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Controlled Release of a Poorly Water-Soluble Drug from Hot-Melt Extrudates Containing Acrylic Polymers

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ABSTRACT Controlled release tablets containing a poorly water-soluble drug, indomethacin (IDM), acrylic polymers (Eudragit® RD 100, Eudragit® L 100, or Eudragit® S 100), and triethyl citrate (TEC) were prepared by hot-melt extrusion. The physicochemical and IDM release properties of the controlled release hot-melt extrudates were investigated. Indomethacin (IDM) was found to be both thermally and chemically stable following hot-melt extrusion processing and displayed a plasticizing effect on Eudragit® RL PO as demonstrated by a decrease in the glass transition temperatures of the polymer. The inclusion of either Pluronic® F68, Eudragit® L 100, or Eudragit® S 100 in the powder blend containing Eudragit® RD 100 prior to processing increased the rate of release of the IDM from the extrudates. An increase in the media pH and a decrease in the granule particle size also increased the rate of release of IDM. The inclusion of TEC up to 8% in the granule formulation or compressing the granules into tablets had no significant effect on the drug release rate. Indomethacin (IDM) was transformed from a crystalline Form I into an amorphous form in the Eudragit® RD 100 granules following hot-melt extrusion. The thermal processing facilitated the formation of a solid solution with a continuous matrix structure that was shown to control drug diffusion from the extrudates.

KEYWORDS Indomethacin, Eudragit® RL PO, L 100, S 100, and RD 100, Controlled release, Hot-melt extrusion, Amorphous form, Solid solution

INTRODUCTION

Controlled release of a poorly water soluble drug is one of the most challenging issues for the pharmaceutical scientist. One strategy to solve this problem is to increase the solubility of the drug in a polymeric carrier and then to control drug release by incorporation of a more soluble polymer into the delivery system.

Several techniques including micronization and salt formation have been employed to enhance the solubility of poorly water-soluble drugs. These methods have limitations due to agglomeration of the micronized powder or

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the reconversion of salts into aggregates of their respective acid or base forms. Even though solid dispersion technology provides many advantages over traditional techniques in enhancing both solubility and dissolution rate (Ford, 1986; Chiou & Reigelman, 1971), only a few products, including a griseofulvin-in-poly(ethylene glycol) solid dispersion (Gris-PEG®, Novartis) and a nabilone-in-povidone solid dispersion (Cesamet®, Lilly) have been marketed. Problems associated with solid dispersion technology include: (a) the method of preparation, (b) reproducibility of physicochemical properties, (c) formulation into dosage forms, (d) scale-up of manufacturing processes, and (e) the physical and chemical stability of drug and vehicle (Serajuddin, 1999). In recent years, solid dispersion technology has gained popularity due to pharmaceutical applications of hot-melt extrusion (Leuner & Dressman, 2000; Zhu et al., 2002, 2002; Zhang & McGinity, 2000; Repka & McGinity, 2001). In melt extrusion processes, the drug/carrier powder blend is exposed to elevated temperatures for approximately two to three minutes. Due to the simplicity of the manufacturing process, the properties of solid dispersions are not expected to change during scale-up, and when solid solutions are formed, the influence of the physical properties of the drug including the particle size distribution on drug release is eliminated.

Although hot-melt extrusion has been used to enhance the bioavailability of poorly water-soluble drugs (Forster et al., 2001), few reports in the literature have focused on the design of controlled release formulations containing poorly water-soluble drugs using this thermal process. In the current study, indomethacin (IDM), a poorly water-soluble drug (solubility in water is 4.0–8.8 μg/mL) (O'Brien et al., 1984) was selected as the model compound. Matrix systems containing the active ingredient and several acrylic polymers were prepared by hot-melt extrusion. Eudragit® RS PO and Eudragit® RL PO are copolymers synthesized from acrylic and methacrylic acid esters. These polymers contain a low level of quaternary ammonium groups with Eudragit® RL PO having a greater molar ratio of these ionizable groups which causes it to be more permeable to aqueous media than Eudragit® RS PO. Eudragit® RD 100 is a powder that is composed of a combination of 91% of Eudragit® RL PO and 9% of sodium carboxymethyl cellulose. The Eudragit® RD 100 was selected since it exhibits higher permeability than both Eudragit® RS PO and Eudragit® RL PO. The thermal and chemical stability of the materials used in the current study formulation as well as the drug release mechanisms were investigated to demonstrate the feasibility of the hot-melt extrusion technology as a viable method to prepare a controlled release delivery system containing a poorly water soluble drug.

MATERIALS AND METHODS

Materials

Indomethacin (IDM) was purchased from Spectrum Quality Products, Inc., (Gardena, CA). The other materials were kindly donated by various manufacturers: Eudragit® RL PO/RD 100/S 100/L 100, Degussa (Piscataway, NJ); triethyl citrate, Morflex, Inc., (Greensboro, NC); Pluronic® F68, BASF (Mt. Olive, NJ); Avicel® PH-101, FMC Corporation (Newark, DE); L-HPC LH-21, Shin-Etsu Chemical Co., Ltd., (Tokyo, Japan).

Methods

Particle Size

Indomethacin (IDM), Eudragit® RD 100, and Eudragit® RL PO were dispersed in distilled water. The particle size of the materials was determined in triplicate using a ZetaPlus Zeta potential analyzer (Brookhaven Instruments Corporation, Holtsville, NY) with BIC particle sizing software.

True Density

Approximately 3–5 g of IDM, Eudragit® RD 100, and Eudragit® RL PO were weighed in triplicate and a helium AccuPyc 1330 pycnometer (Micromeritics Instrument Corporation, Norcross, GA) was employed to determine the true density of these materials.

Differential Scanning Calorimetry

A differential scanning calorimeter (DSC) (TA Instruments, Model DSC 2920 Modulated DSC) was used to determine the melting point of IDM and to investigate the solid-state plasticization effects of IDM and Pluronic® F 68 on the Eudragit® RL PO. A sample of approximately 5–10 mg was weighed and hermetically sealed in an aluminum pan. The sample was equilibrated at –20°C, and the temperature of the

sample was then ramped from –20 to 160°C at a rate of 10.0°C/min. The glass transition temperature was measured in the second cycle as the step transition in the plot of heat flow vs. temperature. The differential scanning calorimetry (DSC) was calibrated using an abbreviated calibration method with an indium standard prior to sample analysis.

Thermogravimetric Analysis

A thermogravimetric analyzer TGA 7 (Perkin-Elmer, Wellesley, MA) was employed to investigate the thermal stability of Eudragit® RL PO, Eudragit® RD 100, Eudragit® S 100, Eudragit® L 100, IDM, and TEC. Samples were maintained at 50°C for 1 min and then heated up to 140°C at a heating rate of 30°C/min. Samples were held at 140°C for 10 min and the percent weight loss was recorded.

Adsorption of Indomethacin on the Acrylic Polymers

Measurements of 2.5, 5.0, 10.0, and 15.0 mL of 100.0 μg/mL IDM pH 6.8 phosphate buffer solution were added into each test tube, respectively, and pH 6.8 phosphate buffer solution was added to obtain a 20.0 mL solution. Either 0.20 g of the Eudragit® RD 100, or a mixture of 0.18 g of the Eudragit® RD 100 and 0.02 g of the Eudragit® S 100, or a mixture of 0.18 g of the Eudragit® RD 100 and 0.02 g of the Eudragit® L 100 was added into each set of test tubes prior to shaking in an air bath that was thermostated at 37°C for 24 h. Samples were filtered, diluted, and analyzed using a UV spectrophotometer at 318 nm with no interference from the employed Eudragits.

Preparation of Solid Dispersions by Hot-melt Extrusion

Hot-melt extrudates were prepared using a vertical single screw Randcastle Model RCP-0750 Microtruder with a screw diameter of 0.750 inches and a working length to diameter ratio of 24 (Randcastle Extrusion Systems Inc., Cedar Grove, NJ). The operating temperatures for Zone 1, Zone 2, Zone 3, and Zone 4 (die) were 90°C, 105°C, 120°C, and 140°C, respectively. The screw rotation speed was 20 rpm and the die diameter was 6.0 mm. Hot-melt extrudates were collected from the end of the die. Granules were prepared by reducing the size of the thermal extrudates with a mortar and pestle at 25°C and granules in the 20–40 and 40–60 mesh range were retained for further evaluation.

Tablet Preparation

Tablets were prepared using a Carver laboratory press (Carver Inc., Wabash, IN). A blend of 250 mg of the hot-melt extruded granules containing 75 mg of IDM, 225 mg of Avicel® PH-101, and 25 mg of L-HPC (LH-21) was transferred to a 6 mm die and compressed with a compression force of 400 Kg. The tablet weight was approximately 500 mg with a hardness of 15 Kg.

