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Research paper

Properties of hot-melt extruded tablet formulations for the colonic delivery of 5-aminosalicylic acid

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Abstract

Hot-melt extruded tablets were prepared using Eudragit® S 100 as the polymeric carrier to target delivery of 5-aminosalicylic acid (5-ASA) to the colon. Scanning electron microscopy, modulated differential scanning calorimetry and X-ray diffraction analysis of the hot-melt tablet extrudates demonstrated that 5-ASA remained crystalline and was homogeneously dispersed throughout the polymer matrix. A pre-plasticization step was necessary when incorporating triethyl citrate (TEC) into the formulation in order to achieve uniform mixing of the polymer and plasticizer, effectively reduce the polymer glass transition temperature (T_g), and to lower the processing temperatures. The concentration of TEC in the extrudates not only influenced the processing temperature, but also influenced the drug release rates from the extruded tablets due to leaching of the TEC during dissolution testing. Citric acid monohydrate was found to plasticize Eudragit® S 100, and when combined with TEC in the powder blend, the temperatures required for processing were reduced. Tablets containing citric acid released drug at a slower rate as a result of the suppression of polymer ionization due to a decrease in the micro-environmental pH of the tablet. The drug release profiles of the extruded tablets were found to fit both diffusion and surface erosion models.

Keywords: Hot-melt extrusion; Colonic drug delivery; 5-ASA; Mesalamine; Thermal processing; Eudragit® S 100; Micro-environmental pH

1. Introduction

5-Aminosalicylic acid, also known as 5-ASA or mesalamine, is used for the treatment of ulcerative colitis and Crohn's Disease. These diseases are characterized by acute non-infectious inflammation of the colorectal mucosa. It is known that 5-ASA is the therapeutic moiety of sulphasalazine, a pro-drug that consists of two compounds, sulphapyridine and 5-ASA, joined by a diazo bond that is cleaved by bacteria in the colon [1,2]. The use of sulphasalazine has been limited due to adverse reactions including allergy, intolerance and male infertility [3]. As a result, preparations of 5-ASA including enemas, suppositories and oral modified release dosage forms have been marketed. Delivery of 5-ASA to the colon is necessary since its mode of action is topical and the compound is extensively absorbed by the small intestine [3,4]. Oral solid dosage forms, such as Pentasa® and Asacol®, utilize pH dependent film coatings which allow the dosage form to remain intact in the stomach and small intestine until reaching the higher pH environment of the colon where the coating dissolves and the 5-ASA is then released.

Hot-melt extrusion has been widely used in the plastics industry and is becoming more widely utilized in the production of immediate and sustained release drug delivery systems [4–8]. A hot-melt extruder consists of either a single or twin rotating screw inside a heated barrel having three different sections, including the feed, melt and metering sections and the die. A powder blend consisting of drug, excipients and polymeric carrier is mixed and transferred into the melting section. The polymeric carrier gradually melts or softens and the materials are mixed and compressed. The molten mixture finally passes through

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a rod-shaped die, and after cooling, the extrudate may then be cut into tablets, granules or pelletized. Hot-melt extrusion offers several advantages in the preparation of modified release tablets. It is a fast, simple, continuous, solvent free process requiring fewer processing steps than traditional tableting techniques. Additionally, there are no requirements for compressibility of the materials used in the formulation.

The objective of the current project was to investigate the properties of tablets prepared by hot-melt extrusion targeting delivery of 5-ASA to the colon. Combinations of 5-ASA with Eudragit® S 100 (an anionic copolymer based on methacrylic acid and methyl methacrylate with a 1:2 ratio of carboxyl groups to ester units, dissolving at pH 7.0), Eudragit® L 100 (an anionic copolymer based on methacrylic acid and methyl methacrylate with a 1:1 ratio of carboxyl groups to ester units, dissolving at pH 6.0) and excipients were extruded and cut into tablets. The drug release properties of the hot-melt extruded tablets were investigated. Furthermore, the influence of additives on the drug release properties of 5-ASA tablets, and the processability of the powder blend were also investigated.

2. Materials and methods

USP grade 5-amino salicylic acid (5-ASA, mesalamine), citric acid monohydrate, hydrochloric acid (HCl), sodium phosphate tribasic, potassium bromide (KBr), HPLC grade acetonitrile and acetone were all purchased from Spectrum Chemical, Gardena, CA.

Eudragit® S 100 and Eudragit® L 100 were donated by Degussa Corp., Piscataway, NJ. Triethyl citrate (TEC) was donated by Morflex, Inc., Greensboro, NC; Imwitor 191 (Glycerol monostearate, GMS) was donated by Sasol North America, Inc., Westwood, NJ.

2.1. Hot-melt extruded tablet formulations

The dry materials were mixed together in a Robot-Coupe® model RSI 3VG (Robot-Coupe® USA, Inc., Ridgeland, MS, USA) high shear granulator for 2 min at 3000 rpm. The compositions for each formulation investigated are summarized in Table 1. The Eudragit® S 100 dry powder was pre-plasticized with TEC in the Robot-Coupe® by pipeting TEC into the granulator and mixing the polymer and plasticizer together at 2000 rpm for 1 min. After pre-plasticization of the polymer, further ingredients were added to the granulator and blended for 2 min at 3000 rpm. This powder was then sieved through an 18 mesh screen three times to ensure a homogenous blend of all tablet ingredients.

Formulation A_1 was prepared without the polymer pre-plasticization step by combining ingredients into the Robot-Coupe® and then granulating with 12% w/w (total formula weight) TEC.

Table 1
Hot-melt extrusion tablet formulations

Components (%)	Formulations					
	A	B	C	D	E	F
5-ASA	25	25	25	25	25	50
Eudragit® S 100	58	46	43	40	45	30
Eudragit® L 100					10	
TEC	12	23	20	20	15	15
Citric acid monohydrate				10		
GMS	5	6	12	5	5	5

2.2. Preparation of hot-melt extruded tablets

The dry powder blends were processed into hot-melt extrudates using a Randcastle Microtruder extruder (model RCP-0750 Cedar Grove, NJ, USA) fitted with a 6 mm die. The temperatures of the four heating zones of the extruder varied depending upon the formulation. The processing parameters for the formulations are summarized in Table 2. The extrudate resembled a long rod-like material that was cooled and cut into tablets having a weight of either 130 ± 5 or 250 ± 5 mg.

2.3. Drug release studies

The drug release properties of the hot-melt extruded tablet formulations were studied using a modified procedure of USP 27 delayed release articles method A, with a VanKel 600 apparatus and a Van Kel 8000 autosampler (Varian, Inc., Cary, NC, USA). The dissolution medium was maintained at 37 °C using apparatus 2 set at 100 rpm and consisted of 750 ml of 0.1 N HCl, pH 1.2 during the first two hours of the dissolution test. After two hours, the media pH was increased to 6.8 by the addition of 250 ml of 0.2 M sodium triphosphate buffer. The dissolution media pH was increased to 7.4 after 6 h with the addition of a sodium hydroxide solution. A 3 ml sample was withdrawn every two hours during the 12 h dissolution study. Sink conditions were maintained. Dissolution studies were also conducted in 1000 ml at pH 7.4 in 50 mM potassium phosphate buffered solution, maintained at 37 °C and a paddle speed of 100 rpm for 12 h.

2.4. HPLC analysis

Dissolution samples were analyzed for 5-ASA content using a reversed-phase isocratic HPLC method on a Waters

Table 2
Hot-melt extrusion processing conditions for tablet formulations A–F

Zone temperatures (°C)	Formulations					
	A	B	C	D	E	F
1	149	113	113	102	116	113
2	154	117	118	104	121	117
3	157	118	121	107	129	118
4	162	121	124	110	132	121

system equipped with a 501 pump, a 996 PDA detector and a 717 autosampler (Waters, Milford, MA, USA). A Spherisorb ODS-2, 5 μm, 250×4.6 mm column was purchased from Column Engineering and used to separate and analyze 5-ASA. A 50 μl sample was injected onto the column at a flow rate of 1 ml/min. The mobile phase consisted of a buffer system composed of a combination of 200 ml of 67 mM potassium phosphate monobasic and 800 ml of 67 mM sodium phosphate dibasic. The final mobile phase consisted of a 80:20 ratio of buffer solution combination to methanol. The retention time for 5-ASA was 2.9 min and the compound was detected at 290 nm. A stock solution was prepared by diluting 5-ASA in 0.1 N HCl. The standard solutions were diluted with mobile phase.

