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RESEARCH PAPER

Properties of Hot-Melt Extruded Theophylline Tablets Containing Poly(Vinyl Acetate)

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ABSTRACT

The objectives of this study were to investigate the properties of poly(vinyl acetate) (PVAc) as a retardant polymer and to study the drug release mechanism of theophylline from matrix tablets prepared by hot-melt extrusion. A physical mixture of drug, polymer, and drug release modifiers was fed into the equipment and heated inside the barrel of the extruder. The cylindrical extrudates were either cut into tablets or ground into granules and compressed with other excipients into tablets. Due to the low glass transition temperature of the PVAc, the melt extrusion process was conducted at approximately 70°C. Theophylline was used as the model drug in this study. Theophylline was present in the extrudate in its crystalline form and was released from the tablets by diffusion. The Higuchi diffusion model and percolation theories were applied to the dissolution data to explain the drug release properties of the matrix systems. The release rate was shown to be dependent on the granule size, drug particle size, and drug loading in the tablets. Water-soluble polymers were demonstrated to be efficient release rate modifiers for this system.
Key Words: *Higuchi diffusion model; Hot-melt extrusion; Poly(vinyl acetate); Sustained release.*

INTRODUCTION

Hot-melt extrusion is one of the most widely applied processing techniques in the plastics industry. Hot-melt extrusion is used not only in the production of plastic goods, but also in polymer production and compounding. More than half of all plastic products, including plastic bags, sheets, and pipes, are manufactured by this process. During hot-melt extrusion of pharmaceutical dosage forms, a blend of active ingredient, thermoplastic

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polymeric carrier, and other processing aids, including plasticizers and antioxidants, is heated and softened inside the extruder and then pressurized through a die into granules, cylinders, or films. Hot-melt extrusion has many advantages over the traditional methods to prepare sustained-release dosage forms. Because hot-melt extrusion is a solvent-free process, there are no concerns with solvent handling or recovery after processing. Hot-melt extrusion is a simple and continuous process for the preparation of tablets and granulations. The process is faster, and there are fewer steps than the wet granulation method. When the extrudate is cooled to room temperature, the polymeric thermal binder solidifies and bonds the excipients together to form a matrix.

The hot-melt extrusion technique has previously been used successfully to prepare pharmaceutical dosage forms. Folloniers et al. (1,2) extruded sustained-release diltiazem hydrochloride granules. Aitken-Nichol et al. (3) and Repka and coworkers (4) reported on the properties of hot-melt extruded polymeric films for transdermal drug delivery and wound care. The properties of hot-melt extruded sustained-release matrix tablets containing polyethylene oxide (PEO) were reported by Zhang and McGinity (5).

Since both the drug and the polymer must remain stable during processing, polymeric materials suitable for thermal processing require either a low glass transition temperature or a low melting point in the case of semicrystalline polymers. Poly(vinyl acetate) (PVAc) is a homopolymer synthesized from a vinyl acetate monomer via a free-radical polymerization technique. It is amorphous due to the presence of an acetate ester side chain in the backbone structure. The glass transition temperature of PVAc is relatively low due to its highly flexible backbone structure. Although water insoluble, it is slightly hydrophilic and is able to absorb water to a slight extent. The polymer has been used in the preparation of matrix pellets (6), sustained-release coatings (7), and buccal drug delivery systems (8).

The objectives of the present study were to investigate the properties of PVAc as a drug carrier and to study the release mechanisms of theophylline from matrix dosage forms prepared by hot-melt extrusion. The influence of granule size, drug-loading level, and particle size on the drug release properties was studied. The thermal stability of PVAc was also investigated. Wide-angle X-ray diffraction (WAXD) and differential scanning calorimetry (DSC) were used to characterize the crystalline and thermal properties of the granules and the extruded dosage forms.

EXPERIMENTAL

Materials

PVAc of molecular weight 12,000 (Sentry® Plus 12) and 45,000 (Sentry Plus 40) were purchased from the Union Carbide Corporation (Danbury, CT) under the trade name Sentry Plus. Theophylline and polyethylene glycol 400 (PEG400) were purchased from Spectrum Chemical Manufacturing Corporation (Gardena, CA).

Pulverization of Polymeric Raw Materials

The PVAc was received as beads. A cryogenic grinder (model CF, Micron Powder System, Summit, NJ) was used to pulverize the raw material into powder particles that were then passed through a 60-mesh screen. PVAc beads were first soaked in liquid nitrogen (−123°C) for 2 to 3 min and then fed inside the cryogenic grinder, in which they were impacted against the stainless steel wall of the grinding chamber by a rotating metal bar.

Hot-Melt Extrusion Process

A dry blend of drug, polymer, and the other excipients was processed using a single-screw Brabender extruder (C. W Brabender Instrument, Inc., S. Hackensack, NJ). The extruder was driven by a Plasticorder® (model EPL-V5501, C. W. Brabender Instrument) electronic torque rheometer unit. The L/D ratio of the barrel, which had two heating zones, was 15:1. A single flight screw of uniform pitch was used, and a rod-shaped die was attached to the end of the barrel. A physical blend of the ingredients of each formula was prepared by mixing the powders in a V-shell blender for 10 min. The mixture was then fed into the extruder. The two heating zones and the die temperature of the extruder were set at 50°C, 60°C, and 75°C, respectively. The dwell time of the feeding stock inside the barrel was approximately 2 min. The cylindrical extrudate was either cut into tablets (8 mm in diameter and 3.5 mm thick) or fed into a pelletizer after being cooled to room temperature in an air tunnel. Further reduction in the particle size of the pellets was made using the cryogenic grinder. These fine granules were then blended with microcrystalline cellulose (Avicel® PH-200) and magnesium stearate (0.5%) and compressed into 400-mg tablets. The magnesium stearate was present as the lubricant.