HPLC Method for Indomethacin

The chromatographic system consisted of a Waters 501 High Performance Liquid Chromotography (HPLC) pump, a Waters 996 photodiode array detector set at 254 nm, an Alltech 570 Autosampler, and a Waters C18 3.9 × 300 mm μBondabpak analytical column (10 μm). The mobile phase was a mixture of 0.02 *M* monobasic sodium phosphate and 0.02 *M* dibasic sodium phosphate water solution:acetonitrile (60:40). The flow rate was 1.0 mL/min and injection volume was 20 μL. The typical retention time for IDM was 4.5 min. Linearity of the system was demonstrated over the working sample concentration range with a correlation coefficient greater than 0.99. The absence of interference from excipients was demonstrated and the reproducibility of the system for multiple injections ($n = 6$) was less than 0.5% relative standard deviation.

Chemical Stability of IDM Content in the Formulation

Hot-melt extrudates were dissolved in 20 mL ethanol in a 100 mL volumetric flask and then phosphate buffer solution (pH 7.4) was added to volume. Samples were filtered through a 0.45 μm filter and analyzed by the HPLC method described above.

Dissolution Studies

(A). USP 27 Method 2

Dissolution properties of the sustained release tablets were determined using a VanKel 7000 dissolution system with a VanKel 7500 temperature control system and a VanKel 8000 autosampler. The dissolution medium consisted of 900 mL of pH 6.8 phosphate

buffer solution, maintained at 37°C, and the paddle speed was maintained at 75 rpm. Samples were collected at predetermined time intervals and analyzed by HPLC. Each experiment was conducted in triplicate.

(B). USP 27 Method 3

VanKel Bio-Dis II was employed in the study with the following parameters: 250 mL of different pH release media pH 1.2 (0–2 h), pH 5.0 (2–4 h), pH 6.8 (4–8 h), and pH 7.4 (8–12 h) maintained at 37°C. The dipping rate was 20 dips per min. Samples were collected and filtered through a 0.45 μm filter at predetermined time intervals and then analyzed by the HPLC method described above. The experiments were conducted in triplicate.

Scanning Electron Microscopy

Samples were coated with gold-palladium for 60 sec under an argon atmosphere using a Pelco Model 3 sputter coater (TED Pella Inc., Tustin, CA) in a high vacuum evaporator equipped with an omni-rotary stage. The morphologies of the samples were investigated by using a Hitachi S-4500 Scanning Electron Microscope (Hitachi, Ltd., Ibaraki-Ken, Japan) at 5 KV.

X-ray Diffractometry

An APD 3520 Philips X-ray diffractometer with a PW 1720 x-ray generator and a PW 1710 diffractometer control (Philips Electronic Instrument, Mount Vernon, NY) was employed to study the crystallinity of IDM alone, in a physical mixture with Eudragit® RD 100, and in the hot-melt extruded granules. The generator operating voltage and current were 40 KV and 40 mA, respectively. The scanning speed was 2°/min, and the 2θ scanning range was from 5° to 50°.

RESULTS AND DISCUSSION

Particle Size, True Density, Melting Point, and Glass Transition Temperature

The particle size of IDM, Eudragit® RL PO, and Eudragit® RD 100 are shown in Table 1. The average effective diameters for these three materials as received were 14.0 μm, 41.0 μm, and 43.1 μm, respectively. The true density of IDM, Eudragit® RL PO, and Eudragit® RD 100 was determined and the average true densities for these three materials as seen in Table 1 were 1.38 g/cm^3, 1.19 g/cm^3, and 1.21 g/cm^3, respectively. These values were used to calculate the K (a constant in the Gordon-Taylor equation) values in order to predict the glass transition temperatures of the mixtures containing these materials as discussed in the following section.

Due to its different molecular arrangements and/or conformations, IDM has been shown to exhibit four polymorphs with different melting points (Grant, 1999). The melting point of IDM for Form I was 160–161.5°C, and for Form II, III, and IV the melting points were reported to be 154.5–155.5°C, 148°C, and 134°C, respectively (O'Brien et al., 1984). The melting point of the IDM powder as received was determined to be 162.46°C as seen in Fig. 1, and this result showed that IDM was in the crystalline Form I prior to hot-melt extrusion. Form I is the most stable polymorph and has the lowest aqueous solubility. The energy required for a molecule to escape from a crystal is much greater than the energy required to escape from an amorphous powder, thus the crystalline form of a compound is always less soluble than the corresponding amorphous form (Ansel et al., 1999). The amorphous form of IDM was formed as a result of the quenching process in the first run. A glass transition phenomenon for IDM was observed in the second run using DSC and the glass transition temperature was

TABLE 1 **Particle Size and True Density of IDM and the Acrylic Polymers (*n* = 3)**

Materials	Indomethacin	Eudragit® RL PO	Eudragit® RD 100
Average Effective Diameter (μm)	14.0	41.0	43.1
SD	0.71	5.89	3.31
Average Density (g/cm^3)	1.38	1.19	1.21
SD	0.0006	0.0012	0.0047

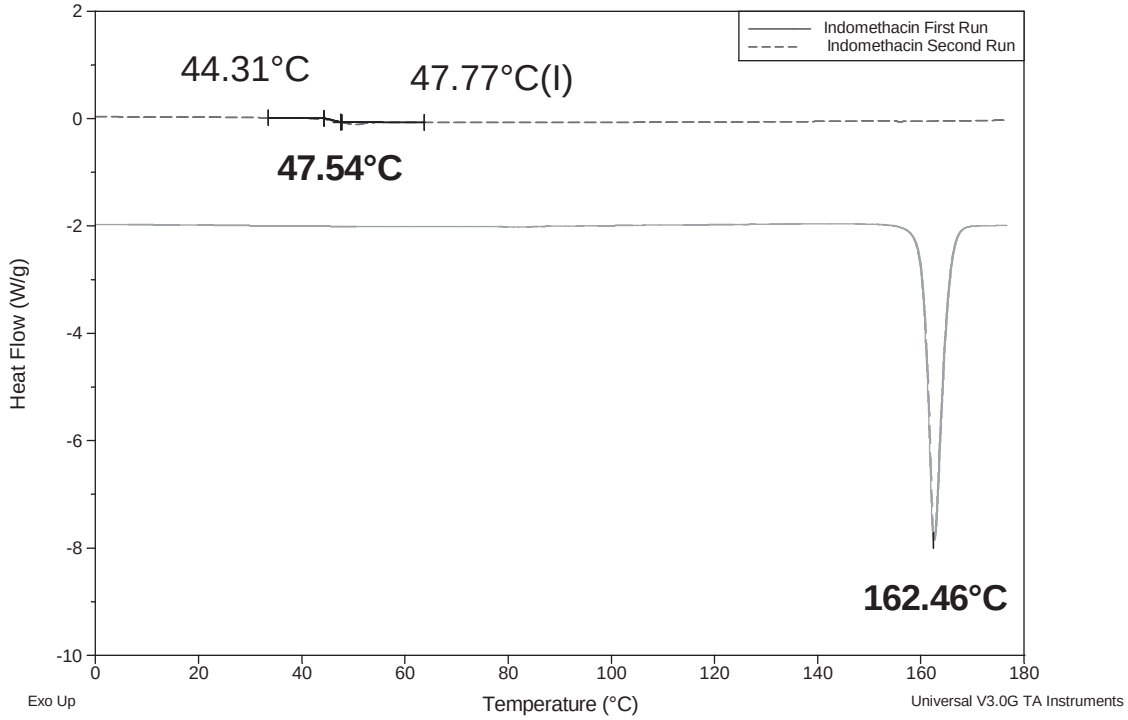


FIGURE 1 **Thermal Analysis Diagram of IDM by DSC.**

found to be 47.5°C which is close to the reported values of 45°C (Taylor & Zografi, 1998), and 50°C (Yoshioka et al., 1994).

Plasticization Effect of Indomethacin on Eudragit® RL PO

The solid-state plasticization effect of IDM on Eudragit® RL PO was determined by DSC. The differential scanning calorimeter (DSC) profile of the mixture of IDM and Eudragit® RL PO from the first run showed an endothermal peak of 157.8°C due to the melting behavior of the IDM. The glass transition temperatures (Tg) of the mixtures of Eudragit® RL PO and IDM from the second run, are reported in Table 2. A slight decrease in the Tg was seen using 40% IDM in the Eudragit® RL PO mixture. As a comparison to our previous work on the solid-state plasticization effect on the Eudragit® RS PO with chlorpheniramine maleate (Zhu et al., 2002), it was seen that the solid-state plasticization effect was weaker for the mixture containing IDM in Eudragit® RL PO. Glass transition temperatures (Tg) for pharmaceutical chemicals are generally found to be about two thirds that of the melting temperatures (Guillory, 1999), and the melting point of IDM is 162.5°C and chlorpheniramine maleate is 130–135°C (The Merck Index, 2001). When a compound is miscible with the polymer in the molten state to lower the melting point, a plasticizing effect on the polymer will be seen. Even though the solid-state plasticization effect of IDM on Eudragit® RL PO was weak, this study demonstrated that IDM was miscible with Eudragit® RL PO and a solid solution of IDM could be formed during the extrusion process.

