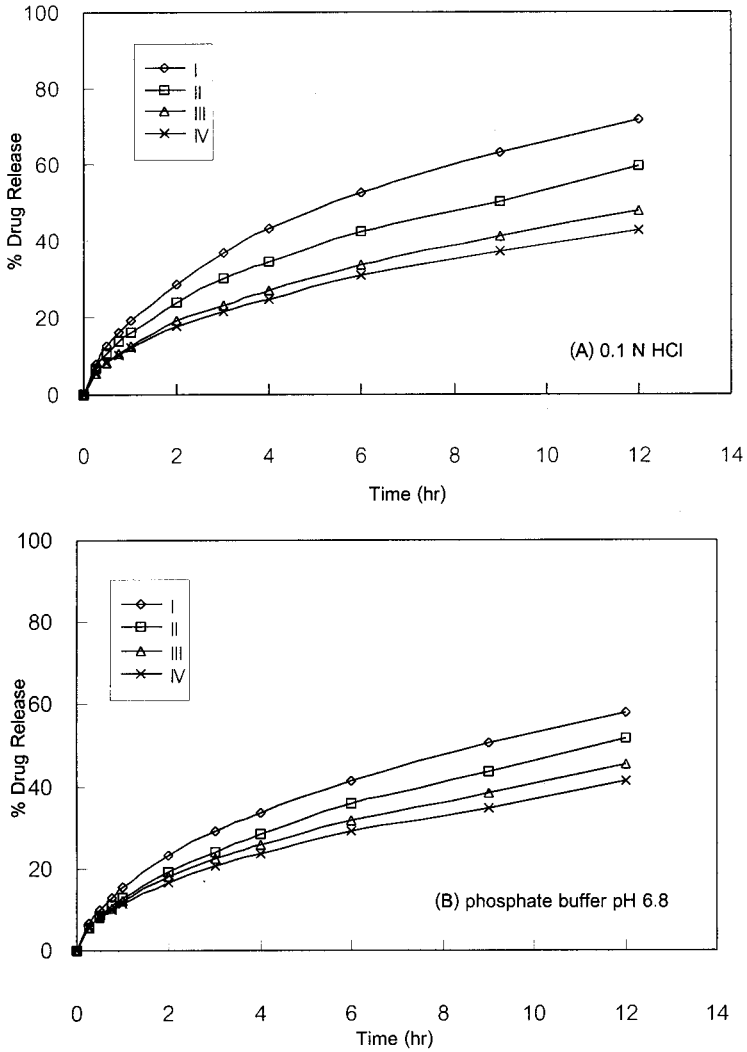


Figure 3. The release profiles of the matrices prepared from Formulations I–IV in (A) 0.1 N HCl, (B) phosphate buffer pH 6.8.

ethylcellulose content are presented in Fig. 6. Less effect of the dissolution medium on the release rate of the drug was observed when the ethylcellulose concentration in matrices was increased.

The channeling agent is a hydrophilic additive which is incorporated into the matrix for the purpose of altering the release rate of the drug. It will be leached from the system to form the pore structure or channel which then allows the active substance to diffuse out faster than it would have done, and also the penetration of dissolution medium into the matrix is facilitated. In order to modify the release rate of the drug, PVP K30 and lactose were selected to be added in co-spray-dried formulations containing 5% ethylcellulose.

The release profiles of Formulations V and VI, when PVP K30 was incorporated into the formulations, are shown in Fig. 7. It was found that PVP K30 had no enhancing effect on drug release. Formulations with PVP K30 had a decreased drug release compared with formulations with no PVP. This might be an increase of matrix hardness, hence the reduction of porosity within the matrices. In addition, the portion of PVP K30 was not easily leached out from the matrices due to its viscosity, induced when contacted with the penetrated

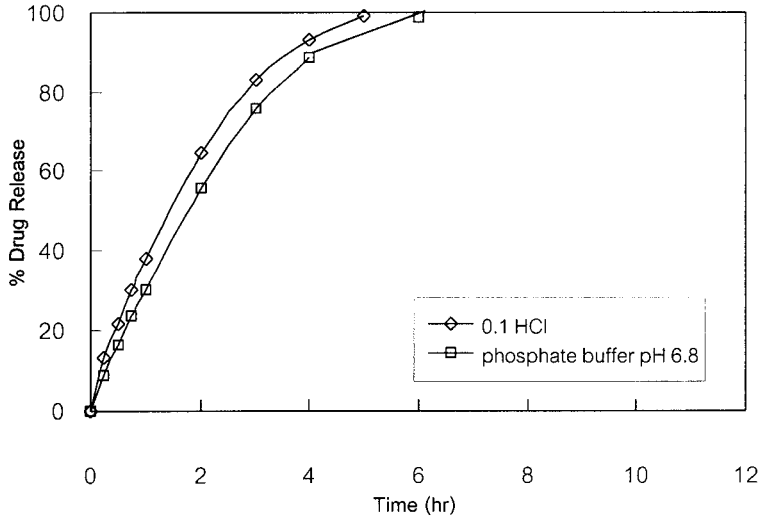


Figure 4. The dissolution profiles of the theophylline compacts without additive in 0.1 N HCl and phosphate buffer pH 6.8.