Dissolution Study

Dissolution testing was performed according to method II of the USP 23. The dissolution medium (900

ml of purified water) was maintained at 37°C and agitated at 100 rpm. Theophylline was analyzed by UV spectroscopy using a Hewlett Packard® diode array spectrophotometer (model 8452A) at a wavelength of 260 nm.

Physical Characterizations of the Polymer and Extrudate

DSC (model 2920, TA Instrument, New Castle, DE) was used to characterize the thermal properties of the drug, polymer, physical mixture, and extrudate. Ultrahigh purity nitrogen was used as the purge gas at a flow rate of 150 ml/min. Approximately 15 mg of sample was weighed into a nonhermatically sealed aluminum pan. The temperature ramp speed was set at 10°C per minute for all samples.

WAXD was performed to characterize the crystalline properties of the excipients and the extrudate. A Philips vertical scanning diffractometer (type 42273, Philips Electronic Instrument, Mount Vernon, NY) was used. The X-ray source was CuK_α radiation under 35 kV and 20 mA. The wavelength of the X-ray was 1.5404 Å. The angle of the scan ranged from 5° to 45° in increments of 0.05° per second.

Scanning electron microscopy was used to study the surface morphology of the hot-melt extruded tablets. The sample was mounted on a brass stage using an adhesive carbon tape and placed in a low-humidity chamber for 12 hr prior to testing. The sample was coated with gold-palladium using a Pelco® model 3 cold sputter module (TED Pella, Inc., Tustin, CA) in a high-vacuum chamber. Scanning electron microscopy was performed using a JEOL model 35 scanning electron microscope (JEOL, U.S.A., Inc., Peabody, MA) at 25 kV. A Polaroid® 545 Land Camera with 4 inch by 5 inch exposure was used to take the micrographs.

Thermal Stability of the Poly(Vinyl Acetate)

Gel permeation chromatography was used to study the stability of the polymer (Waters® system, Waters Association, Inc., Milford, MA). Polystyrene was used as the calibration standard, and tetrahydrofuran containing butylated hydroxytoluene as a stabilizer was used as the solvent and mobile phase.

A Brabender Plasticorder rheometer (mixer type P 600) was used to determine the thermal and shear stability of the PVAc. During the test, the polymer was fed into a preheated chamber containing two counterrotating blades. The torque needed to rotate the blades was then monitored since a change in the torque would be indicative of thermal degradation, shearing degradation, or cross-linking of the polymer. A 40-g sample of PVAc was used. The chamber temperature was set at 70°C. A Perkin-Elmer 7 series thermal gravimetrical analysis system (Norwalk, CT) was also employed to determine the thermal degradation temperature of the polymer. A PVAc sample was monitored from 30°C to 900°C at a ramp speed of 40°C per minute.

THEORETICAL DISCUSSION

In 1963, Higuchi (9) developed a mathematical analysis of the release properties of solid drug particles dispersed in a solid matrix. The solid matrices included both homogeneous matrices and granular matrices with connecting capillaries. In the homogeneous matrix, the molecules of the active ingredient diffuse from the surface of the drug particles through the surrounding matrix and into the dissolution medium. In the granular matrix model with connecting capillaries, the dissolution medium penetrates the drug/polymer matrix through pores, cracks, and intragranular spaces during the dissolution test. Drug particles slowly dissolve in the dissolution medium, and the drug molecules diffuse into the bulk dissolution medium through channels that are filled with the release medium. Equations were developed for the planar and spherical drug release system. The percentage of drug released was proportional to the square root of time in the planar systems. For the spherical system, the following equation was derived:

$$1 + 2 \times (\alpha'/\alpha_0)^3 - 3 \times (\alpha'/\alpha_0)^2 = \frac{6DKC_s t}{\tau \alpha_0^2} \qquad (1)$$

In Eq. 1, $(\alpha'/\alpha_0)^3$ represents the residual fraction of the drug inside the matrix at time *t*. *D* is the diffusivity of the drug in the dissolution medium, *K* is equal to the specific volume of the drug, C_s is the solubility of the drug in the surrounding medium, and τ represents the tortuosity of the matrix. Equation 1 is based on the following three assumptions: (*a*) pseudo–steady state; (*b*) amount of drug inside the granules at least three to four times higher than could be dissolved in the capillaries present in the granules; (*c*) drug particles are relatively small compared to the distance of diffusion and uniformly distributed (9). Equation 1 has been successfully applied to model the drug release kinetics of several matrix systems (10,11) . However, the model has been oversimplified in some cases, and significant deviation from the Higuchi equation has been observed at low levels of drug loading (12).

During the past 10 years, the percolation theory has been successfully used to explain the mechanism of drug

release from matrix systems (13–15). The percolation theory is a statistical theory that is related to the formation of clusters and the presence of either site and/or bond percolation. This theory has been applied in many scientific disciplines. Leuenberger and coworkers first introduced the percolation theory into the pharmaceutical field in the late 1980s (16,17). According to this theory, when a matrix is composed of a water-soluble drug and a water-insoluble polymer, the active ingredient will be present as clusters composed of interconnecting drug particles. At low drug-loading levels, the drug is not accessible to the dissolution medium, and most of the clusters of drug particles are completely ''encapsulated'' by the water-insoluble polymeric materials. These drug clusters are called *finite clusters*. Drug release normally shows a ''burst effect,'' followed by a slow-release phase. The initial burst is attributed to the low percentage of drug clusters located at the surface of the tablet in direct contact with the dissolution medium, while slow drug release corresponds to the diffusion of drug molecules from the encapsulated finite clusters through the polymeric materials and into the dissolution medium. Drug molecules in those finite clusters have to diffuse through the polymeric barrier to be released. Compared with the direct dissolution of drug molecules into the dissolution medium, diffusion through a water-insoluble polymeric material is a much slower process. Incomplete drug release is often observed at low drug-loading levels. When drug loading reaches a certain level, the interconnecting network of drug particles spans the entire tablet volume, and all the drug particles are accessible to the surrounding dissolution medium. This type of cluster that spans the whole tablet is referred to as an *infinite cluster* (13). The critical drug-loading value is called the drug percolation threshold P_{c1}. The Higuchi equation was reported to be invalid at and below the percolation threshold (12). Above the drug percolation threshold level, the dissolution kinetics follow the Higuchi equation.