2.5. TEC release studies

The release of TEC from the hot-melt extruded tablets was measured during the 12 h dissolution test. The amount of TEC that leached into the dissolution media was determined using a reversed-phase HPLC method on a Waters model 501 pump and a 996 PDA detector equipped with a 717 autosampler. A sample volume of 50 μl was injected onto a Phenomenex Luna C18(2) column 150× 4.6 mm, 3 μm at 1 ml/min. TEC was detected at 210 nm at a retention time of 7.5 min. The mobile phase consisted of 63% w/v 25 mM sodium phosphate monobasic (pH adjusted to 2.3 using phosphoric acid) and 37% w/v acetonitrile. Standards were diluted in mobile phase and a stock standard solution of TEC was prepared in methanol.

2.6. Tablet drug content determination

The drug content of the extruded tablets was determined following the extrusion process by placing the tablets in a scintillation vial with 5 ml of acetone in order to dissolve the polymeric matrix. This mixture was placed on a shaker at slow speed for 30 min until the tablet matrix was completely disintegrated and dissolved. The mixture was then transferred to a volumetric flask containing pH 7.4, 50 mM potassium phosphate buffer and diluted to a final volume of 500 ml. After mixing, a sample was removed from the volumetric flask and filtered through a 0.45 μm syringe filter for HPLC analysis. Three tablets were extracted and analyzed for each tablet formulation.

2.7. Morphology of hot-melt extrudates

The hot-melt extruded tablets were broken in half and the surface morphology at the center of the tablet was examined using a Philips model 515 Scanning Electron Microscope (SEM) (FEI Company, Hillsboro, OR, USA) at 15 kV accelerating voltage. Samples were sputter coated with 60/40 Au/Pd for 60 s using a Ladd bench top sputter coater (Ladd Research, Williston, VT, USA).

2.8. Thermal analysis

A modulated differential scanning calorimeter (MDSC model 2920, TA Instruments, Newcastle, DE, USA) was used to investigate the potential for interaction between 5-ASA and tablet ingredients (pre- and post-extrusion), and to determine the glass transition temperature of the polymeric carrier. A 10–20 mg sample was accurately weighed and sealed in an aluminum pan and heated at a rate of 5 °C/min with a 1 min modulation at a temperature range from 20 to 300 °C under a nitrogen atmosphere. The determination of glass transition temperature was calculated as the midpoint of the step transition. The MDSC was calibrated using an indium standard.

2.9. Thermal stability of tablet ingredients

A thermogravimetric analyzer (TGA Perkin–Elmer 7-series Perkin-Elmer Corp., Shelton, CT, USA) was used to investigate the thermal stability of 5-ASA and the excipients used in the preparation of the hot-melt extruded tablets. Each sample was heated from 50 to 500 °C with a temperature ramp speed of 10 °C/min. The weight percent of sample remaining was plotted as a function of temperature. Nitrogen was used as the purging gas for the furnace chamber.

2.10. Crystalline properties of hot-melt extrudates

Powder X-ray diffraction patterns of the hot-melt tablet extrudates were obtained using a Philips vertical scanning diffractometer (type 42273, Philips Electronic Instrument, Mount Vernon, NY, USA). The samples were exposed to Cu K alpha radiation under 40 kV and 40 mA. Measurement was conducted using a 2θ scanning range from 5 to 50° at a scanning rate of 2°/min. Diffraction patterns were determined for physical mixtures of the tablet ingredients and granules of the extruded tablets to determine the effect of the extrusion process on drug crystallinity.

2.11. 5-ASA and Eudragit® S 100 complexation and adsorption study

To determine if complexation occurred between 5-ASA and Eudragit® S 100, a stock solution of 5-ASA was prepared in pH 7.4, 50 mM potassium phosphate buffer at a concentration of 800 μg/ml. To 20 g of this solution, increasing increments of Eudragit® S 100 polymer (0, 5, 10, 20, 50, 100, 200 and 500 mg) were added and diluted with buffer solution to a 25 g final amount. The mixtures were protected from light and placed on a rotating shaker for 24 h maintained at 37 °C. After 24 h, the mixtures were centrifuged at 2000 rpm for 10 min, filtered using a 0.45 μm Acrodisc® GHP syringe filter and analyzed by HPLC for 5-ASA content. The amount of 5-ASA remaining in solution was plotted vs Eudragit® S 100 amount added to

the mixture. Adsorption of the drug to Eudragit® S 100 was determined at pH 1.2 using the same procedure and the same concentration of 5-ASA solution and polymer amounts. The 5-ASA stock solution and polymer mixtures were prepared in 0.1 N HCl.

2.12. 5-ASA and citric acid chemical interaction study

Citric acid and 5-ASA were combined and blended in a 1:2.5 w/w ratio (to simulate the ratio used in the extruded formulation) using a mortar and pestle. A sample of the mixture was stored at ambient conditions and sealed in a scintillation vial. Further samples were heat-treated by placing aliquots in open aluminum weigh boats and heat-treating for 0, 1, 2, 5, 10 and 20 min in an oven maintained at 110 °C. After heat-treatment, the samples were sealed in a scintillation vial. Each sample was then prepared for HPLC analysis by adding 5 ml of acetone to the vial. This suspension was quantitatively transferred to a 500 ml volumetric flask containing 50 mM, pH 7.4 potassium phosphate buffer solution. An aliquot of the solution was analyzed by HPLC to determine the 5-ASA content and presence of impurities. Acetone used in the sample preparation process was observed in the chromatogram at a retention time of 4.4 min.

2.13. Solids probe mass spectrometry

Mass spectrometry (Finnigan TSQ 70, Thermoquest, San Jose, CA, USA) consisting of direct chemical ionization (DCI) with methane gas as the ionizing agent and a solids probe was used as a qualitative method to study the interaction between 5-ASA and citric acid monohydrate. A physical mixture maintained at ambient conditions and a sample that was heat-treated for 20 min at 110 °C were placed inside a glass capillary tube and inserted into the tip of a probe. The probe tip temperature was programmed to ramp from 30 to 300 °C within 10 min after placing the probe tip inside the mass spectrometer. Methane gas was used as the ionizing agent, and a pressure of 3 Torr and a temperature of 150 °C was maintained inside the mass spectrometer chamber. A spectral scan was performed to determine the most abundant compound in *m*/*z* (mass to charge) units in the spectra.

2.14. FT-IR analysis

FT-IR analysis was performed on samples consisting of physical mixtures at 1:2.5 w/w ratios of citric acid to 5-ASA maintained at ambient conditions or heat-treated for 20 min at 110 °C. The samples were blended with KBr and the mixture was compressed to prepare a disk. Samples were analyzed using a Nicolet model 360 FT-IR (Thermo Electron Corp., Mountain View, CA, USA) with Omnic E. S. P. software.

3. Results and discussion

3.1. Thermal stability of tablet ingredients

5-ASA was selected as the model compound for hot-melt extrusion processing due to its high melting and decomposition temperatures at 278 and 298 °C, respectively [9]. The thermal stability of 5-ASA, Eudragit® S 100 and the additional tablet ingredients was determined using thermal gravimetric analysis (TGA), and the results from the TGA study are shown in Fig. 1. All excipients were thermally stable at temperatures used for processing the hot-melt extruded tablets (Table 2). Eudragit® S 100, Eudragit® L 100 and 5-ASA did not begin to show signs of thermal decomposition until reaching approximately 250 °C, whereas TEC and citric acid began to demonstrate a loss in weight due to volatilization and decomposition at approximately 160 °C. Formulation A was extruded with the die temperature set at 162 °C, but the blend was only briefly exposed to this temperature and no sign of thermal decomposition was evident in the HPLC chromatograms of the tablet extrudates.