dissolution media and filling up the pores to make the dissolved drug more difficult to diffuse out of the matrix. An increase in PVP K30 from 5 to 10% made no difference in release profiles in both media. Also, the drug release profiles of Formulations V and VI were affected by the pH of the dissolution media.

Lactose exhibited an increasing effect on drug release rates when it was added into the formulations containing 5% ethylcellulose (Formulations VII and VIII). More than a 10% increase of drug release at 12 hr was observed (Fig. 8). However, the change of lactose quantity from 15 to 25% did not exert much more effect on drug release characteristics in both media. This indicated that the type of channeling agent rather than the amount played the significant role in drug release. Different release models were applied to characterize the release data of Formulations V–VIII. It was apparent that the Higuchi model was the best fit, as shown in Figs. 9 and 10.

Following the release studies of Formulations VII and VIII, Formulation IX which contained 3% ethylcellulose and 25% lactose as channeling agent was then developed in order to adjust the release properties of co-spray-dried matrices to be compared with the standard marketed products (Theodur® and Neulin®). The release properties of this formulation in acid and alkali media are shown in Fig. 11 and the Higuchi plots are presented in Fig. 12.

Figure 13 displays the comparative release patterns of Formulation IX and two other commercial products in pH change medium. The release profile of the developed product was comparable to those of Theodur and Neulin. The release pattern of the co-spray-dried matrices was characterized by a smooth convex curve without an inflection point. The release pattern of Theodur was slower in the first 2 hr compared with spray-dried matrices and Neulin, and faster at the end of the release profile. Theodur consists of pellets embedded in a base which contains a fraction of the drug as well as other excipients to control its release (11). So the additional drug outside the pellets formed the initial phase of drug release, followed by the latter phase of drug release provided by the coated pellets. This wavelike appearance of the release profile was in agreement with previous reports (9,12). Neulin is a slowly eroding matrix. The release rate was relatively fast at the initial stage, caused by the drug on the surface of the matrix, followed by a stage with a decreased rate. But after the third hour, the erosion of the outer layer of the tablet caused a gradual increase of drug release, showing an inflection in the release curve.

The surface topography of the co-spray-dried matrices (Formulation IX) before and after release testing by surface and cross-section views is displayed in Fig. 14. The photomicrographs show that the matrices were composed of compressed microspheres (Fig. 14A).

The microcrystal covering on the surface of the co-spray-dried microspheres, which might be the crystals of theophylline, was also observed on the