RESULTS AND DISCUSSION

The DSC profiles in Fig. 1 demonstrate that PVAc is amorphous, and the glass transition temperatures of the two grades of the PVAc of molecular weight 12,000 and 45,000 were 32.7°C and 35.9°C, respectively. The tablet formulations and the respective processing conditions are seen in Table 1. Due to the low glass transition temperature of the PVAc, the hot-melt extrusion processing temperature was approximately 70°C.

Dissolution tests were performed according to the USP 23 dissolution method II to investigate the drug release properties of theophylline from the matrix tablets. PVAc was in a rubbery state during the dissolution test since the glass transition temperature of PVAc was lower than the temperature of the dissolution medium (37°C). Tablets containing extruded granules maintained their original shape throughout the dissolution process due to the sticking of PVAc granules at 37°C. For a polymeric matrix drug release system, the active ingredient may be released by either diffusion of the drug from the matrix or erosion of the matrix. Since PVAc is a water-insoluble polymer, theophylline was released from the matrix granules by a diffusion process.

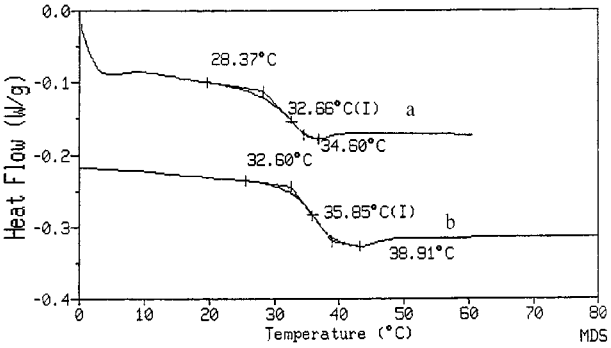


Figure 1. Differential scanning calorimetry of poly(vinyl acetate): a, Sentry Plus 12 (MW 12,000); b, Sentry Plus 40 (MW 40,000).

The rod-shaped extrudates were ground into granules and then compressed into tablets with the combination of microcrystalline cellulose for formulations 1 through 8 (Table 1). The influence of granule size on the release rate of theophylline from the compressed tablets containing the hot-melt extruded granules is seen in Fig. 2. As the size of hot-melt extruded theophylline/PVAc granules was increased, there was a significant decrease in the release rate of the theophylline. Less than 50% theophylline was released from tablets containing 500 to 600 μm granules after 12 hr in 900 ml of purified water. Since the drug was released from the matrix by a diffusion mechanism, the decrease in the drug release rate from the tablets containing larger granules was a result of a longer diffusion pathway. The dissolution data were plotted according to the Higuchi equation; the profiles appear in Fig. 3. A higher deviation from the theoretical prediction was observed for tablets containing granules smaller than 125 μm. Since the Higuchi equation is based on the assumption that the size of the matrix is significantly larger than the drug particles, this assumption was not valid for granules smaller than 125 μm when theoph-

Table 1

Formulations and Processing Conditions for Tablets or Granules Prepared by Hot-Melt Extrusion

	Formulation of the Hot-Melt Extrudate (%)										
	Theophylline			PVAc, Sentry	PEG		PEO		HPMC,	Extrusion Torque[a]	Processing Following
Formula	45 μm	75 μm	150 μm	Plus 40	400	Lactose	0.5 m	1.0 m	E5	$N \times M$	Hot-Melt Extrusion
1	5			93	2					18	Matrix tablets containing HME granules
2	15			83	2					20	Matrix tablets containing HME granules
3	25			73	2					16	Matrix tablets containing HME granules
4	50			45	2					18	Matrix tablets containing HME granules
5		25		73	2					22	Matrix tablets containing HME granules
6			25	73	2					20	Matrix tablets containing HME granules
7	25			58	2	15				19	Matrix tablets containing HME granules
8	25			48	2	25				22	Matrix tablets containing HME granules
9	25			30		25	20			40	HME tablets
10	25			30		25		20		45	HME tablets
11	25			30		25			20	42	HME tablets

Zone temperature setting for the extruder was 50°C (zone 1), 60°C (zone 2), and 75°C (die).
The screw rotation speed was set at 35 rpm.

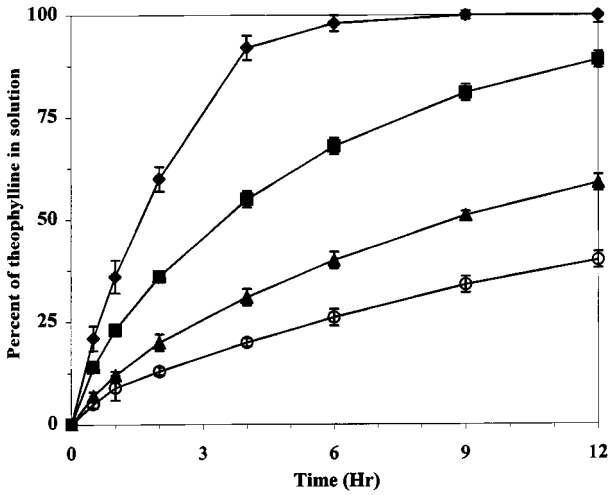


Figure 2. Influence of the granule particle size on the theophylline release properties of the tablets containing hot-melt extruded granules ($n = 3$). Tablets: 20% extruded granules (formula 3: 25% theophylline, 2% PEG, and 73% PVAc), 79.5% Avicel PH-200, and 0.5% magnesium stearate. ◆, Less than 125 μm; ■, 180 to 212 μm; ▲, 300 to 425 μm; ○, 500 to 600 μm.