3.2. Pre-plasticization with TEC

The initial challenge to overcome processing 5-ASA using a hot-melt extrusion method was to effectively plasticize the polymeric carrier. Eudragit® S 100 is a brittle material having a high glass transition temperature of 166 °C. Processing temperatures above the T_g or melting temperature of the polymeric carrier are typically required to soften and lower the polymer melt viscosity to allow adequate flow through the extruder. The addition of a plasticizer will decrease the polymer T_g due to intermolecular interaction with the polymeric chains allowing for

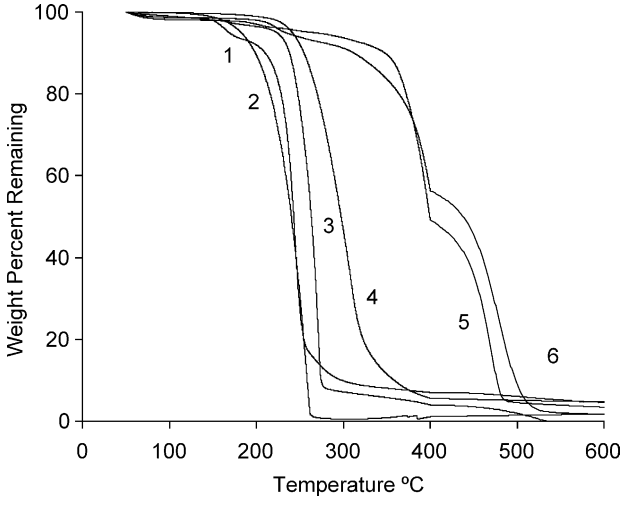

Fig. 1. Thermal gravimetric analysis of tablet ingredients used in the preparation of 5-ASA tablets by hot-melt extrusion processing. (1) Triethyl citrate; (2) citric acid monohydrate; (3) 5-ASA; (4) glycerol monostearate; (5) Eudragit® L100; (6) Eudragit® S 100.

lower processing temperatures. Lowering the polymer T_g with plasticizers, therefore, facilitates thermal stability of the composite materials. For film coating, Eudragit® S 100 is typically dissolved in a solvent and plasticized using a high content of a liquid citrate ester, such as triethyl citrate (TEC). Mixing of solid polymer with a liquid plasticizer is facilitated by dispersing both in a solvent. In the current study, insufficient polymer plasticization resulted due to non-homogeneous mixing of TEC with the dry polymer when all ingredients were combined and blended in one step. As a consequence, high processing temperatures were necessary to extrude the polymer. To promote intermolecular interaction between the dry polymer and plasticizer, a pre-plasticization step was performed where the polymer and the TEC were combined and granulated together prior to the addition of the drug and the excipients. This was more effective in lowering the T_g of Eudragit® S 100 and the required processing temperature.

For comparison, tablets were prepared with and without the pre-plasticization step, designated as formulation A_1 and A_2, respectively. Both formulations contained the same ingredients and were processed at the same temperatures (formulation A, Tables 1 and 2). The pre-plasticization step decreased the tablet-to-tablet drug release variability as demonstrated by the decrease in the standard deviation in the mean drug release values in formulation A_2 compared to A_1 (Fig. 2). Tablet content uniformity was also improved by pre-plasticization as demonstrated by a reduction in the standard deviation for 5-ASA recovery in formulation A_2 compared to A_1 (Table 3). As a result of these findings, the remaining tablet formulations were prepared using the pre-plasticization technique.

Table 3
Hot-melt extruded tablet drug content determination (formulations A–F, $n=3$)

% 5-ASA recovered	Formulations						
	A_1	A_2	B	C	D	E	F
Average	98	104	100	101	95	100	104
Std dev	15.9	1.7	0.6	0.6	0.8	0.8	1.3

The amount of TEC incorporated into the powder blends influenced the processability as well as the release rate of drug from the extruded tablets. When the TEC content was increased from 12 to 23% w/w, formulations A and B, respectively, the melt and die temperatures required for extrusion were decreased significantly (melt temperature was reduced from 157 to 118 °C and die temperatures from 162 to 121°C, Table 2). Both tablet formulations released less than 10% drug after two hours in 0.1 N HCl as shown in Fig. 2. The tablets containing 23% w/w TEC (formulation B) showed an increase in the drug release rate during the 12 h dissolution period compared with tablets containing only 12% w/w TEC (formulation A_1 and A_2, Fig. 2). The increase in 5-ASA release with increasing TEC content in the extruded tablets was attributed to the leaching of the water-soluble plasticizer during the dissolution test, leading to channel formation in the tablet. This was confirmed by measuring the amount of TEC that diffused from the tablet matrices during the dissolution test, and these data appear in Fig. 3. The tablets did not completely dissolve after 12 h in the dissolution media and the total TEC content was not

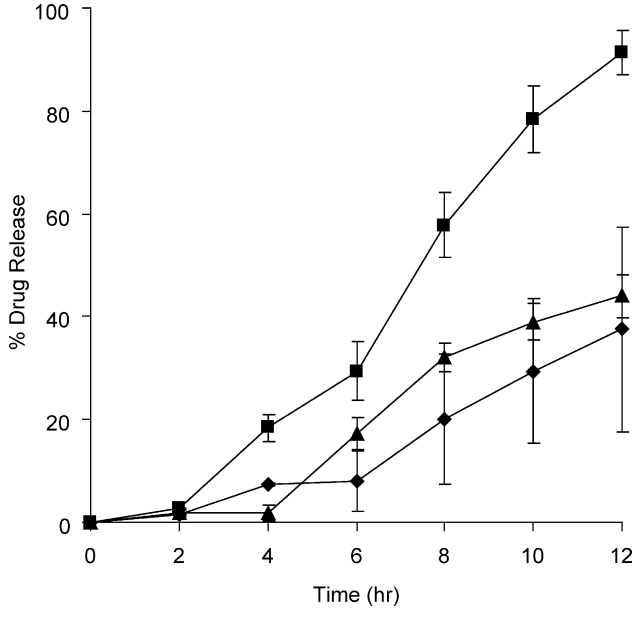

Fig. 2. Influence of TEC concentration and pre-plasticization on the drug release rate of hot-melt extruded tablets containing 25% w/w 5-ASA. (▲) Formulation A_2, pre-plasticized 12% w/w TEC; (♦) Formulation A_1, no pre-plasticization 12% w/w TEC; (■) Formulation B, pre-plasticized 23% w/w TEC; Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0 to 2 h; 50 mM phosphate buffer, pH 6.8 from 2 to 6 h and pH 7.4 from 6 to 12 h, 37 °C, 100 rpm, apparatus 2 ($n=3$).

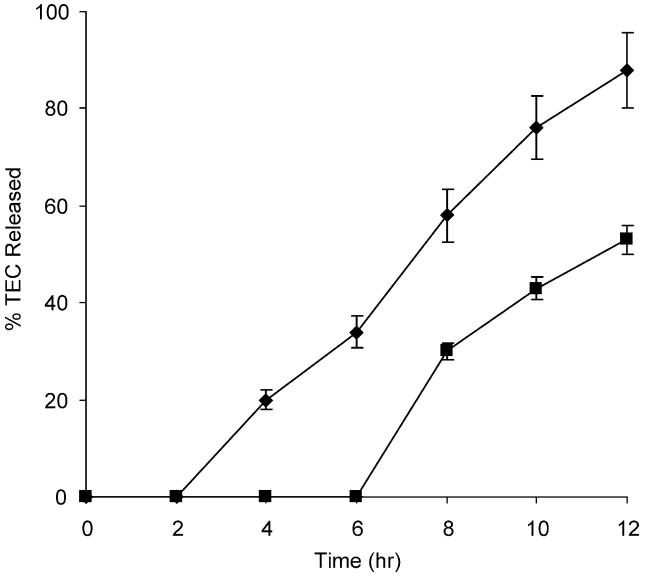

Fig. 3. TEC release from hot-melt extruded tablets containing 12 and 23% w/w plasticizer. (■) Formulation A_2, 12% w/w TEC; (♦) Formulation B, 23% w/w TEC; Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0 to 2 h; 50 mM phosphate buffer, pH 6.8 from 2 to 6 h and pH 7.4 from 6 to 12 h, 37 °C, 100 rpm, apparatus 2 ($n=3$).

recovered during the 12 h dissolution study, but was recovered at the end of 24 h. The rate of TEC release from the tablets corresponds to the release rate of 5-ASA from the tablets. Zhu and coworkers also observed a correlation between plasticizer leaching and drug release from hot-melt extruded tablets containing Eudragit® RS PO [8]. The hot-melt extruded tablets containing 5-ASA and Eudragit® S 100 as the polymeric carrier exhibited drug release behavior in pH 6.8 and 7.4 media that was due to polymer erosion and drug diffusion [10].