TABLE 2 The Experimentally Determined Tg and Predicted Tg of the Mixtures of IDM and Eudragit® RL PO

% of IDM	Determined Tg (°C)	Predicted Tg (°C)
0%	62.9	62.8
10%	61.5	61.4
20%	60.8	60.0
30%	60.2	58.6
40%	56.2	57.1

The glass transition temperature (Tg) of Eudragit® RL PO was 62.88°C, and for IDM, the Tg was 47.77°C as determined by DSC. After determining the Tg of the pure materials of IDM and Eudragit® RL PO, the Tg of the mixture of Eudragit® RL PO and IDM were calculated by using the following Gordon-Taylor equation (Carstensen, 2001).

$$Tg,_{mixture} = [(m_1 Tg_1) + (Km_2 Tg_2)]/[m_1 + (Km_2)] \quad (1)$$

$Tg_{,mixture}$, Tg_1, and Tg_2 are the glass transition temperatures of the mixture, component 1, and component 2. The weight percentages of component 1 and component 2 are m_1 and m_2 respectively. From Eq. (2), K can be calculated.

$$K \approx \rho_1 Tg_1/\rho_2 Tg_2 \quad (2)$$

The true densities of component 1 and component 2 are ρ_1 and ρ_2. By comparing the determined values with the predicted values as shown in Table 2, it can be seen that the determined values fit the Gordon-Taylor equation very well.

The glass transition temperature (Tg) of the powder blend was decreased with an increase of IDM, as described by the Gordon-Taylor equation, demonstrating the solid-state plasticization effect on the polymer by this model drug.

Plasticization Effect of Pluronic® F68 on Eudragit® RL PO

Pluronic® F68 was passed through a 30 mesh screen before blending with Eudragit® RL PO in different ratios. The melting peak of Pluronic® F68 was observed both in the first and second run of all samples, and the melting points of Pluronic® F68 in these mixtures in the range of 53.57°C to 58.09°C did not decrease significantly as seen in Table 3. This demonstrated that there was no plasticization effect of Pluronic® F68 on the Eudragit® RL PO, indicating that the formation of the IDM solid solution was solely due to the thermal miscibility of IDM with the acrylic polymer.

TABLE 3 Melting Points of Pluronic® F68 in the Mixture of Eudragit® RL PO

% of Pluronic® F68	First run melting point°C	Second run melting point°C
10%	54.26	55.22
20%	53.57	55.22
30%	54.26	55.70
40%	54.74	56.17
50%	53.78	54.98
100%	56.17	58.09

Thermal Stability

The thermal stability of IDM, Eudragit® RL PO, Eudragit® RD 100, Eudragit® S 100, Eudragit® L 100, and Pluronic® F68 was investigated at the thermal processing temperature of 140°C. Table 4 illustrates the weight percentage of these materials remaining after being maintained at 140°C for 10 min. The loss of mass of these materials at 140°C for 10 min was less than 1%, indicating that IDM and the other excipients had good thermal stability. The chemical stability of IDM was verified by HPLC in the following section.

Adsorption of Indomethacin on the Acrylic Polymers

The adsorption of IDM to Eudragit® RL 100 has been reported to prevent the drug from being completely released during a dissolution study (Oth & Moës, 1989). The adsorption of IDM in the pH 6.8 phosphate buffer solutions to acrylic polymers, including either the Eudragit® RD 100, or Eudragit® RD 100 with 10% Eudragit® S 100 or with 10% Eudragit® L 100, is seen in Fig. 2. Indomethacin (IDM) was found to be strongly bonded to Eudragit® RD 100 due to the existence of the quaternary ammonium groups in the acrylic polymer. When 10% of Eudragit® S 100 was blended with Eudragit® RD 100, this interaction was weaker than that with Eudragit® RD 100 alone. This effect was attributed to the anionic functional groups in Eudragit® S 100 and the decreased amount of Eudragit® RD 100 present in the powder blend. When Eudragit® L 100 was added to the Eudragit® RD 100 blend, higher amounts of the anionic functional groups were present and the binding of IDM to the Eudragit® RD 100 was significantly reduced as seen in Figure 2.

TABLE 4 Thermal Stability of IDM and Other Excipients (Isothermal at 140°C for 10 Min Determined by Thermogravimetric Analysis)

	Materials					
	IDM	Pluronic® F68	Eudragit® RD 100	Eudragit® RL PO	Eudragit® S 100	Eudragit® L 100
Remaining Weight %	99.8	99.9	99.3	99.8	99.8	99.8

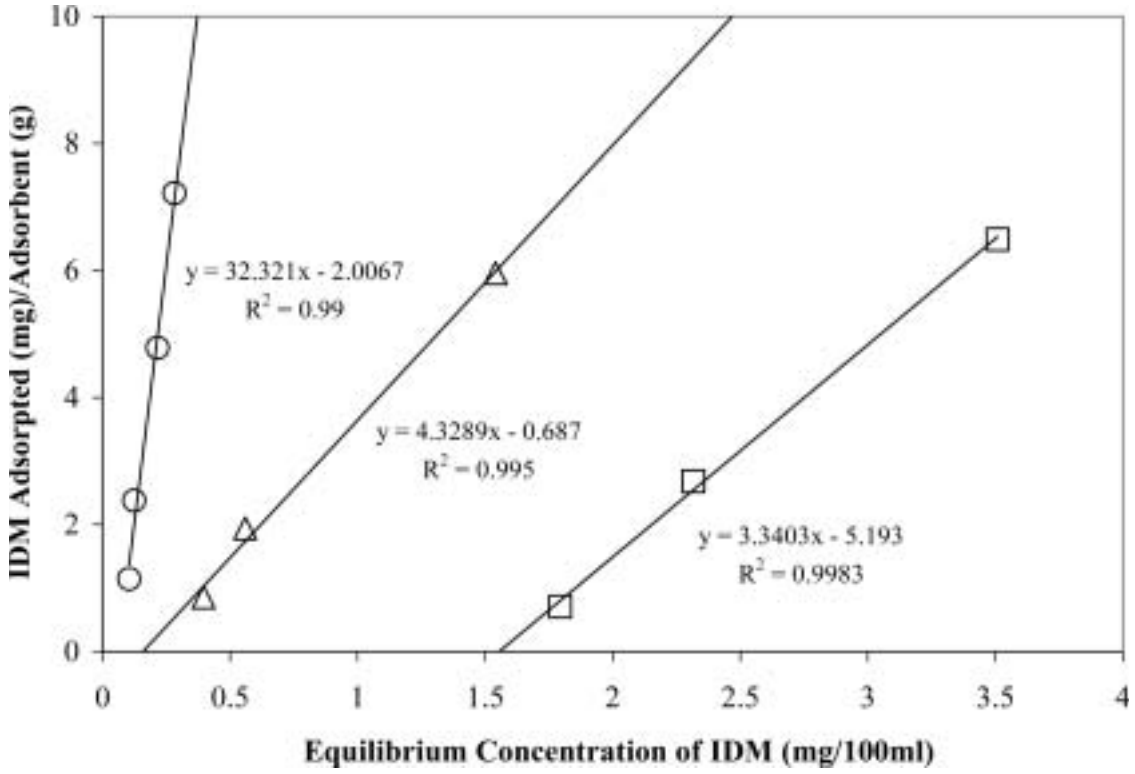


FIGURE 2 **Adsorption of IDM in the pH 6.8 Phosphate Buffer Solutions on the Acrylic Polymers. (o) 0.2 g of Eudragit® RD 100; (Δ) A Mixture of 0.18 g of Eudragit® RD 100 and 0.02 g of Eudragit® S 100; (□) A Mixture of 0.18 g of Eudragit® RD 100 and 0.02 g of Eudragit® L 100.**

