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Research paper

The manufacture and characterisation of hot-melt extruded enteric tablets

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Abstract

The aim of this highly novel study was to use hot-melt extrusion technology as an alternative process to enteric coating. In so doing, oral dosage forms displaying enteric properties may be produced in a continuous, rapid process, providing significant advantages over traditional pharmaceutical coating technology. Eudragit® L100-55, an enteric polymer, was pre-plasticized with triethyl citrate (TEC) and citric acid and subsequently dry-mixed with 5-aminosalicylic acid, a model active pharmaceutical ingredient (API), and an optional gelling agent (PVP® K30 or Carbopol® 971P). Powder blends were hot-melt extruded as cylinders, cut into tablets and characterised using powder X-ray diffraction (PXRD), differential scanning calorimetry (DSC) and dissolution testing conducted in both pH 1.2 and pH 6.8 buffers. Increasing the concentration of TEC significantly lowered the glass transition temperature (T_g) of Eudragit® L100-55 and reduced temperatures necessary for extrusion as well as the die pressure. Moreover, citric acid (17% w/w) was shown to act as a solid-state plasticizer. HME tablets showed excellent gastro-resistance, whereas milled extrudates compressed into tablets released more than 10% w/w of the API in acidic media. Drug release from HME tablets was dependent upon the concentration of TEC, the presence of citric acid, PVP K30, and Carbopol® 971P in the matrix, and pH of the dissolution media. The inclusion of an optional gelling agent significantly reduced the erosion of the matrix and drug release rate at pH 6.8; however, the enteric properties of the matrix were lost due to the formation of channels within the tablet. Consequently this work is both timely and highly innovative and identifies for the first time a method of producing an enteric matrix tablet using a continuous hot-melt extrusion process.

Keywords: Enteric coating; Eudragit®; Hot-melt extrusion; Polymer processing

1. Introduction

Following administration, oral dosage forms are exposed to a broad range of physiological conditions in the gastrointestinal tract (GIT), making it extremely important to understand GIT transit and the effect this may have on the active pharmaceutical ingredient (API) within a formulated medicine [1]. One of the first environments encountered by orally administered APIs is the harsh acidic and enzymatic conditions of the stomach prior to reaching the small intestine, the major site of drug absorption. Low pH or the presence of particular enzymes may be sufficient to hydrolyze or degrade the API in the stomach [2]. Furthermore, consideration must be given to the potentially irritating effects of the API on the gastric mucosa. Consequently, there have been numerous studies conducted that have investigated the use of polymeric coatings to modify or control the release of an API within the GIT. Enteric coatings using cellulosic polymers and methacrylic acid co-polymers have been extensively studied [3]. In applying such film coats to solid oral dosage forms,

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the API may be delivered to the site of absorption/action without significant degradation and/or irritation to susceptible mucosa.

The manufacturing processes typically used for the production of conventional dosage forms (tablets, granules, pellets) include wet granulation, dry granulation, direct compression and wet mass extrusion. Although such processes have been successfully used for many years there is an increasing interest in novel techniques such as injection moulding, hot-melt extrusion (HME) and fluidized hot-melt granulation [4,5]. These pioneering processes can be used to manufacture a wide range of dosage forms to produce more stable drug products, wherein the API may be dispersed and/or solubilized within a polymeric carrier whilst also improving process efficiency by avoiding the need for solvents, lowering the number of processing steps required and eliminating the need for good compression properties. In addition, such technologies may improve drug/polymer mixing, drug distribution, product homogeneity and clinical efficacy [6].