3.3. Solid-state plasticization

Compounds such as methylparaben, ibuprofen, chlorpheniramine maleate and lidocaine HCl have been cited as having a plasticizing effect on pharmaceutical polymers [8,11,12]. Citric acid is a small molecule similar in structure to TEC and was shown in the current research to also act as a plasticizing agent. Physical mixtures of citric acid and Eudragit® S 100 were prepared at 1:1 and 1:4 w/w ratios. These mixtures yielded T_g values of 75.2 and 103 °C, respectively. The T_g values indicated that citric acid could function as sole plasticizer in the formulation at a 1:1 w/w ratio with Eudragit® S 100. Higher levels of citric acid, however, could potentially decrease the drug release rate from the matrix due to lowering of the tablet micro-environmental pH. Therefore, citric acid was incorporated into the formulation at a 1:4 ratio with the polymer in formulation D along with 20% w/w TEC. This combination of citric acid and TEC resulted in the lowest required processing temperatures compared with all hot-melt formulations extruded (melt temperature = 107 °C, die temperature = 110 °C, Table 2).

Drug release profiles for formulations B–E containing various levels of plasticizer and additives are compared in Fig. 4. Formulation D containing citric acid, demonstrated a slower rate of 5-ASA release in buffered media compared to formulation B containing no citric acid and having a similar TEC to polymer ratio. The delay in 5-ASA release for formulation D in buffered media may be attributed to a lowering of the tablet micro-environmental pH by the citric acid. Organic acids have been reported to delay or sustain drug release in formulations where enteric and colonic polymers were used as matrix and film forming agents as a result of lowered micro-environmental pH [13–15]. A low micro-environmental pH in the hot-melt extruded tablets suppressed ionization of the carboxylic groups in the acrylic polymer when exposed to pH 7.4 phosphate buffer solution, delaying the erosion of the tablet matrix and the release of 5-ASA. Although the micro-environmental pH of the tablet was low enough to delay polymer erosion in phosphate buffer, the dissolution of the citric acid did not change the overall pH of the dissolution medium. At the end of the dissolution study, the pH of the medium measured 7.4.

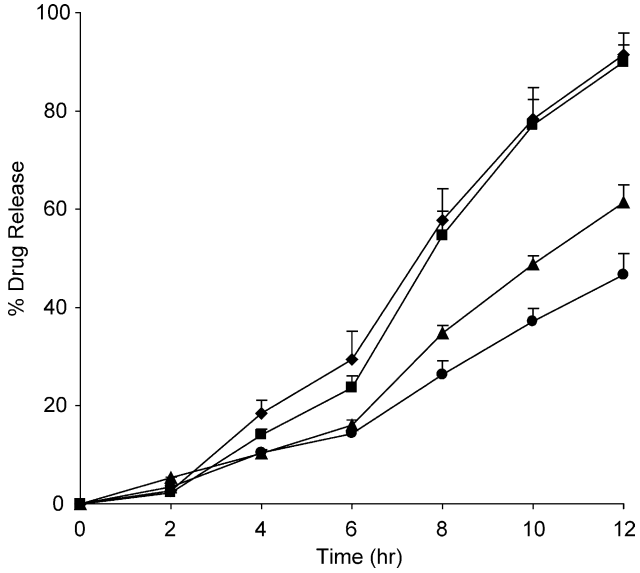

Fig. 4. Influence of additives and drug content on the release of 5-ASA from hot-melt extruded tablets containing 25% w/w 5-ASA. (♦) Formulation B, 23% w/w TEC; (■) Formulation E, 10% w/w Eudragit® L 100; (▲) Formulation D, 10% w/w citric acid; (●) Formulation C, 12% w/w GMS. Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0 to 2 h; 50 mM phosphate buffer, pH 6.8 from 2 to 6 h and pH 7.4 from 6 to 12 h, 37 °C, 100 rpm, apparatus 2 ($n = 3$).

3.4. Solid-state lubrication

In addition to plasticizers, additives such as lubricants are utilized in hot-melt extrusion to facilitate processing. Drag flow is one of the main forces influencing flow of the melt, and it occurs when the melt adheres to two solid surfaces that are moving relative to each other such as the extruder screw and barrel [16]. Lubricants can aid in decreasing the drag flow during extrusion and in lowering the melt viscosity of the polymer. In the current study, glycerol monostearate (GMS) was investigated as a solid-state thermal lubricant and was incorporated at 6 and 12% w/w, respectively, into tablet formulations B and C containing 25% w/w 5-ASA (Table 1). The drug release profiles in Fig. 4 demonstrate a slower rate of drug release from tablets containing 12% w/w of the lubricant compared with formulation B. GMS is a lipophilic, water-insoluble molecule with a melting temperature measured at approximately 70 °C. GMS is represented in the MDSC analysis of the tablet extrudate by a melting endotherm ranging from 53 to 62 °C. The presence of the melting endotherm indicated the GMS remained crystalline and immiscible within the polymer. Some molecular interaction between the polymer and the GMS occurred as represented by the depression of the GMS melting point 8–17 °C. Increasing the content of GMS (lipophilic ingredient) in the formulation decreased the tablet wettability and the penetration of the dissolution media into the tablet. This resulted in a slower release rate of 5-ASA.

3.5. Influence of Eudragit® L 100 on 5-ASA Release from hot-melt extruded tablets

Eudragit® L 100 has previously been used to modify the release properties of solid dosage forms coated with Eudragit® S 100. Khan and coworkers found that the addition of Eudragit® L 100 into coating suspensions containing Eudragit® S 100 resulted in pore formation in the Eudragit® S 100 film coating yielding a faster drug release rate from tablets containing 5-ASA [17]. Eudragit® L 100 begins to ionize and dissolve at pH 6.0 due to the 1:1 ratio of carboxylic to ester functional groups. Eudragit® L 100 (10% w/w) was included in the powder blend, along with 45% w/w Eudragit® S 100 to increase the drug release rate of the tablets in pH 7.4 phosphate buffered media. The polymer blend was pre-plasticized with 15% w/w TEC prior to hot-melt extrusion. The 1:4.5 w/w ratio of Eudragit® L 100 to Eudragit® S 100 in the hot-melt formulation (formulation E) did not significantly alter the release rate of 5-ASA compared to tablets containing no Eudragit® L 100 (formulation B) as shown in Fig. 4. Two distinct glass transitions temperatures were observed at 80 and 147 °C for Eudragit® L 100 and Eudragit® S 100, respectively, when the tablet extrudates were analyzed. The level of TEC was therefore not high enough to lower the T_g of the two polymers sufficiently to reduce the processing temperature. The formulation, as a result, was difficult to extrude.