Chemical Stability of IDM in the Extrudates

For methyl methacrylate copolymers, previous research has shown that scission of polymer chains at elevated temperatures (300°C) resulted in a monomeric product (McNeill, 1968). The depolymerization of poly(methl methacrylate) is a free-radical process that is initiated from the ends of the chain. Each initiated chain unzips rapidly to yield monomer formation. Thus, at any instant, the system contains only unreacted polymer and monomer (Allcock & Lampe, 1996). Since the chemical stability of Eudragit® RS PO is well documented (Follonier et al., 1994), only the stability of IDM in the formulations following hot-melt processing was determined, and the results are shown in Table 5. Indomethacin (IDM) content before and after hot-melt extrusion was determined. Using a stability-indicating RP-HPLC, no additional peaks were detected, indicating IDM was chemically stable when subjected to the thermal and pressure stresses of the extrusion process. Other researchers have demonstrated that IDM was quite stable in the molten state (Carstensen & Morris, 1993). It was reported that only 1% of crystalline IDM was decomposed at 145°C after 48 h. Amorphous IDM was less stable than its crystalline form, however, several hours were required to initiate the degradation of the compound (Carstensen & Morris, 1993). The chemical stability of IDM in PVP/IDM (1:1) and PVP/IDM

TABLE 5 **Chemical Stability of IDM in the Powder Blends Containing Acrylic Polymers Following Hot-melt Extrusion Determined by HPLC**

Formulations*	IDM content before hot-melt extrusion	IDM content after hot-melt extrusion
Eudragit® RD 100 (61%)	97.09 ± 0.88%	97.69 ± 0.95%
Eudragit® RD 100 (51%)	101.9 ± 1.01%	99.83 ± 0.19%
Eudragit® L 100 (10%)		
Eudragit® RD 100 (51%)	103.5 ± 1.57%	103.3 ± 0.24%
Eudragit® S 100 (10%)		

*In addition, all formulations contain 30% of IDM, 5% of Pluronic® F68, and 4% of TEC.

(4:1) systems processed at 170°C was found to be stable and less than 1% of the active drug was chemically degraded (Forster et al., 2001).

Drug Release from Hot-Melt Extrudates

Influence of Pluronic® F68 Level and Tablet Processing on Drug Release Rate

A powder blend containing 30% IDM, 66% Eudragit® RD 100, and 4% TEC was processed by hot-melt extrusion. The extrudates were reduced into granules in a particle size range of 20–40 mesh and the drug release properties were determined. It was found that only 36% of the drug was released after 12 h in pH 6.8 using the USP 27 paddle method. This was due to a binding interaction between the acidic functional group in the drug and the quaternary amino group in the Eudragit® RD as described previously in this article.

A non-ionic surfactant, Pluronic® F68, a polyoxyethylene-polyoxypropylene copolymer with a melting point of 56.2°C, was incorporated into the formulation to replace an equivalent amount of Eudragit® RD 100. As shown in Fig. 3, an increase in drug release was observed with increasing levels of Pluronic® F68 in the granules. This effect was attributed to the lower interfacial tension between the drug and the dissolution medium which increased the wettability of the drug and the polymer in the granules. The drug release data showed a better fit with the Higuchi equation than with the first order drug release equation by comparing the linear regression coefficients. The drug release rate constants were calculated and the drug release mechanism was shown to be a diffusion-controlled process. The drug release rate constant increased from 10.2% $h^{-1/2}$, to 15.3% $h^{-1/2}$, and to 20.2% $h^{-1/2}$ when the Pluronic® F68 level in the hot-melt extrudates increased from 0%, 5%, to 10%, respectively. Other researchers have shown that adding increasing levels of Pluronic® F68 to nifedipine gradually promoted the dissolution rate of nifidipine as well as enhancing the extent of drug release (Ho et al., 2000).

The dissolution properties of IDM from hot-melt extrudates containing different levels of Pluronic® F68 for granules in the particle size range of 40–60 mesh were also studied, and the results are seen in Fig. 4. Comparing the profiles in Figs. 3 and 4, the drug release rate was increased as particle size decreased. From the Noyes-Whitney equation, drug dissolution rate is proportional to the surface area available for dissolution. A decrease in the particle size of the extrudate increased the surface area exposed to the dissolution medium, resulting in an increased drug release rate, as shown in Fig. 4.

Tablets containing 50% of the granules of the solid solutions and 45% of Avicel® PH-101 were compressed.

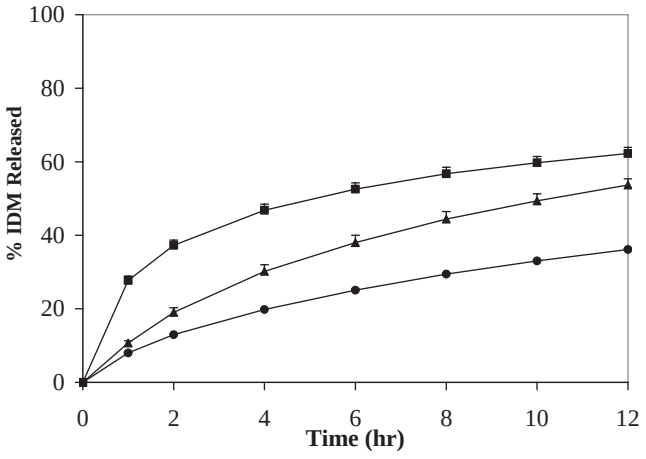


FIGURE 3 Influence of Pluronic® F68 on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% of IDM, Eudragit® RD 100, Pluronic® F68, and 4% of TEC. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●) 0% of Pluronic® F68; (▲) 5% of Pluronic® F68; (■) 10% of Pluronic® F68.

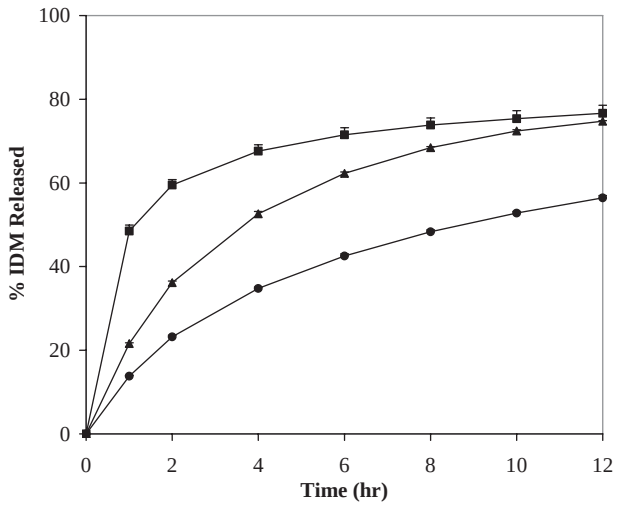


FIGURE 4 Influence of Pluronic® F68 on IDM Release from Hot-melt Extrudated Granules (40–60 Mesh) Containing 30% of IDM, Eudragit® RD 100, Pluronic® F68, and 4% of TEC. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●): 0% of Pluronic® F68; (▲) 5% of Pluronic® F68; (■) 10% of Pluronic® F68.

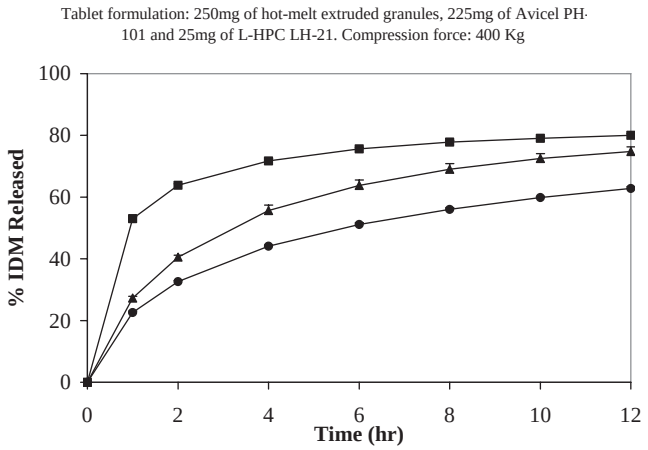


FIGURE 5 **Influence of Tableting on IDM Release from Tablets Made with the Granules (40–60 Mesh) Containing 30% of IDM, Eudragit® RD 100, Pluronic® F68, and 4% of TEC Prepared by Hot-melt Extrusion. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●) 0% of Pluronic® F68; (▲) 5% of Pluronic® F68; (■): 10% of Pluronic® F68.**

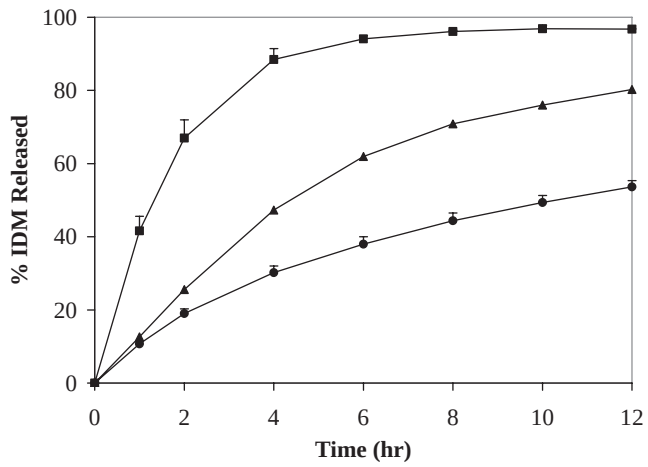


FIGURE 6 **Influence of Eudragit® L 100 on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% IDM, Eudragit® RD 100, 5% of Pluronic® F68, and 4% TEC. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●) 0% of Eudragit® L 100; (▲) 10% of Eudragit® L 100; (■): 20% of Eudragit® L 100.**

To minimize the influence of the tablet formulation and the tableting processing on the disintegration of the tablets, 5% L-HPC (LH-21), a super disintegrant, was added to the formulation to ensure fast disintegration of the compressed tablets. At a compression force of 400 Kg, the compressed tablets had a hardness of 15 Kg. The drug release profiles from these tablets are seen in Fig. 5. Drug release from the tablets prepared from the hot-melt extruded granules was compared with the drug release from the corresponding hot-melt extruded granules by calculating the similarity factor f_2 values. The f_2 values were greater than 50 for the three formulations, suggesting that both the tablet formulation and the tableting compression did not significantly influence the drug release rate from the hot-melt extruded solid solution granules.