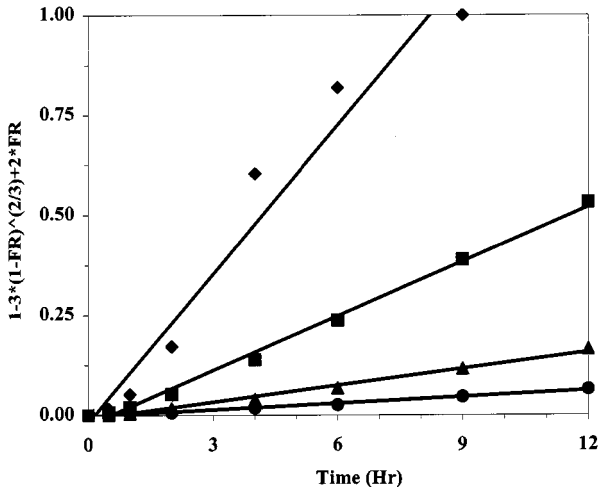


Figure 3. Higuchi diffusion model fitting of the theophylline release data from tablets containing hot-melt extruded granules. Tablets: 20% extruded granules (formula 3: 25% theophylline, 2% PEG, and 73% PVAc), 79.5% Avicel PH-200, and 0.5% magnesium stearate. ◆, Less than 125 μm, $y = 0.1240 \times t - 0.0183$, $r^2 = .9608$; ■, 180 to 212 μm, $y = 0.0453 \times t - 0.0238$, $r^2 = .99945$; ▲, 300 to 425 μm, $y = 0.0138 \times t - 0.0083$, $r^2 = .9902$; ●, 500 to 600 μm, $y = 0.0053 \times t - 0.0022$, $r^2 = .9909$.

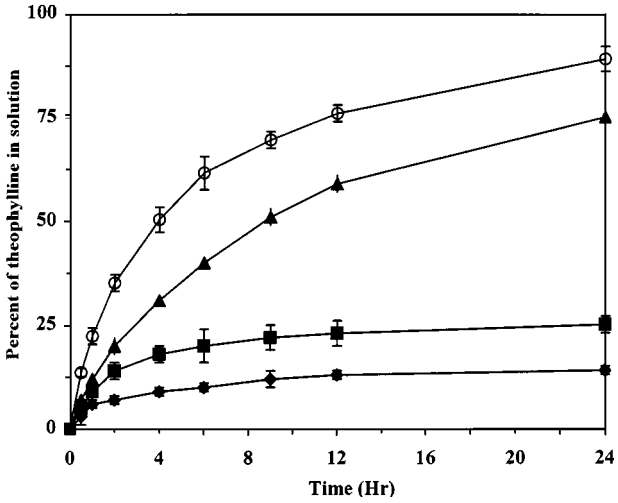


Figure 4. Influence of drug-loading levels on theophylline release properties of the tablets containing hot-melt extruded granules (n = 3). Tablets: 20%, 300 to 425 μm extruded granules (formulas 1–4: theophylline, 2% PEG, and PVAc q.s. to 100%), 79.5% Avicel PH-200, and 0.5% magnesium stearate. ◆, 5% loading; ■, 15% loading; ▲, 25% loading; ○, 50% loading.

ylline particles of 45 μm in diameter were incorporated into the granules. The lag time in Fig. 3 is indicated by the positive intercepts of the linear regression curves on the time axis. It is assumed, for the Higuchi model, that the time for drug to be released from the matrix does not begin until the dissolution medium penetrates the pellet (9). The lag time in Fig. 3 corresponds to the time required for the dissolution medium to wet the matrix and permeate into the capillaries. Ford et al. (18,19) reported that the lag time was longer for hydrophobic drugs.

The influence of theophylline loading on the release properties of tablets containing extruded granules is shown in Fig. 4. The PVAc was demonstrated to have high solids-carrying capacity when processed by hot-melt extrusion. A powder blend containing 50% theophylline could be readily processed. When drug loading was below 25%, less than 20% of the theophylline was released from the matrix after 12 hr, and two distinctive phases were seen in the dissolution profiles (Fig. 4). From percolation theory, only finite clusters that were isolated from the surrounding dissolution medium were formed when drug loading was below the percolation threshold. The initial fast release rate was due to the small percentage of finite clusters located on the surface of the matrix and connected to the dissolution medium. As indicated by the drug release profiles in Fig. 4, the percolation threshold for theophylline was approximately 20%. For granules containing higher levels of theophylline, clusters were more extensive, and the matrix was less tortuous. This contributed to faster drug release rates at higher drug-loading levels.

The influence of drug particle size on the release properties of theophylline from tablets was also investigated. Potter et al. (20) used potassium chloride as a model drug in ethylcellulose matrix tablets, and faster release rates were reported for tablets containing finer particles of the drug. The authors attributed this result to the faster intrinsic dissolution rate of the smaller particles and the increased porosity and decreased tortuosity of the tablet. According to the percolation theory, the total number of particles increases when the drug particle size is reduced. Since more drug lattice sites are generated, the infinite clusters of drug substance can be formed much easier and become more extensive, resulting in faster release rates. Dissolution profiles of tablets containing theophylline with a mean particle size of 150, 75, and 45 μm are shown in Fig. 5. No significant difference in the drug release properties of the tablets containing theophylline particles of mean diameter 45 and 75 μm was observed. Drug particles with a small particle size have a strong tendency to agglomerate. The size of the theophylline agglomer-