HME is a non-ambient drug delivery technology that is receiving increasing attention within the pharmaceutical industry [7]. During this process pharmaceutically approved thermoplastic carrier systems are mixed, heated and sheared inside a closed extruder barrel [8]. After a short period inside the extruder barrel, a molten polymeric mass is forced under high pressure through a die to produce a product of high density and uniformity. Initial studies in this field have focused primarily on understanding the fundamental aspects of the process and the factors that significantly influence the quality of the finished pharmaceutical product [9]. More recently however, there have been several papers describing the use of HME for both sustained release and drug targeting applications [10,11]. In this respect, HME has been shown to be useful for the production of enteric capsules, albeit in a non-continuous manner [12]. The objective of the present study was to investigate the suitability of HME as a continuous method for producing a drug polymer composition capable of minimizing drug release during transit through the acidic environment of the stomach and subsequently provide a sustained release of the API in phosphate buffered media at pH 6.8. Conventional solvent-based coating processes are tedious operations requiring multiple steps, long process times and solvent disposal/removal [13]. The possibility of solventless processing using HME negates such complexities and additionally provides a highly efficient continuous processing method. Although there has been significant interest in alternative coating methods such as dry powder coating [13] there are currently no reports describing the manufacture of enteric tablets using HME. Moreover, whilst Eudragit® polymers have been extensively examined as enteric film coats for tablets, their use in the formation of enteric tablets has not been described. In this respect Eudragit® L100-55 in particular may have considerable potential for the production of HME enteric tablets, as the T_g is relatively low (120 °C) making it processable under moderate thermal conditions. Furthermore, it is insoluble at pH values lower than 5.5. In this study, we address the feasibility of Eudragit® L100-55 HME matrix tablets as gastro-resistant enteric oral dosage forms and further examine the influence of hydrophilic polymers on the drug release performance of the acrylic matrices.

2. Materials and methods

2.1. Materials

Methacrylic acid/ethyl acrylate co-polymer (Eudragit® L100-55) was a gift from Degussa Corp., Piscataway, NJ. Triethyl citrate (TEC) was used in this study as a liquid-state plasticizer and was kindly donated by Morflex, Inc., Greensboro, NC. Polyacrylic acid (Carbopol 971P NF) and polyvinylpyrrolidone (PVP K30) were investigated as hydrophilic swellable polymers and were supplied as gifts from BF Goodrich, Cleveland, OH and BASF, Ludwigshafen, Germany, respectively. 5-Aminosalicylic acid (5-ASA) was used as a model API and was purchased from Acros Organics, NJ, USA. All other chemicals and reagents were purchased from Spectrum Chemicals, Gardena, CA.

2.2. Methods

2.2.1. Material preparation and mixing

Prior to extrusion, dry materials were mixed together in a Robot-Coupe® mixer, model RSI 3VG (Robot-Coupe® USA, Inc., Ridgeland, MS, USA). All formulations were pre-plasticized and blended in the Robot-Coupe® high shear mixer with the required amount of TEC for 1 min at 3000 rpm. After this initial pre-plasticization step, 5-ASA was added to the high shear mixer and formulations were mixed at 3000 rpm for a further 2 min. The composition of each formulation investigated is summarized in Table 1. Prior to extrusion all formulations were passed through a sieve with a 30-mesh screen.

2.2.2. Hot-melt extrusion

Dry powder blends were processed into hot-melt extrudates using a Randcastle Microtruder extruder (model RCP-0750 Cedar Grove, NJ, USA) fitted with an 8 mm die. The temperatures of the four heating zones of the extruder were maintained at 95, 105, 110 and 115 °C. The die pressure and drive amps for each formulation extruded at these temperatures were recorded and are summarized in Table 1. These values were recorded to assess the ease of extrusion of a particular formulation. The cylindrical extrudates that were produced using HME were subsequently air cooled, cut into small tablets and characterised.

2.2.3. Preparation of compressed tablets

A small sample of the melt-extrudate of formulation C was milled at 20 Hz for a period of 2 min using a Retsch mixer mill MM200 (Copley Scientific Limited, Nottingham, UK). The milled sample was sized by passing the