Influence of Eudragit® L100 and Eudragit® S100 Level on Drug Release

The dissolution profiles in both Figs. 3 and 4 demonstrate a tailing effect with the IDM extrudates. After 12 h, more than 20% of drug remained in the granules. An approach to solving this problem was to include an enteric polymer, such as Eudragit® L 100 or Eudragit® S 100, into the powder blend. The Eudragit® L 100 is an anionic copolymer based on methacrylic acid and methyl methacrylate, having carboxylic acid functional groups that ionize at pH 6.8. This polymer exhibits higher water permeability at pH 6.8 than Eudragit® RD 100. With an increase in the amount of Eudragit® L 100 in the extrudates, the drug release rate increased (Fig. 6). In addition, the incorporation of Eudragit® L 100 in the formulation decreased the binding of IDM with the Eudragit® RD 100 as seen in Fig. 2. These two factors contributed to the increased drug release rate of the polymeric systems containing of Eudragit® L 100.

The ratio of the free carboxyl groups to the ester groups is approximately 1:1 in Eudragit® L 100 and about 1:2 in Eudragit® S 100. The Eudragit® S 100 has a lower permeability than Eudragit® L 100 and is not soluble at pH 6.8. Drug release profiles in Fig. 7 demonstrate that the addition of Eudragit® S 100 to the powder blend did not enhance the drug release rate. A dissolution profiles comparison was carried out using a model independent method (Center for Drug Evaluation and Research, 1997). By calculating the similarity factor f_2 values, it can be observed that both of the f_2 values between the top two lines and the bottom two lines were greater than 50, which means that these dissolution profiles can be considered similar. Eudragit® S 100 did not increase the drug release rate to the same extent as Eudragit® L 100 due to its lower permeability and solubility at pH 6.8.

Influence of TEC Level on Drug Release

Pharmaceutical polymers utilized in film coating, hot-melt granulation, and hot-melt extrusion typically require a plasticizer in order to reduce the Tg of the

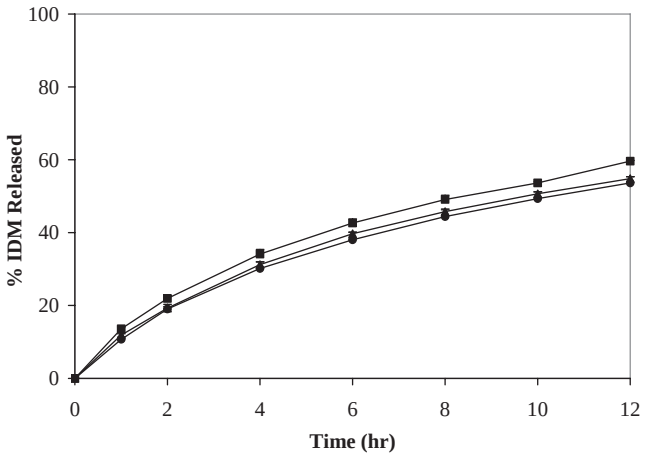


FIGURE 7 **Influence of Eudragit® S 100 on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% of IDM, Eudragit® RD 100, Eudragit® S 100, 5% of Pluronic® F68, and 4% of TEC. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●) 0% of Eudragit® S 100; (▲) 10% of Eudragit® S 100; (■) 20% of Eudragit® S 100.**

polymer and to facilitate the processing. The addition of a plasticizer will usually decrease the drug release rate from polymeric coated systems since the plasticizer increases the coalescence of the polymeric particles (Wu & McGinity, 1999). In a previous study, it was reported that for hot-melt extruded systems containing a highly water-soluble drug, chlorpheniramine maleate, the drug release rate increased with an increase in the plasticizer level (Zhu et al., 2002).

In the current study, the drug release profiles from the hot-melt extrudated granules (20–40 mesh) containing 30% of IDM, Eudragit® RD 100, and 5% of Pluronic® F68 are shown in Fig. 8. A comparison of

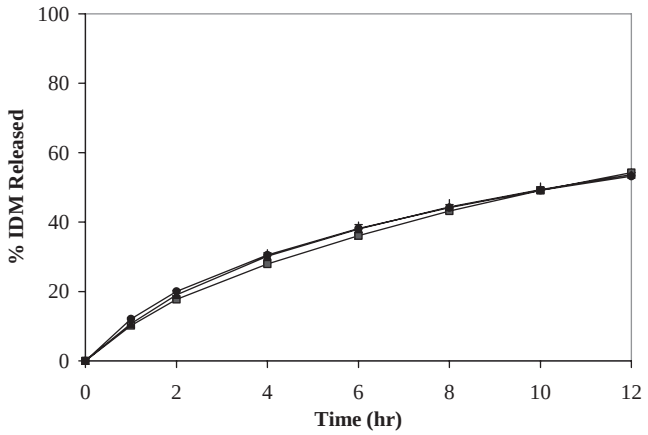


FIGURE 8 **Influence of TEC on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% of IDM, Eudragit® RD 100, and 5% of Pluronic® F68. Dissolution: USP27 Paddle Method, 75 rpm, pH 6.8 PBS, 37°C (n = 3). (●) 0% of TEC; (▲) 4% of TEC; (■) 5% of TEC.**

the profiles was carried out using the method referenced above. The f_2 values were greater than 50 indicating that these dissolution profiles are considered similar. The addition of TEC in the hot-melt extrudate containing a poorly water-soluble drug did not influence the drug release even though TEC had an effect on the structure of the drug delivery systems which governed the drug release from the polymeric delivery systems. For the poorly water-soluble drug, the drug release is controlled by the drug solubility. Kim reported that when a high drug loading is maintained for poorly water-soluble drugs, the addition of a water-soluble excipient to a matrix does not significantly influence the release kinetics (Kim, 1998). Carli and coworkers demonstrated that drug release from the Eudragit® RS or Eudragit® RL system was not influenced by porosity, whereas the drug release rate was controlled by intraparticle diffusion (Carli et al., 1984). Lovrecich and coworkers reported that for the IDM and Eudragit® RS PO solid dispersions, the diffusion coefficient of IDM through the polymer did not change with aging, although the polymer underwent local rearrangement. This suggests that the physical parameters (free volume, short range order) of glassy polymers do not influence the diffusion (Lovrecich et al., 1996).

Influence of pH on Release of Indomethacin from Hot-melt Extruded Granules

The profiles in Fig. 9 A demonstrate the effect of pH on drug release from the hot-melt extrudated granules containing 30% IDM, 61% Eudragit® RD 100, 5% Pluronic® F68, and 4% TEC. Since the solubility of IDM is dependent on the pH of the media, the drug release rate increased with an increase in pH of the media. The pKa value of IDM is 4.5 (Newton & Kluza, 1978). The drug has a low solubility in acidic medium and a higher solubility when the pH is increased.

The release profiles in Fig. 9B demonstrate the influence of media pH on the dissolution properties of IDM from granules containing 30% IDM, 51% Eudragit® RD 100, 10% Eudragit® L 100, 5% Pluronic® F68, and 4% TEC. The drug release rate increased compared to the drug release at the same pH values shown in Fig. 9A, which could be attributed to the higher permeability and solubility of Eudragit® L 100 compared to Eudragit® RD 100 in the corresponding pH media.