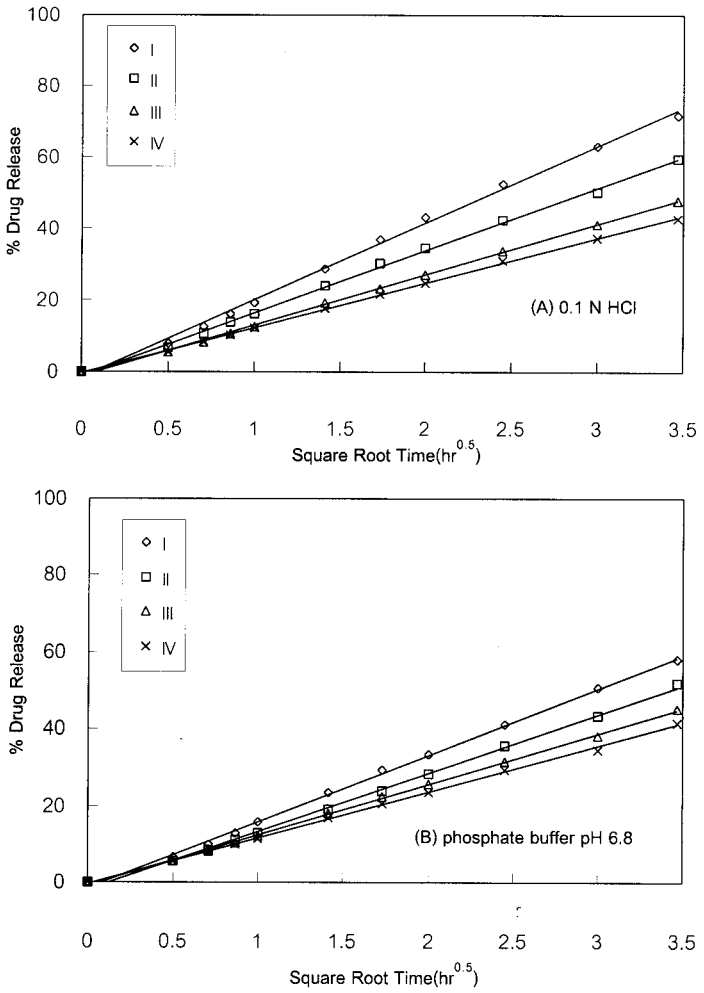


Figure 5. The Higuchi plots of co-spray-dried matrices prepared from Formulations I–IV in (A) 0.1 N HCl, (B) phosphate buffer pH 6.8.

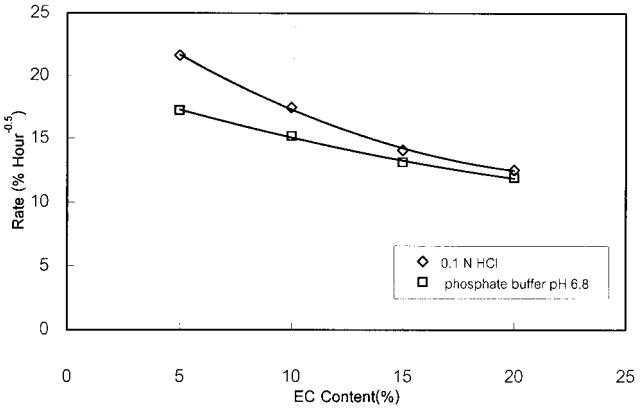


Figure 6. The relationships between the contents of ethylcellulose in the matrices and the Higuchian release rates (% $hr^{-0.5}$) in 0.1 N HCl and phosphate buffer pH 6.8.

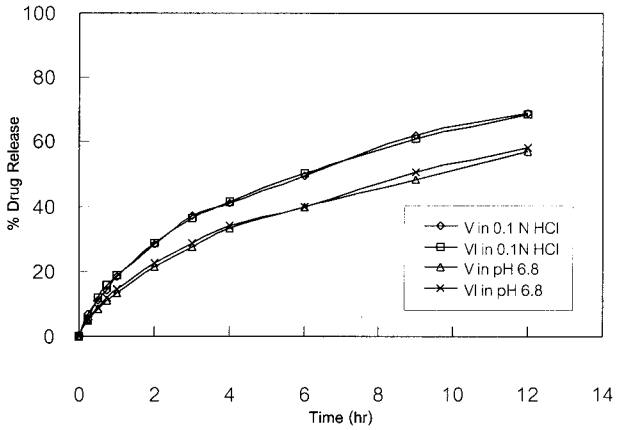


Figure 7. The release profiles of the matrices prepared from Formulations V and VI in 0.1 N HCl and phosphate buffer pH 6.8.

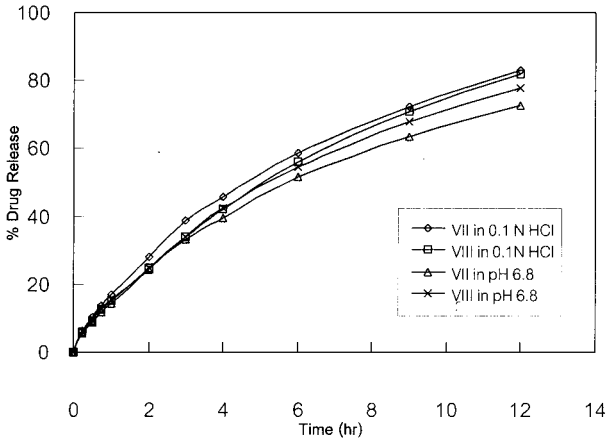


Figure 8. The release profiles of the matrices prepared from Formulations VII and VIII in 0.1 N HCl and phosphate buffer pH 6.8.