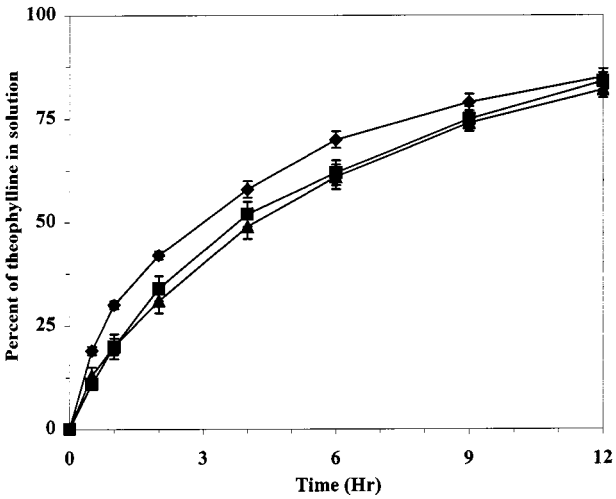


Figure 5. Influence of drug particle size on theophylline release properties of tablets containing hot-melt extruded granules (n = 3). Tablets: 20%, 212–300 μm extruded granules (formulas 3, 5, and 6: 25% theophylline, 2% PEG, and 73% PVAc), 79.5% Avicel PH-200, and 0.5% magnesium stearate. ◆, 150 μm (formula 6); ■, 75 μm (formula 5); ▲, 45 μm (formula 3).

ates was similar despite the difference in the size of the individual particles. Due to this agglomeration, theophylline with a particle size mean diameter of 45 or 75 μm was released at the same rate from tablets containing the hot-melt extruded granules.

As shown in Fig. 6, there was no significant difference in the theophylline release rates from tablets containing hot-melt extruded granules at the 10% and 20% loading levels. A further increase in the level of the granules resulted in a decrease of the drug release rate. At low granule loading in the tablets, hot-melt extruded granules were separated from each other inside the matrix tablets. As the concentration of PVAc granules in the tablets increased, the polymeric particles fused together during the compression process due to the low glass transition temperature and hydrophobicity of the PVAc. The fused granules formed hydrophobic domains that were larger than the individual granules. Drug release from these domains was significantly slower than from the individual particles due to the resultant increase in tablet tortuosity.

Lactose was added as a water-soluble additive to modify the release profile of theophylline from the matrix tablets. An increase of approximately 12% in the theophylline release rate was achieved when the lactose loading level reached 25% (Fig. 7). During the dissolution process, the lactose leached into the dissolution medium and created a porous matrix through which the theophylline diffused. Based on the percolation theory, water-soluble excipients could facilitate the drug release process by increasing the formation of infinite clusters.

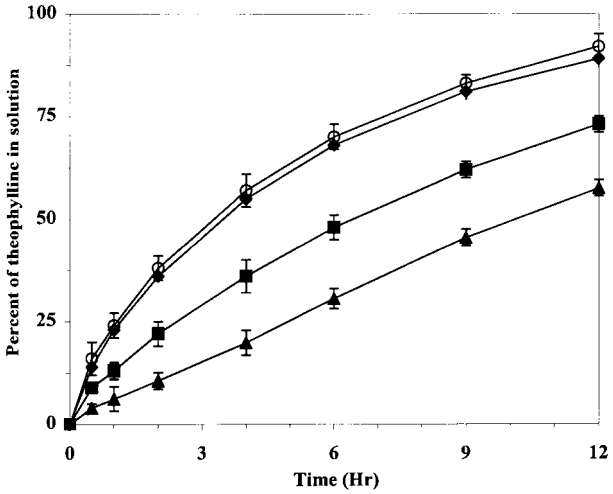


Figure 6. Influence of the loading level of hot-melt extruded granules on theophylline release from the tablets ($n = 3$). Tablets: 180 to 212 μm extruded granules (formula 3: 25% theophylline, 2% PEG, and 73% PVAc), 0.5% magnesium stearate, and Avicel PH-200 q.s. to 100%. ○, 10% granule loading; ◆, 20% granule loading; ■, 30% granule loading; ▲, 60% granule loading.

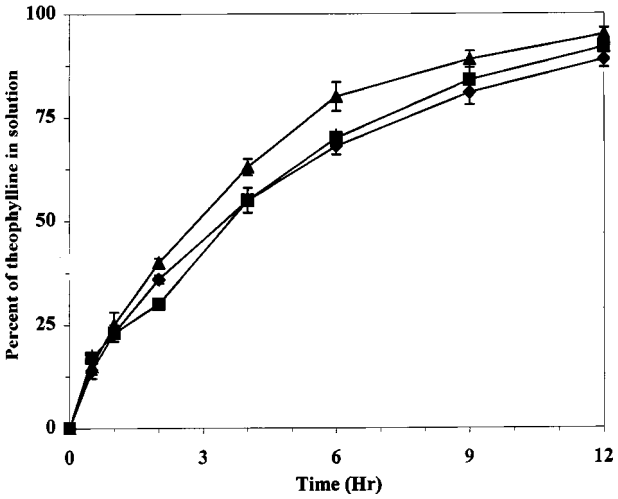


Figure 7. Influence of lactose as a pore-forming agent on theophylline release from tablets containing hot-melt extruded granules ($n = 3$). Tablets: 25%, 180–212 μm extruded granules (formulas 3, 8, and 9), 79.5% Avicel PH-200, and 0.5% magnesium stearate. ◆, 0% lactose; ■, 15% lactose; ▲, 25% lactose.

During the hot-melt extrusion process, polymeric retardants are subjected to both thermal stress and shear stress. The thermal stress is due to the high processing temperature associated with the hot-melt extrusion process. Depolymerization and thermal oxidation of the polymer may occur from high-temperature processing. The shear stress imposed on the polymer by the rotating screw during the extrusion process could also induce a physical scission of the polymeric chains. Stability of PVAc during hot-melt extrusion was investigated in this study. As seen in Table 1, the hot-melt extrusion process was conducted in the temperature range 50°C to 70°C, and the torque during extrusion was less than 30 newton-meters. The low thermal and shear stress conditions were due to the low glass transition temperature of the polymer.