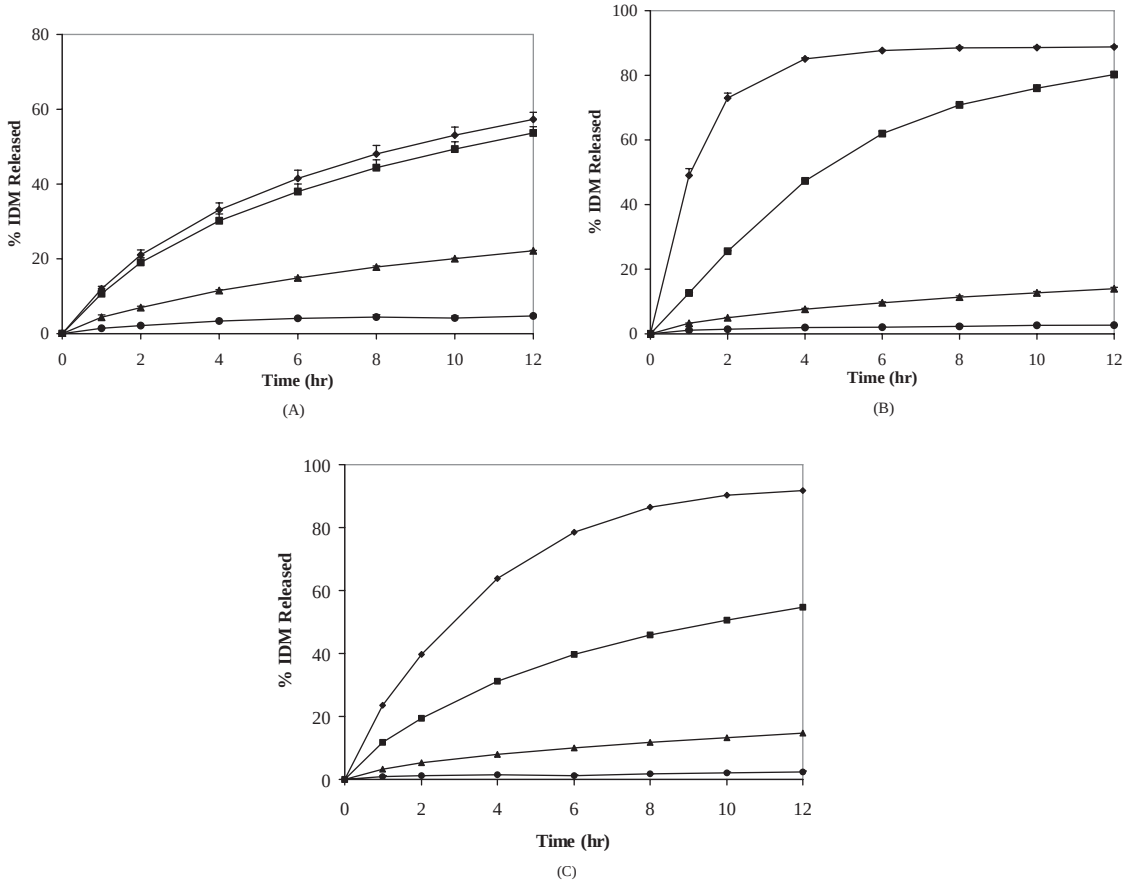


FIGURE 9 **Influence of pH on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% of IDM, 5% of Pluronic® F68, 4% of TEC, and (A): 61% of Eudragit® RD 100; (B): 51% of Eudragit® RD 100 and 10% of Eudragit® L 100; (C): 51% of Eudragit® RD 100 and 10% of Eudragit® S 100. Dissolution: USP27 Paddle Method, 75 rpm, 900 mL Dissolution Media, 37°C (*n* = 3). (●) pH 1.2; (▲) pH 5.0; (■) pH 6.8; (♦) pH 7.4.**

The drug release profiles in Fig. 9C show the influence of media pH on the dissolution properties of IDM from granules containing 30% IDM, 51% Eudragit® RD 100, 10% Eudragit® S 100, 5% Pluronic® F68, and 4% TEC. The drug release rate also increased as compared with the drug release at the same pH shown in Fig. 9A, although to a lesser extent as compared with Eudragit® L 100 formulation. As described earlier, this was due to the lower solubility and permeability of the Eudragit® S 100 than that of Eudragit® L 100 in the corresponding pH media.

The drug release from the delivery systems in different pH media can be determined conveniently by using the Bio-Dis® apparatus. The Bio-Dis® apparatus (USP Method 3) eliminates manual and tedious work in changing dissolution media and provides an advantage when dissolution testing is performed in a pH step gradient (Esbelin et al., 1991; Sorasuchart et al., 1999). Figure 10 shows that the drug release rate increased with both pH and the incorporation of the Eudragit® L100 or the Eudragit® S100. This was attributed to the influence of pH on the solubility of the drug and the solubility and permeability of the acrylic polymers.

Microstructures and Crystallinity of the Hot-Melt Extrudates

The scanning electron micrographs in Fig. 11 demonstrate the microstructure of the hot-melt extrudates containing IDM. A continuous single phase was observed for formulations composed of 30% IDM, Eudragit® RD 100, 5% Pluronic® F68, and either 0% or 4% TEC, demonstrating that IDM was homogenously dispersed in the hot-melt extrudates. In addition to the DSC results in the previous section of plasticization effect of IDM on Eudragit® RL PO, the micrographs in Fig. 11 also demonstrate that IDM was miscible with the acrylic polymer in the molten state. A brittle structure for the formulation with no TEC is

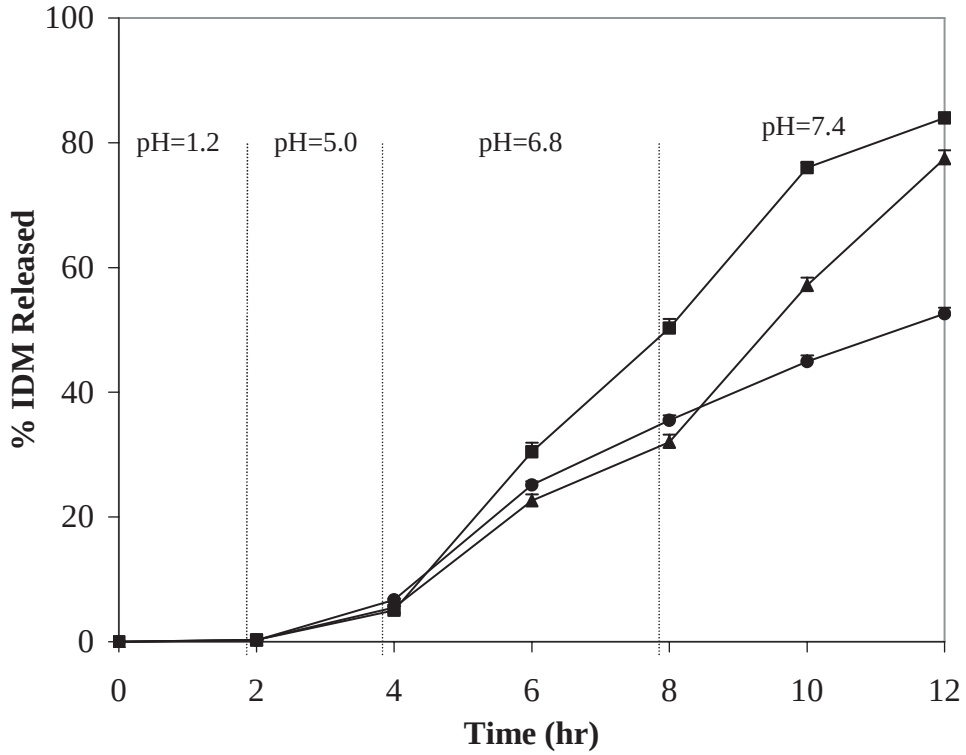


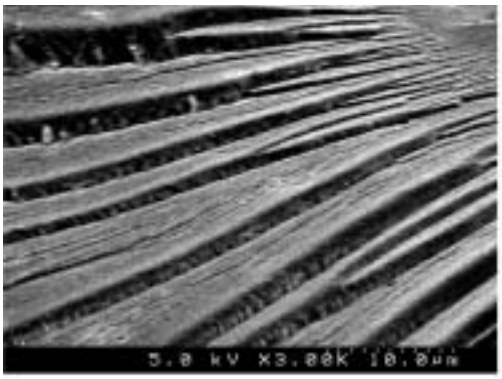
FIGURE 10 **Influence of pH on IDM Release from Hot-melt Extrudated Granules (20–40 Mesh) Containing 30% of IDM, Eudragit® RD 100, 5% of Pluronic® F68, and 4% of TEC. Dissolution: USP27 Method 3, 20 dip/min, 250 mL Dissolution Media, 37°C (*n* = 3). (●) 0% of Eudragit® S 100/L 100; (▲) 10% of Eudragit® S 100; (■) 10% of Eudragit® L 100.**

seen in Fig. 11A. In comparison, when 4% TEC was added to the formulation, a smoother structure with less brittle character appears in Fig. 11B.