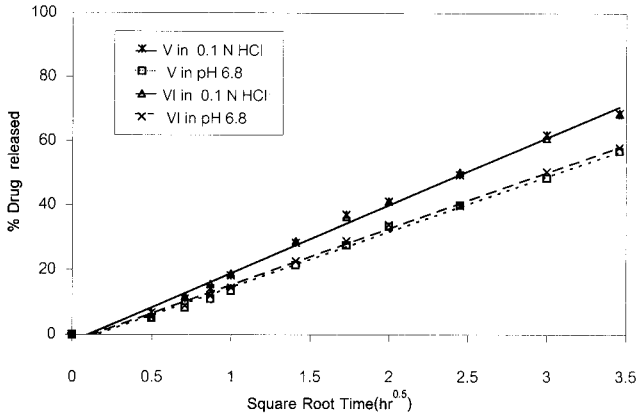


Figure 9. The Higuchi plots of co-spray-dried matrices prepared from Formulations V and VI in 0.1 N HCl and phosphate buffer pH 6.8.

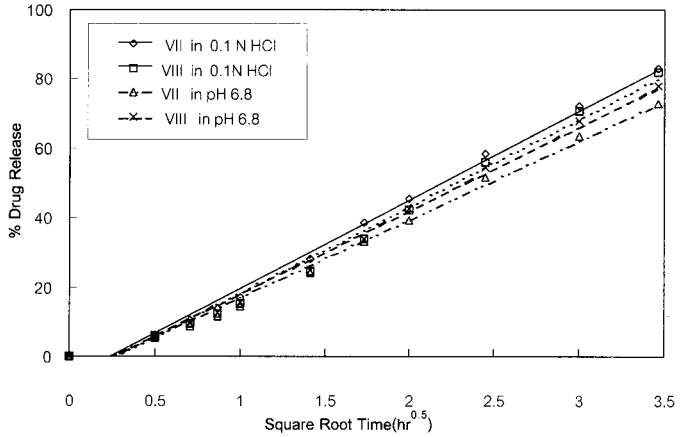


Figure 10. The Higuchi plots of co-spray-dried matrices prepared from Formulations VII and VIII in 0.1 N HCl and phosphate buffer pH 6.8.

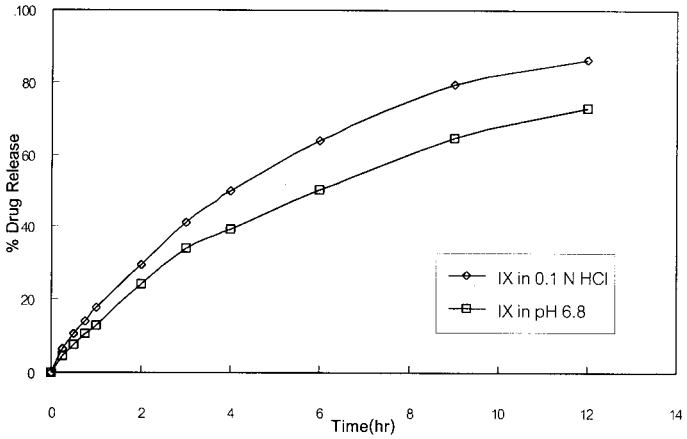


Figure 11. The release profiles of the matrices prepared from Formulation IX in 0.1 N HCl and phosphate buffer pH 6.8.

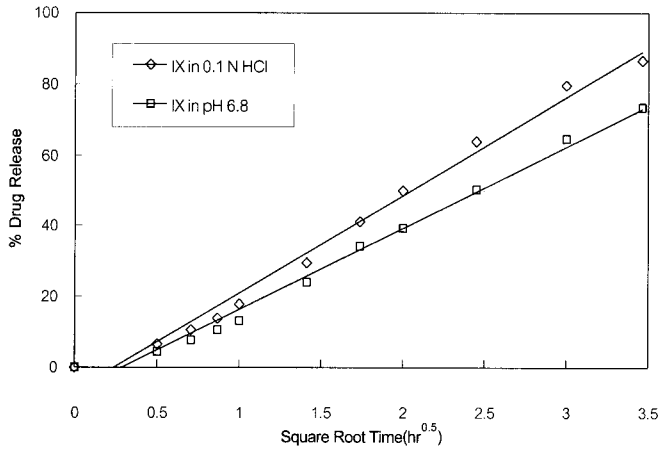


Figure 12. The Higuchi plots of co-spray-dried matrices prepared from Formulation IX in 0.1 N HCl and phosphate buffer pH 6.8.