Table 1
Hot-melt extrusion tablet formulations manufactured using HME

Components (% w/w)	A	B	C	C[1]	C[2]	D	E
5-ASA	15	15	15	15	15	15	15
Eudragit L100-55	76.5	68	51	51	51	34	34
TEC	8.5	17	17	17	17	17	17
Citric acid			17	17	17	17	17
Kollidon 30						17	
Carbopol 971PNF							17
Drive amps	0.52 ± 0.03	0.34 ± 0.02	0.15 ± 0.00	0.15 ± 0.00	0.15 ± 0.00	0.18 ± 0.01	0.14 ± 0.01
Die pressure (bar)	124.0 ± 13.8	44.1 ± 3.2	16.6 ± 2.4	16.6 ± 2.4	16.6 ± 2.4	27.6 ± 0.0	13.8 ± 0.0
Tablet density (g/cm^3)	1.25 ± 0.01	1.21 ± 0.02	1.19 ± 0.01	0.87 ± 0.01	0.98 ± 0.01	1.23 ± 0.00	1.25 ± 0.00
Tablet friability	<1%	<1%	<1%	<1%	<1%	<1%	<1%
Tablet hardness (N)	[a]	[a]	[a]	62 ± 2	230 ± 12	[a]	[a]

[a] HME tablets did not fracture during hardness testing but deformed plastically.

obtained powder through a series of sieves ranging from 710 to 180 μm. The arithmetic mean diameter of the particles was calculated from the sum of the diameters of each of the weight fractions divided by the sum of the weight fractions:

$$(d_p)_{am} = \frac{w_1\overline{d_1} + w_2\overline{d_2} + \ldots}{w_1 + w_2 + \ldots} = \frac{\sum w\overline{d}}{\sum w} \quad (1)$$

The powder was then transferred to a Riva SA Minipress MII single punch tablet press (Copley Scientific). Tablets were pressed using a fill mass of approximately 700 mg to achieve tablets with hardness values of 62 ± 2 N and 230 ± 12 N, respectively.

2.2.4. Tablet density

The density (D) of all tablets was calculated from tablet height, diameter and mass measurements using the following equation [14]

$$D(\mathrm{g/cm^3}) = \frac{w}{(m/2)^2 \times \pi \times h} \quad (2)$$

where w is the mass of the tablet (g), m is the diameter of the tablet (cm) and h is the tablet thickness (cm). Reported values are the average ± SD of six replicates.

2.2.5. Thermal properties of physical mixtures of Eudragit® L100-55/TEC and citric acid

To examine the effect of TEC and citric acid as a liquid and solid-state plasticizer, respectively, physical mixtures of Eudragit® L100-55 and TEC or Eudragit® L100-55 and citric acid were prepared by mixing the required mass of components in a mortar and pestle for 5 min. TEC and citric acid were physically mixed with Eudragit® L100-55 at concentrations of 5, 10 and 20% w/w. The thermal properties of physical mixtures were investigated using a modulated differential scanning calorimeter (MDSC model 2920, TA Instruments, Newcastle, De, USA). Five to ten milligram samples were accurately measured and sealed in an aluminium pan and heated at a rate of 3 °C/min. The modulation of the instrument was set at 1 °C every 60 s and samples were scanned over a temperature range from 20 to 200 °C under a nitrogen atmosphere. The T_g was determined as the mid-point of the step transition.

2.2.6. Drug release studies

The drug release properties of hot-melt extrudates and compressed tablets were assessed under sink conditions using dissolution testing. All dissolution tests were conducted using USP 27 delayed release articles method A, with a VanKel 600 apparatus and a VanKel 8000 autosampler (Varian, Inc., Cary, NC, USA). The dissolution media were maintained at 37 °C using Apparatus II set at 100 rpm and consisted of either,

(a) 750 ml of 0.1 N HCl for the first 2 h of analysis followed by pH 6.8 PBS (addition of 250 ml of 0.3 M sodium triphosphate buffer).
(b) 750 ml of 0.1 N HCl.
(c) 900 ml of pH 6.8 PBS.

A 3 ml sample was withdrawn every 30 min for the initial 2 h of dissolution then at 3 h, 4 h and every 2 h thereafter for 12 h. Sampled 3 ml aliquots were passed through a 0.45 μm filter and the drug content within the samples was determined using UV-spectroscopy with reference to a linear calibration curve ($\lambda_{max(pH\ 1.2)} = 305$ nm, $\lambda_{max(pH\ 6.8)} = 330$ nm).