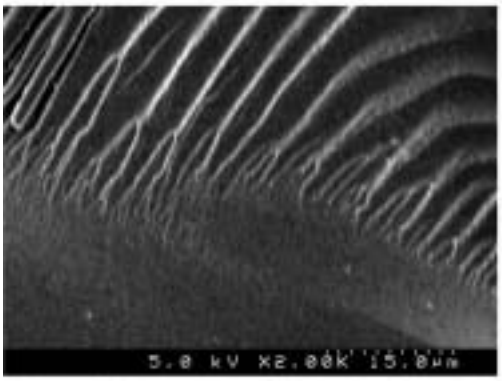
Pluronic® F68 and IDM are crystalline materials as shown in the x-ray profiles presented in Fig. 12. Eudragit® RD 100, which is composed of a mixture of sodium CMC and Eudragit® RL 100, exhibited no evidence of crystalline peaks showing it to be an amorphous polymer. The physical blend containing 30% IDM exhibited some peaks at 12° and 17°. The x-ray profile for the extrudate showed an absence of peaks, indicating that IDM was in an amorphous form and a solid solution was formed following the hot-melt extrusion process. Findings reported by other researchers also revealed that solid dispersions of IDM and Eudragit® RS prepared by the solvent evaporation method resulted in the formation of an amorphous form of IDM when present at concentrations as high as 30% (w/w) (Oth & Moës, 1989).

Several pharmaceutical processes, including spray drying, lyophilization, and milling, have been shown to transform a crystalline drug into different polymorphic structures. An amorphous form of drug is formed first due to a lower interfacial energy of the metastable nucleus against the amorphous matrix than that of the more stable nucleus against this matrix as explained over 100 years ago by Ostwald and later by other researchers (Yoshioka et al., 1994; Ostwald, 1897). The transformation of crystalline IDM into an amorphous form as a result of thermal processing enhanced the solubility of the model drug, thus overcoming the limitation of the low solubility on the drug release from the drug delivery system. In addition, the formation of a molecularly dispersed drug also eliminates the influence of drug particle size on drug release, which is a major concern for poorly water-soluble drugs.

When 10% Eudragit® S 100 replaced an equivalent amount of Eudragit® RD 100 in the hot-melt extrudate formulations as seen in Fig. 13, the peak intensity was higher as compared with the formulation without Eudragit® S 100 (Fig. 12E), since IDM was immiscible with Eudragit® S 100 in the molten state. When more than 10% of Eudragit® S 100 was added to the formulation to replace the same amount of Eudragit® RD 100, a further increase in crystallinity of IDM was found following thermal processing.



(A) 30% of IDM, 65% of Eudragit® RD 100, 5% of Pluronic F68, and 0% of TEC



(B) 30% of IDM, 61% of Eudragit® RD 100, 5% of Pluronic F68, and 4% of TEC

FIGURE 11 **Scanning Electron Microscopy Photographs of IDM Hot-melt Extrudates.**

CONCLUSIONS

Indomethacin (IDM) was found to decrease the Tg of the Eudragit® RL PO demonstrating that IDM exhibited a solid-state plasticization effect on the polymer and IDM was miscible with this polymer in the molten state. Eudragit® RD 100, Eudragit® L 100, and Eudragit® S 100 were thermally stable at 140°C for 10 min. Indomethacin (IDM) was chemically stable in the formulations following hot-melt extrusion. Indomethacin (IDM) exhibited strong binding to Eudragit® RD 100 resulting in incomplete drug release from the extrudated granules. When 10% of either Eudragit® L 100 or Eudragit® S 100 was blended with Eudragit® RD 100, a weaker interaction was observed due to the presence of anionic functional groups. The drug release rate from the hot-melt extrudates solid solutions increased with the addition of Pluronic® F68, Eudragit® L 100, or Eudragit® S 100, and also with an increase in the pH of the dissolution media. This was due to the increased wettability and solubility of the drug, increased permeability of the polymer, and weakened interactions between the drug and polymer. The inclusion of TEC up to 8% in the granule formulation or compressing

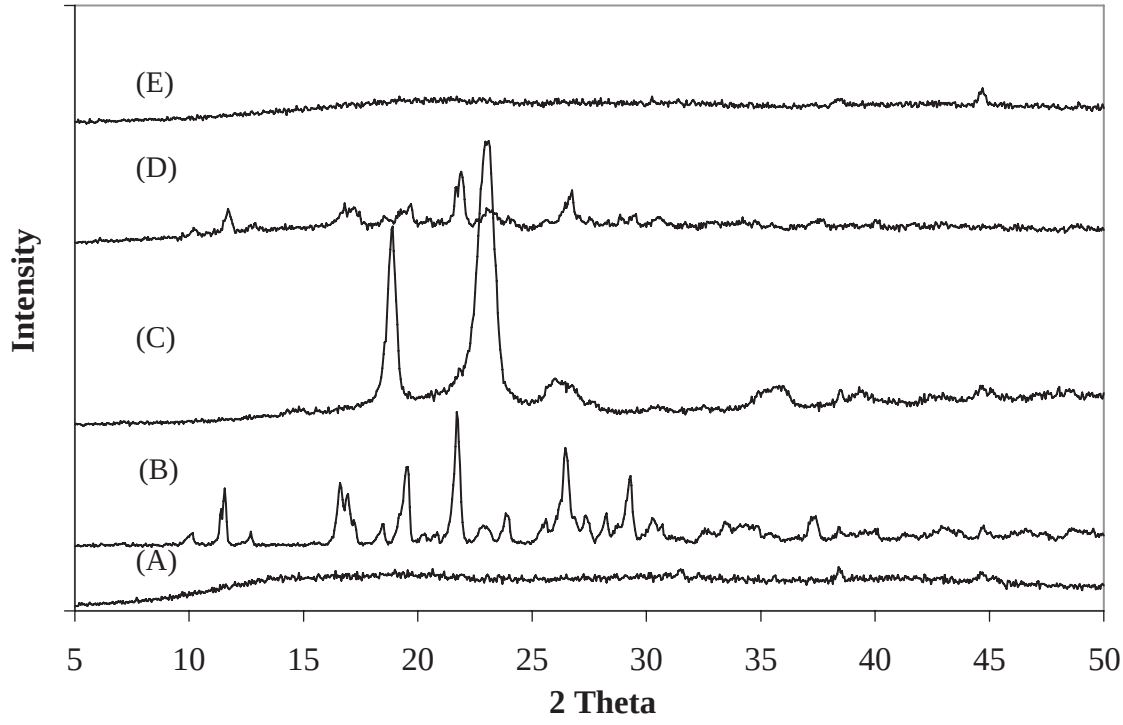


FIGURE 12 **X-ray Diffraction Patterns of IDM, Eudragit® RD 100, Pluronic® F68, and processed materials. (A): Eudragit® RD 100; (B): IDM, (C): Pluronic® F68; (D): Physical Mixture of IDM (30%), Eudragit RD 100 (61%), Pluronic® F68(5%), and TEC (4%); (E): Hot-melt Extrudate of IDM(30%), Eudragit® RD 100 (61%), Pluronic® F68 (5%), and TEC (4%).**