Gel permeation chromatography was conducted to determine the molecular weight of the PVAc before and after thermal processing. The number-average and weight-average molecular weights of PVAc are presented in Table 2. Polystyrene was used as the reference standard. The measured molecular weights of the two polymer samples before processing were in good agreement

Table 2

Stability of PVAc Determined by Gel Permeation Chromatography

	Before Extrusion	After Extrusion	Literature Value[b]
Sentry Plus 12[a]			
Number-average M_W	6612 ± 604	6246 ± 481	
Weight-average M_W	12,720 ± 324	12,795 ± 1233	12,000
Sentry Plus 40[a]			
Number-average M_W	15,739 ± 3102	16,232 ± 2513	
Weight-average M_W	45,979 ± 2325	44,725 ± 1650	45,000

[a]Commercial name of poly(vinyl acetate) manufactured by Union Carbide Corporation.
[b]Value provided in the product technical brochure.

with the values provided by the supplier (Union Carbide Corp.). No change in the molecular weight of the polymer was observed following the hot-melt extrusion process. Thermal gravimetric analysis was also used to determine the thermal stability of the PVAc. The depolymerization temperature of the PVAc occurred at 339°C as (Fig. 8). This result demonstrated that the polymer was completely stable under the processing temperature range. The stability of PVAc to shear stress was studied using a Plasticorder rheometer. As shown in Fig. 9, the initial peak indicated the heating process of the added PVAc. The torque gradually decreased as the temperature of the polymer melt in the chamber increased. No further change in the torque was observed after the initial heating

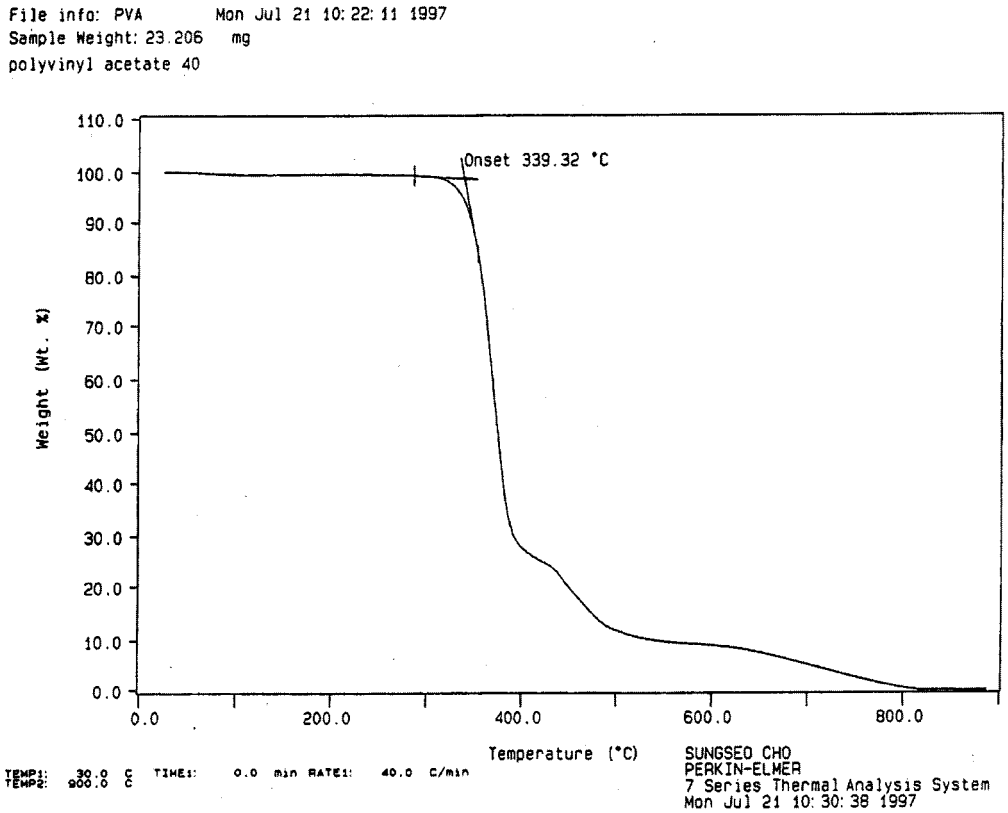


Figure 8. Thermal gravimetrical analysis profile of poly(vinyl acetate).

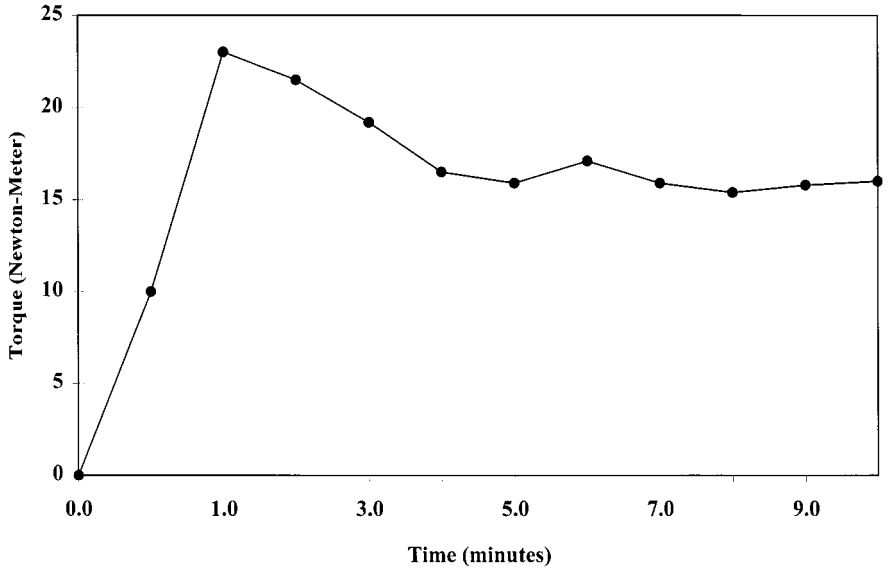


Figure 9. Heat and shear stability of poly(vinyl acetate) monitored via Plasticorder rheometer.

step. This finding confirmed that PVAc was not susceptible to degradation by either thermal or shearing stress under the current processing conditions. The WAXD technique was used to characterize the physical state of the theophylline in the polymeric matrix (Fig. 10). The crystalline state of the theophylline was maintained in the extruded granules.