The mechanism of drug release from the tablets during dissolution testing in both pH 6.8 and 1.2 buffers was determined using the Korsmeyer–Peppas equation [15]

$$m_t/m_\infty = kt^n \quad (3)$$

where m_t corresponds to the mass of drug released at time t, m_∞ is the total mass of drug released at infinite time, k is a constant incorporating structural and geometrical characteristics and n is the release exponent.

Dissolution profiles were compared using a similarity factor (f_2) as described by Shah et al. [16]. In brief, similarity between two dissolution profiles is defined by an f_2 value in the range between 50 and 100. The f_2 value was calculated according to the following equation,

$$f_2 = 50 \times \log\left(\left[1 + \frac{1}{T}\sum_{i=1}^{T}(\bar{x}_{ti} - \bar{x}_{ri})^2\right]^{-0.5} \times 100\right) \quad (4)$$

where T is the number of time points tested, which should not include more than one measurement after 85% of drug released. x_{ti} and x_{ri} are the percentages of drug released from the test and reference matrix at a specific time point, i.

2.3. Mechanical strength of HME tablets (friability testing)

The mechanical strength of HME and compressed tablets was investigated using the European Pharmacopoeia test for tablet friability (Ph. Eur. method 2.9.7). This test is intended to determine, under defined conditions, the friability of uncoated tablets, the phenomenon whereby tablet surfaces are damaged and/or show evidence of lamination or breakage when subjected to mechanical shock or attrition. A maximum loss of 1% of the mass of the tablets tested is considered to be acceptable for most tablet products. The friability was expressed as the loss of mass in each case and it was calculated as a percentage of the initial mass.

2.4. Tablet hardness

Tablet hardness was assessed using a 5Y Hardness tester (Copley Scientific) consisting of two jaws facing each other, one that moves towards the other. The flat surfaces of the jaws which are perpendicular to the direction of movement are used to apply a force to the tablet until it fractures across the diameter. Reported tablet hardness values are the average (±SD) of five replicates.

2.4.1. Crystalline properties of hot-melt extrudates

Powder X-ray diffraction patterns of the hot-melt extruded tablets were obtained using a Philips vertical scanning diffractometer (type 42273, Philips Electronic Instrument, Mount Vernon, NY, USA). The samples were exposed to Cu-Kα radiation under 40 kV and 40 mA. Measurements were collected across a 2θ scanning range from 5 to 35 °C at a scanning rate of 1°/min. To ascertain the effect of hot-melt extrusion on the drug crystallinity, diffraction patterns were collected for physical mixtures of the formulation ingredients and of the extruded tablets.

2.4.2. Statistical analysis

The effect of plasticizer concentration and inclusion of an optional hydrophilic polymer (Carbopol® 971P, Kollidon® K30) on the processing parameters (drive amps and die pressure), tablet hardness and tablet density was statistically analyzed using a one-way analysis of variance (ANOVA, $n \geqslant 5$). The effect of buffer pH, tablet formulation (C, D or E) and manufacturing method on the mechanism of release (n) was studied using a one-way ANOVA. In all analyses, the means of individuals groups were compared using Tukey's post hoc test with $p < 0.05$ denoting significance.