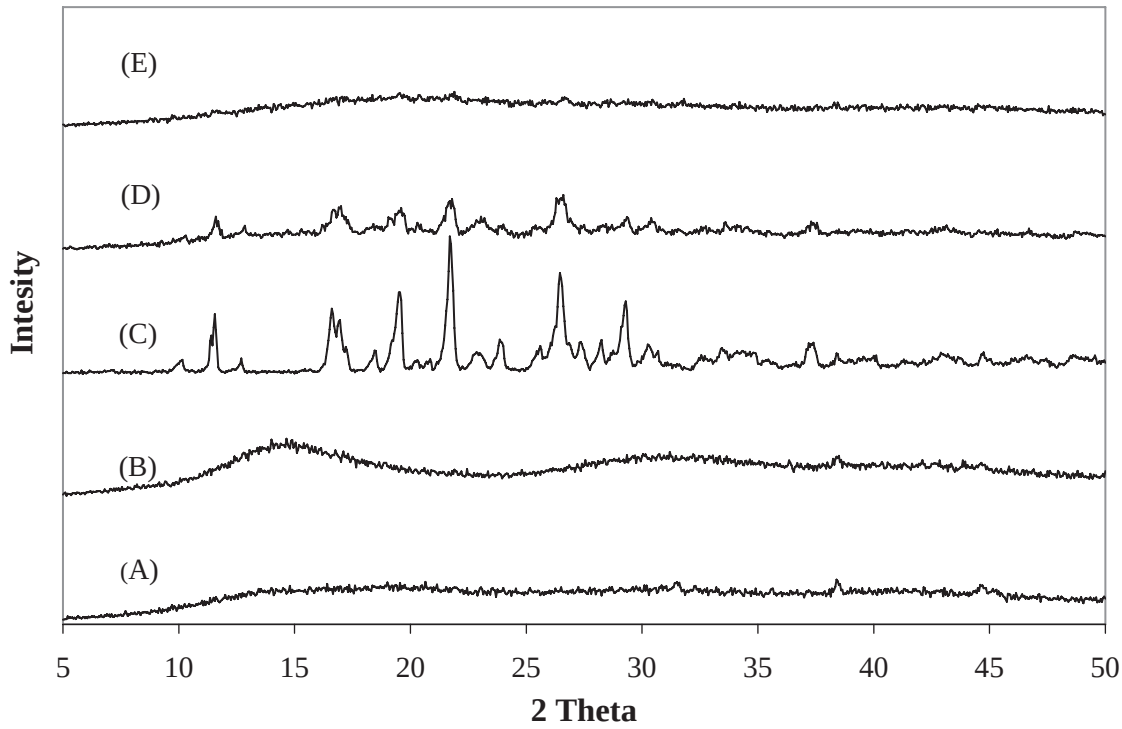


FIGURE 13 **X-ray Diffraction Patterns of IDM, Eudragit® RD 100/Eudragit® S100, and Processed Materials. (A): Eudragit® RD 100; (B); Eudragit® S 100; (C): IDM; (D): Physical Mixture of IDM (30%), Eudragit® RD 100 (51%), Eudragit® S 100 (10%), Pluronic® F68 (5%), and TEC (4%); (E): Hot-melt Extrudates of IDM (30%), Eudragit® RD 100 (51%), Eudragit® S 100 (10%), Pluronic® F68 (5%), and TEC (4%).**

the granules into tablets had no significant effect on the drug release rate.

Controlled release tablets containing a poorly water-soluble drug, IDM, acrylic polymers, and TEC were successfully prepared by hot-melt extrusion. Indomethacin (IDM) was transformed from crystalline Form I into an amorphous form in the Eudragit® RD 100 granules with higher aqueous solubility following hot-melt extrusion. The thermal processing facilitated the formation of a solid solution with a continuous matrix structure that was shown to control the drug diffusivity from the hot-melt extrudates.

REFERENCES

Allcock, H. R., & Lampe, F. W. (1990). *Contemporary Polymer Chemistry*. (2nd ed). New Jersey: Prentice Hall Inc. 146–148.

Ansel, H. C., Allen, Jr., L. V., & Popovich, N. G. (1999). *Pharmaceutical Dosage Forms and Delivery Systems*, (7th ed) Lippincott Williams & Wilkins: Philadephia.

Carli, F., Capone, G., Colombo, I., Magarotto, L., & Motta, A. (1984). Surface and transport properties of acrylic polymers influencing drug release from porous matrices. *Int. J. Pharm.*, *21*, 317–329.

Carstensen, J. T. (2001). Advanced pharmaceutical solids. In *Drugs and the Pharmaceutical Sciences*, v. 110. Marcel Dekker: New York.

Carstensen, J. T., & Morris, T. (1993). Chemical stability of indomethacin in the solid amorphous and molten states. *Journal of Pharmaceutical Sciences*, *82*, 657–659.

Center for Drug Evaluation and Research, (1997). *Guidance for Industry Dissolution Testing of Immediate Release Solid Oral Dosage Forms, BP1*. http://www.fda.gov/cder/guidance/1713bp1.pdf, 1–11.

Chiou, W., & Reigelman, S. (1971). Pharmaceutical applications of solid dispersion systems. *J. Pharm. Sci.*, *60*, 1281–1302.

Esbelin, B., Beyssac, E., Aiache, J.-M., Shiu, G. K., & Skelly, J. P. (1991). A new method of dissolution in vitro, the "Bio-Dis" apparatus: Comparison with the rotating Bottle method and in vitro:in vivo correlations. *J. Pharm. Sci.*, *80*, 991–994.

Follonier, N., Doelker, E., & Cole, E. T. (1994). Evaluation of hot-melt extrusion as a new technique for the production of polymer-based pellets for sustained-release capsules containing high loadings of freely soluble drugs. *Drug Development & Industrial Pharmacy*, *20*, 1323–1339.

Ford, J. L. (1986). Current status of solid dispersions. *Pharmaceutica Acta Helvetiae*, *61*, 69–88.

Forster, A., Hempenstal, J., & Rades, T. (2001). Characterization of glass solution of poorly water soluble drugs produces by melt extrusion with hydrophilic amorphous polymers. *J. Pharmacy Pharmacology*, *53*, 303–315.

Grant, D. J. W. (1999). Theory and origin of polymorphism. In *Polymorphism in pharmaceutical solids*; Brittain, H. G. Ed. Maral Dekker: New York, pp. 1–33.

Guillory, J. K. (1999). Generation of polymorphs, hydrates, solvates, and amorphous solids, in *Polymorphism in pharmaceutical solids*, Brittain, H. G. Ed. M. Dekker: New York, pp. 183–226.

Ho, H. O., Chen, C. N., & Sheu, M. T. (2000). Influence of pluronic F-68 on dissolution and bioavailability characteristics of multiple-layer pellets of nifedipine for controlled release delivery. *Journal of Controlled Release*, *68*, 433–440.

Kim, C. J. (1998). Effects of drug solubility, drug loading, and polymer molecular weight on drug release from Polyox tablets. *Drug Development & Industrial Pharmacy*, *24*, 645–651.

Leuner, C., & Dressman, J. (2000). Improving drug solubility for oral delivery using solid dispersions. *European Journal of Pharmaceutics & Biopharmaceutics*, *50*, 47–60.

Lovrecich, M., Nobile, F., Rubessa, F., & Zingone, G. (1996). Effect of aging on the release of indomethacin from solid dispersions with Eudragits. *International Journal of Pharmaceutics*, *131*, 247–255.

McNeill, I. C. (1968). A study of the thermal degradation of methyl methacrylate polymers and copolymers by thermal volatilization analysis. *Eur. Polymer J.*, *4*, 21–30.

The Merck Index. (13th ed.) 2001. New Jersay: Merck & Co., Inc.

Newton, D. W., & Kluza, R. B. (1978). pKa values of medicinal compounds in pharmacy practice. *Drug Intelligence and Clinical Pharmacy*, *12*, 546–554.

O'Brien, M., McCauley, J., & Cohen, E. (1984). Indomethacin. In *Analytical profiles of drug substances*; Florey, K. Ed., Academic Press, Inc. Orlando, 211–238.

Ostwald, W. (1897). Studien uber die bildung und umwandlung fester korper. *Zeitschrift Physikalische Chemmie*, *22*, 289–330.

Oth, M. O., & Moës, A. J. (1989). Sustained release solid dispersions of indomethacin with Eudragit RS and RL. *Int. J. Pharm.*, *55*, 157–164.

Repka, M. A., & McGinity, J. W. (2001). Bioadhesive properties of hydroxypropyl cellulose topical films produced by hot melt extrusion. *Journal of Controlled Release*, *70*, 341–351.

Serajuddin, A. T. M. (1999). Solid dispersion of poorly water-soluble drugs: early promises, subsequent problems, and recent breakthroughs. *J. Pharm. Sci.*, *88*, 1058–1066.

Sorasuchart, W., Wardrop, J., & Ayres, J. W. (1999). Drug release from spray layered and coated drug-containing beads: effects of pH and comparison of different dissolution methods. *Drug Development & Industrial Pharmacy*, *25*, 1093–1098.

Taylor, L. S., & Zografi, G. (1998). Quantitative analysis of crystallinity using FT-Raman spectroscopy. *Pharmaceutical Research*, *15*, 755–761.

Wu, C., & McGinity, J. W. (1999). Non-traditional plasticization of polymeric films. *International Journal of Pharmaceutics*, *177*, 15–27.

Yoshioka, M., Hancock, B. C., & Zografi, G. (1994). Crystallization of indomethacin from the amorphous state below and above its glass transition temperature. *Journal of Pharmaceutical Sciences*, *83*, 1700–1705.

Zhang, F., & McGinity, J. W. (2000). Properties of hot melt extruded theophylline tablets containing polyvinyl acetate. *Drug Development & Industrial Pharmacy*, *26*, 931–942.

Zhu, Y., Shah, N. H., Malick, A. W., Infeld, M. H., & McGinity, J. W. (2002). Influence of thermal processing on the properties of chlorpheniramine maleate tablets containing an acrylic polymer. *Pharm. Dev. Tech.*, *7*, 481–489.

Zhu, Y., Shah, N. H., Malick, A. W., Infeld, M. H., & McGinity, J. W. (2002). Solid-state plasticization of an acrylic polymer with chlorpheniramine maleate and triethyl citrate. *Int. J. Pharm.*, *241*, 301–310.