3.6. Influence of plasticizers on processing and tablet drug release properties

The plasticizers included in the hot-melt extruded powder blends influenced processing by lowering the glass transition temperature and the melt viscosity of the Eudragit® S 100. Higher melt and die temperatures were required to process the powder blends when the polymeric carrier was insufficiently plasticized. The glass transition temperatures of physical mixtures of the plasticized Eudragit® S 100 polymer corresponding to the polymer/plasticizer combinations used in formulations A_2, B and D were determined by modulated differential scanning calorimetry (MDSC). A direct correlation was observed between the T_g of the polymer and the temperature of the die required for processing the material and the data are shown in Fig. 5. Since the melt viscosity controls polymer flow behavior in the molten state, it is, therefore, an important property in hot-melt extrusion processing. The polymer viscosity will be influenced by material composition, pressure, shear rate and temperature. In order for the polymer melt to flow, the chain segments must be able to move (possess free volume) and must have sufficient thermal energy to overcome barriers that impede motion. Above the polymer T_g there is sufficient free volume for chain movement to occur and, as a result, polymer viscosity decreases. Viscosity decreases at temperatures ranging from the T_g to $T_g + 100$ °C as predicted by the Williams–Landel–Ferry or WLF equation due to increases in polymer free volume [18]. The die temperature required to process the dry powder blends was

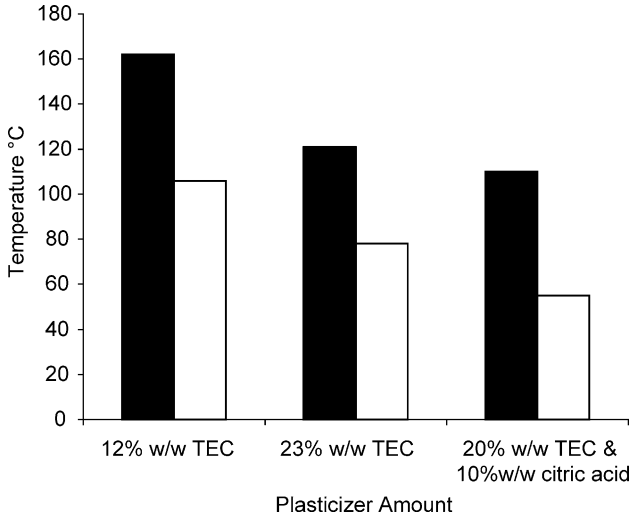

Fig. 5. Influence of Eudragit® S 100 glass transitions temperature on hot-melt extrusion processing temperatures. (■) Die Temperature; (□) Polymer Glass Transition Temperature (T_g).

40–60 °C above the T_g determined for the polymer/plasticizer physical mixtures. Lowering the polymer T_g thus lowered the temperature required for extrusion due to a lowering of the polymer melt viscosity. Determination of the T_g for proposed polymer/plasticizer combinations is necessary in predicting the temperatures required for hot-melt processing.

3.7. Influence of 5-ASA concentration on drug release properties of hot-melt extruded tablets

The influence of 5-ASA at the 25 and 50% w/w levels on the dissolution properties of tablets prepared by hot-melt extrusion is shown in Fig. 6. Increasing the level of 5-ASA

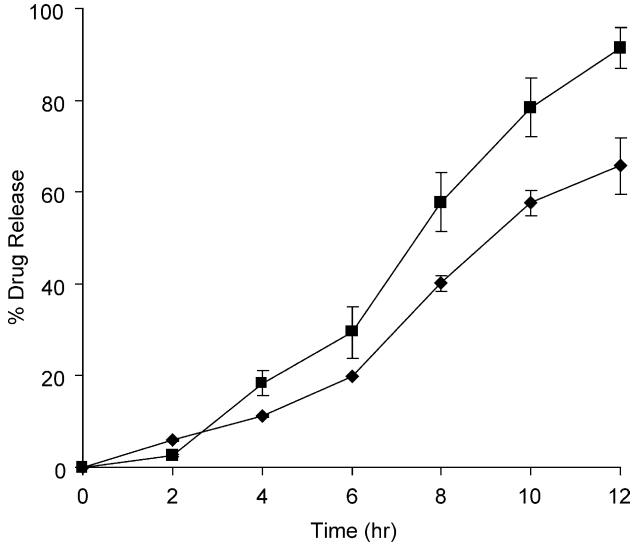

Fig. 6. Influence of 5-ASA concentration on drug release properties of hot-melt extruded tablets containing Eudragit® S 100. (■) Formulation B, 25% w/w 5-ASA; (♦) Formulation F, 50% w/w 5-ASA. Dissolution media consisting of 0.1 N HCl, pH 1.2 from 0 to 2 h; 50 mM phosphate buffer, pH 6.8 from 2 to 6 h and pH 7.4 from 6 to 12 h, 37 °C, 100 rpm, apparatus 2 ($n = 3$).

resulted in a decreased rate of drug release in pH 7.4 phosphate buffered media. At the end of the 12 h dissolution test, tablets containing 50% w/w 5-ASA released 66% drug (formulation F), compared to 91% release from tablets containing 25% w/w 5-ASA (formulation B). 5-ASA is an amphoteric compound having pK_a values of 2.3 and 5.69 for the carboxylic and amine functional groups, respectively. As the pH increases, 5-ASA solubility increases due to ionization of the carboxyl group. The slower drug release rate was therefore not attributed to a reduced solubility of the compound in the pH 7.4 phosphate buffered media. A saturated solution of 5-ASA in water has a reported pH value of 4.05 [19]. The higher level of 5-ASA incorporated was therefore capable of maintaining the micro-environmental pH of the tablet core at a low enough pH to hinder ionization and erosion of Eudragit® S 100 in buffered media. A reduction in drug release rate in phosphate buffer was also found when citric acid was incorporated into the tablet matrix. Other authors have observed that lowering of micro-environmental pH in solid dosage forms by acidic drug compounds decreases drug release by suppressing ionization of enteric polymer film coatings [20,21]. This phenomenon also explains the decrease in release rates of 5-ASA as the drug content in the hot-melt extruded tablets was increased.

3.8. Drug-polymer and drug-excipient interactions

5-ASA has functional groups capable of binding with the anionic polymeric carrier Eudragit® S 100. At pH 7.4, the carboxylic groups on the polymer are ionized and can interact with the amine group on the 5-ASA molecule through ionic bond formation or hydrogen bonding during the dissolution process. An interaction study was conducted in order to ensure that no complexation occurred between the anionic polymer and the 5-ASA in pH 7.4 media, as this would lead to a delay in release of the drug from the polymeric matrix. There was no change in 5-ASA concentration in pH 7.4 phosphate buffer solution at 37 °C after equilibration of the 5-ASA solution and Eudragit® S 100 for 24 h. This indicated that no complexation occurred between the 5-ASA and the polymer. In addition, an adsorption study was conducted at pH 1.2 in 0.1 N HCl at 37 °C. It was hypothesized that adsorption may occur at this pH due to the ionization of the amine functional group on the 5-ASA molecule resulting in chemical or physical interaction with the Eudragit® S 100 functional groups. Results of this study indicated that 5-ASA was not adsorbed to the acrylic polymer since the concentration of 5-ASA in the bulk solution remained unchanged. It was concluded that neither complexation nor adsorption influenced drug release from the hot-melt extruded tablets in pH 7.4 phosphate buffered media or in pH 1.2, 0.1 N HCl solution.

Following hot-melt extrusion, the 5-ASA melting endotherm was still present in MDSC thermograms for all tablet formulations, indicating that 5-ASA was not completely soluble in the Eudragit® S 100 carrier, and it remained in the crystalline state (Fig. 7). In all extruded tablets, the melting point of the 5-ASA was depressed from 14 to 17 °C, depending on the combination of excipients used in the formulation. This was due to incorporation of the polymer and excipients into the crystal lattice of the 5-ASA molecule during heating, mixing and compression inside the extruder resulting in depression of the 5-ASA melting point. Similar results were reported for hot-melt extruded tablets containing CPM [7], as well as solid solutions of chloramphenicol [22] and griseofulvin [23]. No additional peaks appeared in the MDSC thermograms for formulations B, C, E and F, or in the HPLC chromatograms of the tablet extrudates to indicate that complexation had occurred between the drug and the other tablet ingredients.