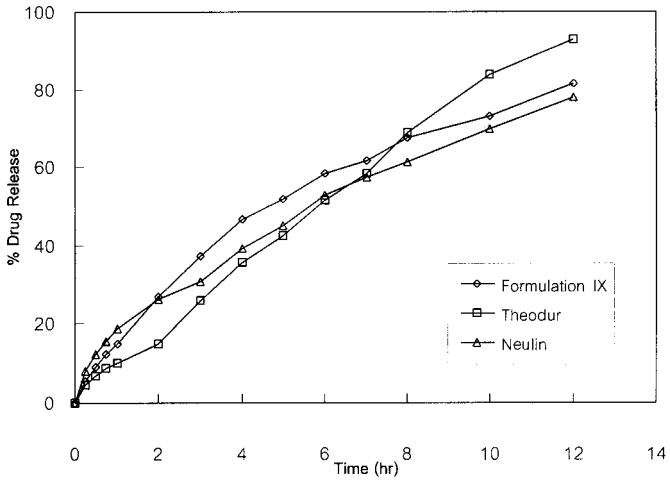
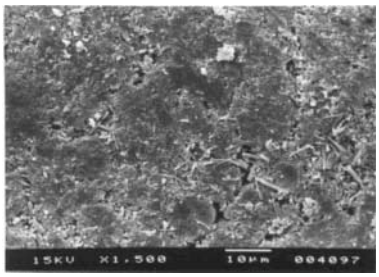
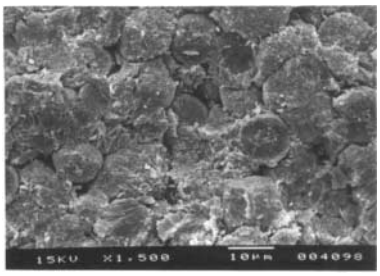


Figure 13. The release profiles of matrices prepared from Formulation IX, Neulin, and Theodur in pH change medium.

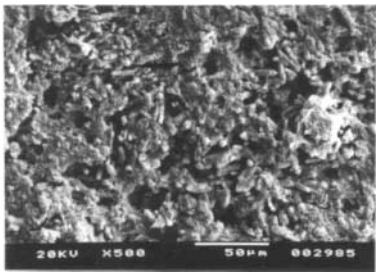


Surface View(X1500)

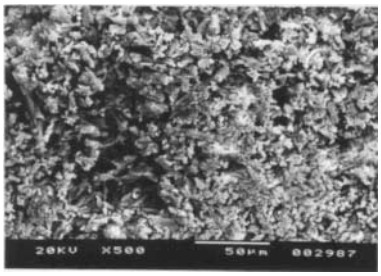


Cross-Section View(X1500)

(A) Before Release Testing

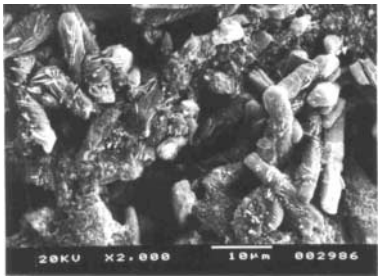


Surface View(X500)

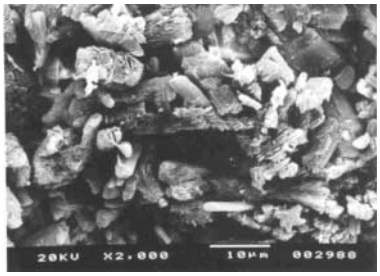


Cross-Section View(X500)

(B) After Release Testing



Surface View(X2000)



Cross-Section View(X2000)

(B) After Release Testing

Figure 14. Photomicrographs of surface and cross-section view of the co-spray-dried matrices (A) before and (B) after release testing at different magnifications.

surface view of the matrices. These theophylline microcrystals might cause the rather initial fast release of co-spray-dried matrices in comparison with the release of the other two commercial products, as described previously. On the cross-section view of the matrices, interparticulate spaces could clearly be seen at the contact points of adjacent microspheres.

Figure 14B shows the matrices after the release testing at different magnifications. After the drug and other soluble components were leached, the polymeric network of the ethylcellulose fibers was clearly observed. The porous structure formed by the polymer fibers would control the diffusion rate of the drug. It is interesting to note that an increase of ethylcellulose concentration would result in more polymer fibers, which would increase the tortuosity of the matrices. This causes the diffusion of the drug from the matrices to be more difficult, hence decreasing the release rate.

CONCLUSIONS

Aqueous ethylcellulose dispersion, as demonstrated in this investigation, has been applied in conjunction with spray drying techniques to produce drug–polymer co-spray-dried powders for manufacture of sustained release matrices. The resultant powders could be directly compressed into tablets without further processing. Desired release rates of the drug from the matrices could be obtained by proper alteration of the ethylcellulose content and other components in the formulation, e.g., types and concentrations of channeling agents.

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