As shown in Fig. 7, the lactose was a very inefficient drug release modifier. The extrudate (formulations 1 to 8, Table 1) had to be ground into granules to achieve complete drug release even when 25% lactose was added in the hot-melt extruded granules. Water-soluble polymers have been reported to be very effective in accelerating drug release from melt-granulated wax pellets (21).

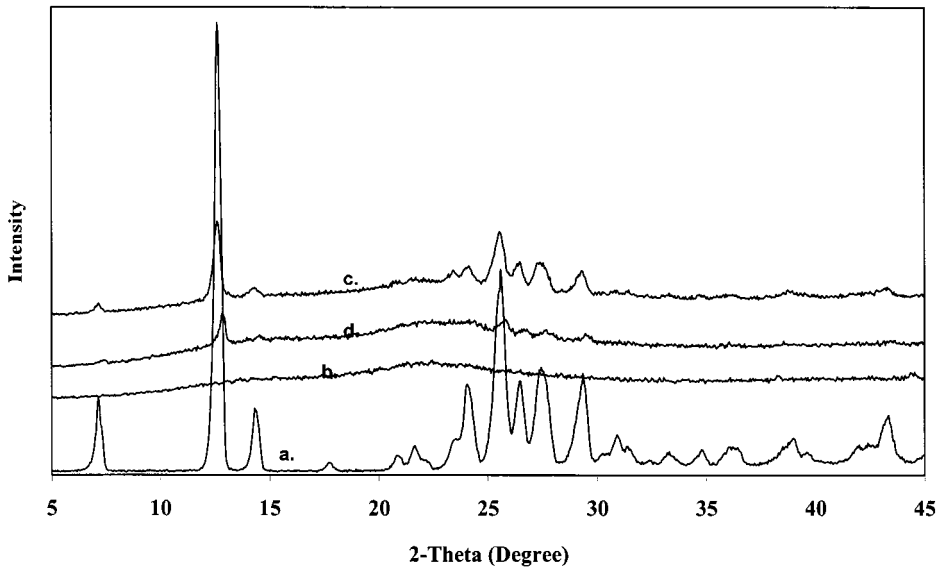


Figure 10. Wide-angle X-ray diffraction profiles of the raw materials and extrudates: a, theophylline; b, poly(vinyl acetate); c, physical mixture (5% theophylline and PVAc); d, hot-melt extrudate (5% theophylline, 3% PEG400, and PVAc40).

Further studies were pursued to investigate the efficiency of water-soluble polymeric materials, such as hydroxypropylmethylcellulose (HPMC) and PEO, in facilitating drug release from the PVAc matrix systems. The hot-melt extrusion of the PVAc matrix granules containing the water-soluble polymers was conducted at 60°C. Since the glass transition temperature of HPMC and the melting point of PEO were above the processing temperature, those polymeric additives were present as individual particles in the matrix. Lactose was also added to the matrix tablets at the 25% level. With the addition of lactose, there was an increase in the brittle character of the extrudate, which allowed the extrudate to be readily cut into tablets. As seen in Fig. 11, the theophylline release rate was significantly increased when a water-soluble polymer was present. Sato et al. (21) discussed the structural changes that occurred in granules containing water-soluble polymers during the dissolution test, and cracking caused by the swelling of the polymers was reported.

Scanning electron microscopy was used to investigate the surface structure of the PVAc matrix tablets prior to and following the dissolution test. The surface morphology of the hot-melt extruded tablets with and without water-soluble polymers is shown in Figs. 12 and 13, respectively. A smooth surface was observed for the tablets containing PVAc after the dissolution test. PVAc was in a rubbery state at 37°C, and the smooth surface was the result of the hydrodynamic shearing force imposed on the surface of the tablet by the agitated dissolution medium. Pores on the tablet surface resulted from the capillary diffusion of the theophylline and lactose. The surface of the extruded tablets containing PEO 300,000 prior to the dissolution test was significantly rougher. PEO is a water-soluble polymer and is not miscible with PVAc. Hot-melt extruded matrix tablets were therefore less cohesive when PEO was added. As seen in Fig. 12, the surface of the PVAc matrix tablets with PEO was porous following the dissolution test when examined by a scanning electron microscope. Following the completion of the dissolution study, the hot-melt extruded tablets that contained PEO were freeze-dried, and the weight of the