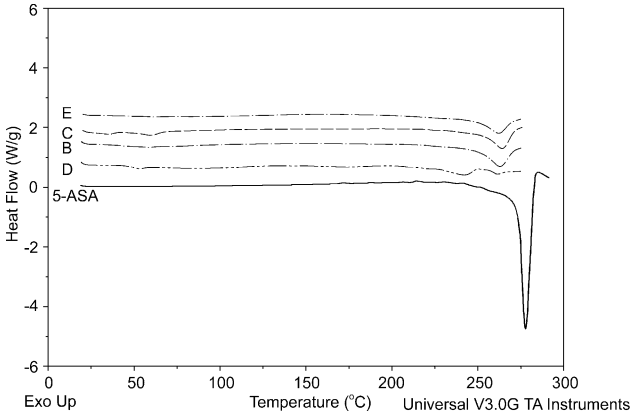

Fig. 7. MDSC thermograms of hot-melt tablet extrudates formulations B–E and 5-ASA.

A chemical interaction was observed between 5-ASA and citric acid present in extruded formulation D. The interaction was characterized by the formation of a new melting endotherm at 242 °C in the MDSC thermograms. An impurity peak was also observed in HPLC chromatograms having a retention time of 2.7 min. This interaction accounted for the lower 5-ASA recovery in tablets containing citric acid (formulation D) compared with other hot-melt extruded tablet formulations (Table 3).

A physical mixture of citric acid and 5-ASA at a 1:2.5 ratio was subjected to heat treatment to simulate the formulation and extrusion processing conditions and analyzed by HPLC. The impurity peak corresponding to a retention time of 2.7 min was not present in the physical mixture when maintained at ambient conditions, but the peak was observed in the heat-treated sample, and the area of the peak increased as a function of heating time. HPLC chromatograms of the unheated and heat-treated physical mixtures are shown in Fig. 8. The impurity peak was not observed in heat-treated samples containing only 5-ASA. It was postulated that the observed peak was due to chemical bonding between the ammonium group of the 5-ASA compound and the carboxylate groups of the citric acid. This theory was further investigated by analyzing the heat-treated and unheated physical mixtures using solids probe

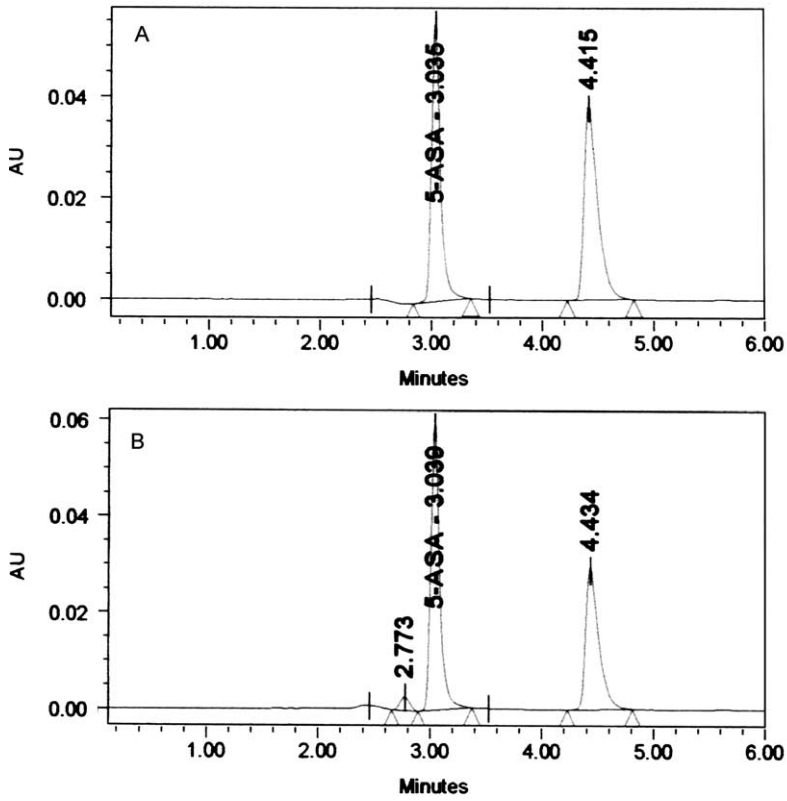

Fig. 8. HPLC chromatograms demonstrating the heat induced interaction phenomenon between citric acid and 5-ASA. (A) Citric acid and 5-ASA 1:2.5 w/w ratio physical mixture with no heat treatment. (B) Citric acid and 5-ASA 1:2.5 w/w ratio physical mixture heat-treated at 110 °C for 20 min. The impurity is represented at 2.7 min. The peak at 4.4 min is acetone that was used in the sample preparation process.

mass spectrometry analysis. The 5-ASA alone was ionized during analysis and its presence is verified in both spectra of the heat-treated and non heat-treated physical blend as 154 *m/z*. In addition, an abundance of a compound having a mass to charge ratio of 310 was observed in the heated sample representing amide bond formation and the loss of two water molecules between citric acid and 5-ASA. The mass spectra of the unheated and heat-treated physical mixtures are shown in Fig. 9. Amide formation is a dehydration reaction due to the combination of carboxylic acid and amine functional groups. The heat during the extrusion process functions as the dehydration reagent. Small amounts (under 20% relative intensity) of the compound identified with 310 *m/z* was also found in the unheated sample. The compound was generated during the short duration of heat exposure in the chamber of the mass spectrometer during analysis. The compound identified having a mass to charge ratio 310 was not found in pure 5-ASA analyzed by mass spectrometry. This confirmed that the compound was formed during heating in the presence of citric acid, and the amount of the impurity increased with heat exposure. The same samples were also analyzed by FT-IR in order to identify molecular changes in heated and unheated mixtures of citric acid and 5-ASA. New peaks were observed in the heated physical mixture ranging from 1690 to 1640 cm^{-1}, and indicated the formation of an amide bond (Fig. 10). These results provide further support for the interpretation of the data obtained by mass spectrometry analysis.

3.9. Powder X-ray diffraction studies

The results of powder X-ray diffraction analysis performed on the tablet physical mixtures and extrudates were in good agreement with the MDSC data. X-ray diffraction results for formulation B are shown in Fig. 11 and are representative of results obtained for all formulations analyzed. Characteristic peaks (observed at 2θ angles equal to 8, 15, 17, 27 and 28°) were observed in both physical mixtures and hot-melt extrudates, demonstrating that the 5-ASA crystal structure remained unchanged. Drug crystallinity was shown to be less intensive after hot-melt extrusion as a result of the partial solubilization of 5-ASA in the amorphous polymer. The X-ray data supported the conclusion that 5-ASA did not form a solid solution but was dispersed in the Eudragit® S 100.

3.10. SEM morphology of hot-melt extrudates

The crystalline nature of 5-ASA was clearly present in the morphology of all tablet extrudates when examined by SEM. The 5-ASA appeared as long needle or rod-like structures dispersed throughout the matrix material.

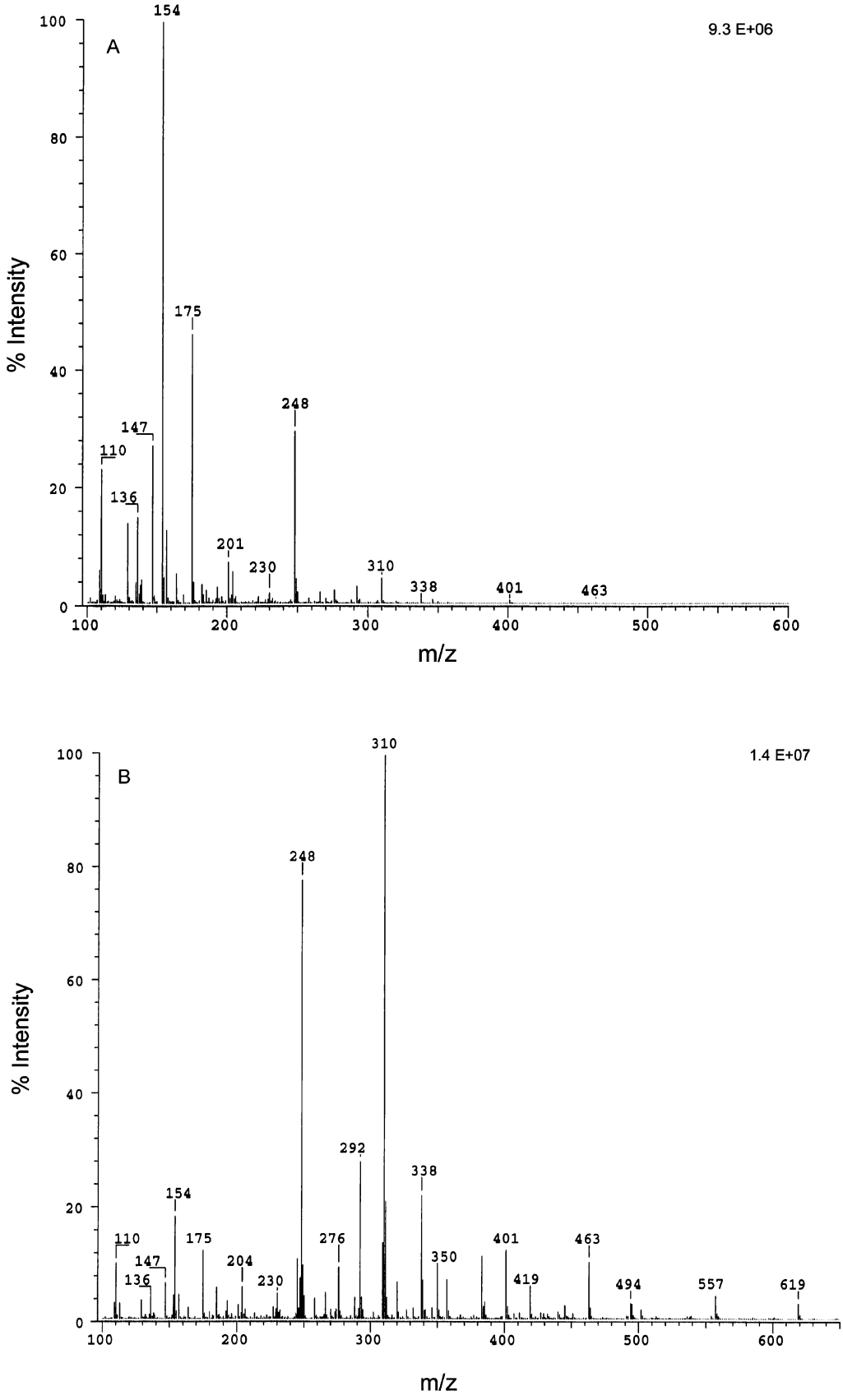

Fig. 9. Mass spectra of heated and unheated physical mixtures of citric acid and 5-ASA. (A) Citric acid and 5-ASA 1:2.5 w/w ratio physical mixture, no heat treatment. (B) Citric acid and 5-ASA 1:2.5 w/w ratio physical mixture heat-treated at 110 °C for 20 min.

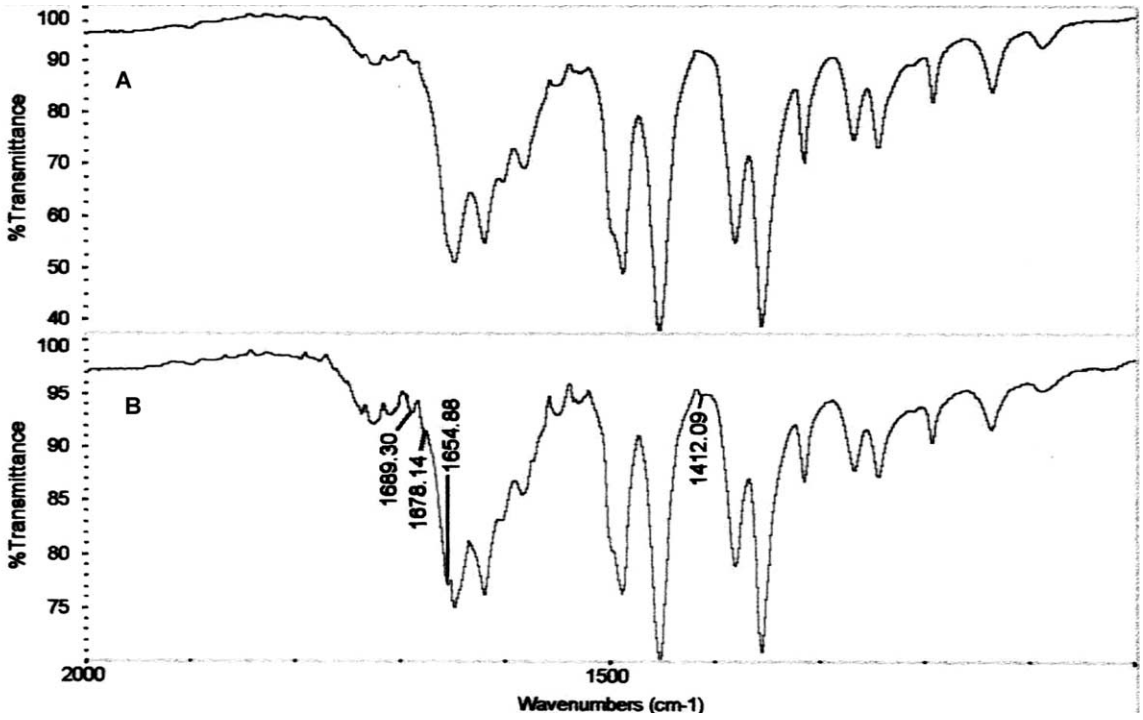

Fig. 10. FT-IR analysis of physical mixtures of citric acid and 5-ASA. (A) Citric acid and 5-ASA 1:2.5 w/w ratio physical mixture, no heat treatment. (B) Citric acid and 5-ASA 1:2.5 w/w ratio physical mixture heat-treated at 110 °C for 20 min.

The crystalline properties of 5-ASA in the hot-melt extrudate Formulation B are shown in Fig. 12. The morphology of formulation B is representative of all the extruded 5-ASA containing formulations. No pores were observed in the extrudates prior to dissolution and examination of the tablet morphology suggested that 5-ASA was homogeneously distributed throughout the polymeric carrier in the tablet matrix.

3.11. Drug release mechanism

Polymer erosion may occur by either surface or bulk erosion mechanisms. For surface eroding polymer matrices, the composite will get smaller while retaining its original geometric shape [24–26]. For bulk eroding polymers, the size of the device will remain constant during the dissolution process. The hot-melt extruded tablets containing 5-ASA were observed to shrink in size while retaining their original shape during dissolution testing indicating polymer surface erosion. The erosion process was due to the ionization and dissolution of the polymer in pH 7.4 phosphate buffered media. The drug release rate of 250 mg sized hot-melt extruded tablets containing 25% w/w 5-ASA was measured in pH 7.4 phosphate buffer media, and the data fit the Higuchi model for drug release from an insoluble matrix [27]. A plot of the percent drug release vs the square root of time is shown in Fig. 13. The r^2 value for the plot was 0.99, indicating the drug release followed Fickian diffusion. A value of 0.98 was obtained for r^2 when drug release was plotted vs time indicating pseudo-steady state drug release behavior. Multiple mechanisms, therefore, govern the rate of drug release from the hot-melt extruded matrix. Drug release systems governed by multiple mechanisms such as diffusion and erosion can exhibit pseudo-steady

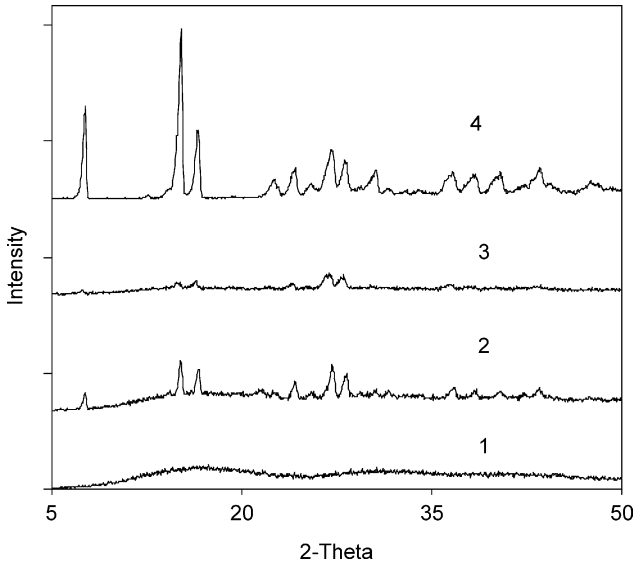

Fig. 11. Influence of the hot-melt extrusion process on the crystalline properties of 5-ASA in tablet formulations containing Eudragit® S 100. (1) Eudragit® S 100; (2) formulation B, physical mixture; (3) formulation B, hot-melt extrudate; (4) 5-ASA.