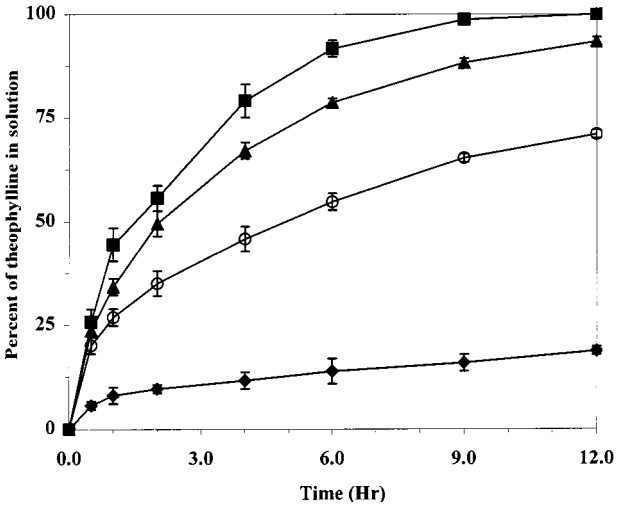
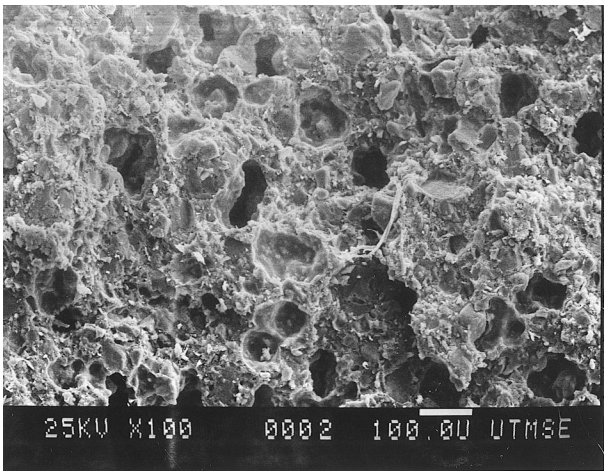
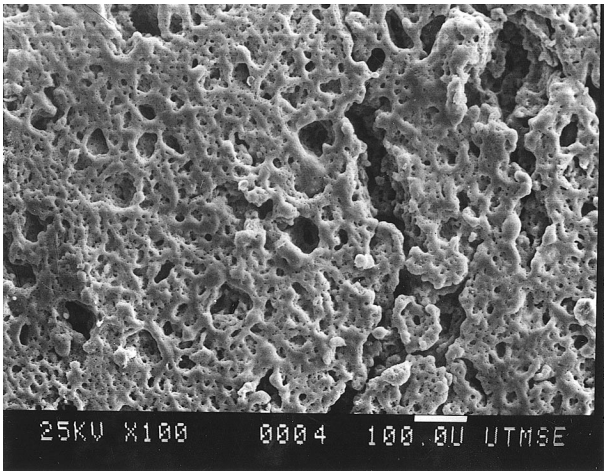


Figure 11. Influence of water-soluble polymer on the drug release properties of the hot-melt extruded theophylline tablets ($n = 3$). ◆, Lactose (formula 8); ■, PEO 300,000 (formula 9); ▲, PEO 1.0 m (formula 10); ○ HPMC E5P (formula 11).

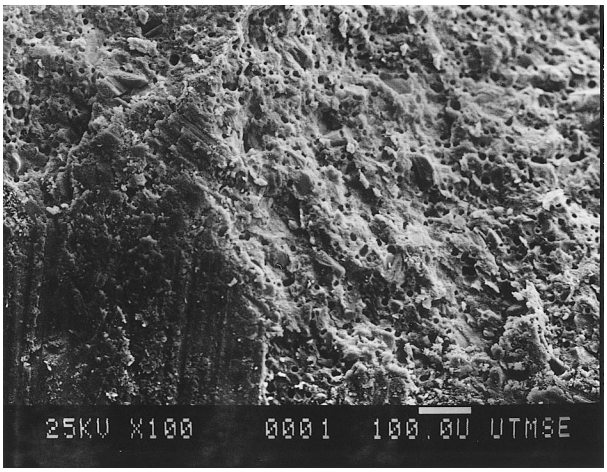


(a)

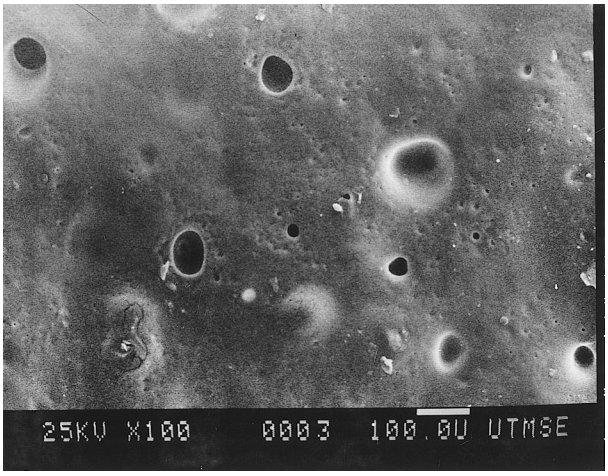


(b)

Figure 12. Surface morphology of hot-melt extruded tablets. Tablet (25% theophylline, 25% lactose, 20% PEO 1,000,000, and 30% PVAc): (a) prior to dissolution test; (b) following 12-hr dissolution test.



(a)



(b)

Figure 13. Surface morphology of hot-melt extruded tablets. Tablet (25% theophylline, 45% lactose, and 30% PVAc): (a) prior to dissolution test; (b) following 12-hr dissolution test.

tablets was found to be equal to the theoretical weight of the PVAc in the tablets. The water-soluble polymer was demonstrated to be more effective in facilitating the drug release process since the tablets were more porous, and the drug was able to diffuse through the hydrated gel layer during the dissolution process. With lactose, the dissolution and movement of drug molecules through the capillary channels could be hindered by the dissolution of the lactose. Drug release was slower when PEO (MW 1,000,000) was used in the extrudate since both the hydration and dissolution of the PEO were slower, and the diffusivity of theophylline in the polymeric hydrogel also influenced the dissolution process.

CONCLUSION

PVAc was demonstrated to be an excellent carrier for the preparation of controlled-release granules processed by hot-melt extrusion. Due to the low glass transition temperature of the polymer, the melt extrusion process could be conducted at temperatures within the range 50°C to 70°C. During processing, the extrudate was subjected to minimal thermal and mechanical stresses. In the absence of water-soluble polymers as drug release modifiers, the extrudates had to be ground into fine powder and compressed into tablets with directly compressible excipients to achieve desirable drug release profiles. Water-soluble polymers such as PEO and HPMC were shown to facilitate the drug release to a much greater extent than lactose. Tablets with desirable release properties could be made by cutting the extrudate when water-soluble polymers were added as drug release modifiers. Theophylline was released from the melt-extruded systems by diffusion. Drug release data for the PVAc matrix tablets were in good agreement with the Higuchi model and the percolation theory.

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