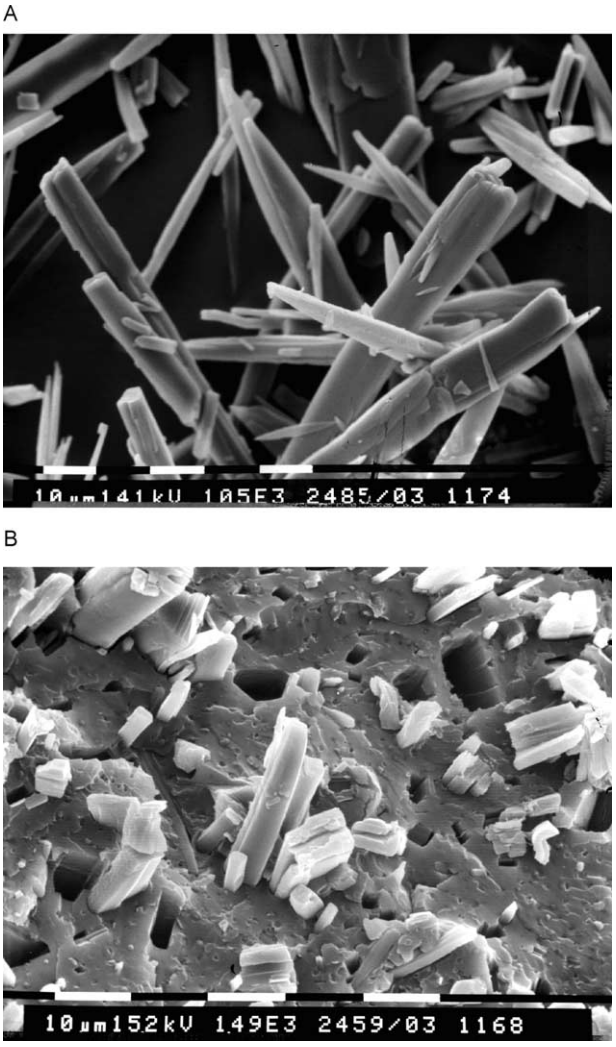

Fig. 12. SEM photomicrographs of 5-ASA and hot-melt extrudate formulation B. (A) 5-aminosalicylic acid; (B) extrudate, Formulation B.

state approaching zero-order release rates [10,25,26]. A zero-order release is observed when the diffusion rate of the dissolution media into the matrix and the polymer dissolution rate are equal, resulting in a synchronized or constant drug-depleted layer [10,28].

4. Conclusions

Hot-melt extruded tablets containing 25% w/w 5-ASA and Eudragit® S 100 released less than 10% after 2 h in acid, with controlled release of 5-ASA demonstrated in pH 7.4 phosphate buffered media. Excipients including lubricants and plasticizers influenced the drug release properties of the tablets. The Eudragit® S 100 and TEC were mixed together separately in a pre-plasticization step prior to the incorporation of the remaining dry ingredients into the blend. This was necessary to ensure adequate polymer plasticization in order to reduce processing temperatures and decrease the variability in tablet-to-tablet drug release rates. Temperatures required to process powder blends by hot-melt extrusion were determined by measuring the T_g of the polymer/plasticizer physical blends. The process temperatures for the 5-ASA powder blends were 40–60 °C above the T_g of the plasticized polymer. Increasing the TEC content of the tablets resulted in an increase in drug release rates due to leaching of the plasticizer from the tablet matrix. Citric acid functioned as a solid-state plasticizer and was included in formulations at 10% w/w along with 20% w/w TEC. Citric acid delayed the release of 5-ASA in phosphate buffer solution due to a lowering of the micro-environmental pH of the tablet matrix which suppressed ionization of the Eudragit® S 100. A heat induced interaction between citric

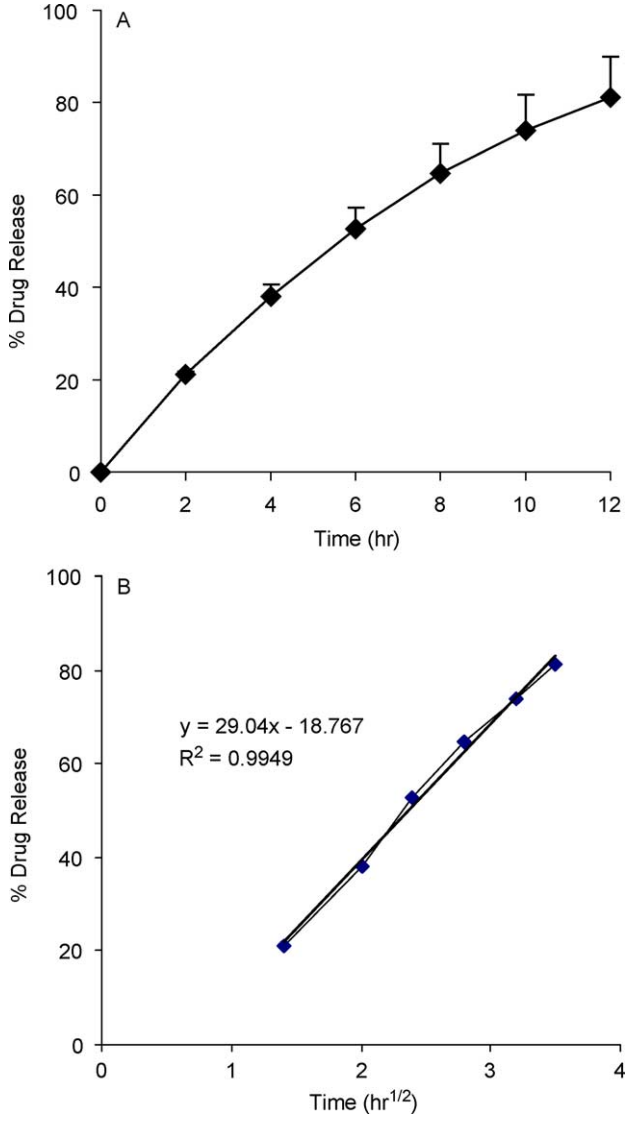

Fig. 13. Plot of 5-ASA percent release vs time from hot-melt extruded tablets using Eudragit® S 100 as the polymeric carrier, compared to percent drug release plotted against square root of time (Higuchi kinetics model). (A) Drug release profile for 250 mg hot-melt extruded tablets, Formulation B; (B) square root of time fit for the drug release profile for 250 mg hot-melt extruded tablets, Formulation B. Dissolution media consisting of 1000 ml 50 mM phosphate buffer pH 7.4, 37 °C, 100 rpm, apparatus 2 ($n=3$).

acid and 5-ASA was observed and attributed to an amide bond formation between 5-ASA and citric acid during hot-melt processing.

Increasing the concentration of 5-ASA in the tablets from 25 to 50% w/w resulted in a delay in tablet drug release rate due to lowering of micro-environmental pH by the increased amount of the acidic compound in the tablets. There was no evidence of a binding interaction between 5-ASA and the polymeric carrier. Release of 5-ASA from the matrix tablets was governed by multiple mechanisms and was shown to fit diffusion and surface erosion models in pH 7.4 phosphate buffered dissolution media.

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