3. Results and discussion

Given that HME is a non-ambient process, it is essential that the components of a melt extrudable formulation be thermally stable for the duration of the process. The thermal stability of all excipients used in this investigation and hence their suitability for use in melt extrusion has been reported elsewhere [17,7]. Eudragit® L100-55 is a co-polymer of methacrylic acid and ethyl acrylate with a T_g of approximately 120 °C. During melt extrusion, in order for the polymer to flow effectively from the extruder, temperatures above the T_g are required. The flow behaviour of polymeric materials above the T_g is governed by polymer molecular weight and molecular chain mobility. Given that polymer chain diffusion is largely dependent upon the frictional forces existing between polymer chains, a functional excipient that reduces these frictional forces (plasticizers) will ultimately aid extrusion and thus processing. In this investigation, TEC was chosen as a liquid-state plasticizer because it has been shown in previous studies to be extremely miscible with Eudragit® polymers and highly effective in reducing the T_g [18]. Plasticization of Eudragit® L100-55 was confirmed by investigating the effect of TEC on the T_g of physically mixed TEC/L100-55 blends. The T_g of Eudragit® L100-55 was observed at 120.16 ± 0.74 °C whereas all TEC/Eudragit® L100-55 physically mixed blends displayed a significantly lower T_g. For example, adding 10% w/w TEC to Eudragit® L100-55 significantly reduced the T_g by approximately 30 °C to 93.51 ± 1.25 °C. The plasticization effect of TEC on Eudragit® L100-55 observed for physically mixed blends was apparent during polymer processing as evidenced by decreased screw torque and die pressure values. The drive amp and die pressure values observed during melt processing were significantly reduced upon increasing the concentration of TEC from 8.5% w/w to 17% w/w (Table 1). These effects may be ascribed to a reduction in polymer–polymer inter-chain association. As expected, the incorporation of TEC significantly improved polymer mobility and aided polymer extrusion.

Although effective plasticization could be achieved using high concentrations of TEC, it has been previously reported that citric acid is an effective solid-state plasticizer for Eudragit® polymers when used in combination with TEC [17]. In this investigation, we examined the suitability of citric acid, as a solid-state plasticizer for Eudragit® L100-55. Formulation C containing citric acid exhibited improved flowability, reduced die pressure and screw torque values when melt extruded (Table 1). Whilst structurally related to citric acid, TEC is a liquid at ambient temperatures whereas citric acid is a solid. Although a high percentage of pharmaceutical plasticizers are liquids, solid-state plasticization has been previously reported [19]. At high temperatures, solid-state plasticization is thought to

occur through solubilization of the plasticizer in the polymer network, a process that is actively facilitated through secondary interactions. Given that TEC and citric acid possess functional groups capable of hydrogen bonding with Eudragit® L100-55, it is proposed that both these molecules function in a similar fashion by occupying 'active sites' along the polymer and thus prevent inter-chain association.

An optional gelling agent was included in the matrix tablets to assess the ability of such polymers to retard drug release by reduction of drug diffusion from the tablet core. PVP and Carbopol are amorphous polymers with relatively high glass transition temperatures that may therefore affect the thermal processability of the formulation. The incorporation of PVP K30 significantly increased the die pressure and drive amp values observed during extrusion, whereas the inclusion of 20% w/w Carbopol 971P had no effect upon processability. Carbopol 971P has a T_g at approximately 135 °C while PVP K30 exhibits a T_g at 175 °C [20,21]. Given that the glass transition temperatures of Carbopol 971P and Eudragit® L100-55 are similar, and that both possess functional groups capable of interacting with TEC and citric acid, the solubilization and interaction of both liquid and solid-state plasticizers may be equally likely. Consequently, the mobility of the polymer chains within the extruder does not change significantly upon the incorporation of Carbopol 971P. Whilst PVP K30 also possesses functional groups capable of interacting with both TEC and citric acid, the higher T_g of this polymer means that the frictional forces between the polymer chains are much higher. Consequently, when 20% w/w was blended with Eudragit® L100-55, the overall mobility within the bulk molten mass was greater than for formulations devoid of this polymer.

The PXRD patterns of 5-ASA, physical mixtures of selected formulations and extruded samples are shown in Fig. 1. 5-ASA displayed six distinctive peaks, indicative of a highly crystalline material (7.48°, 15.07°, 16.47°, 24.08°, 27.00°, and 28.12° 2θ). All extruded and physically mixed samples displayed peaks at 2θ values characteristic of crystalline 5-ASA. The intensity of the peaks observed for physically mixed samples was greater than in extruded samples. Drug solubilization within polymeric platforms has been reported by many authors and has been used as a technique to improve the solubility of poorly water-soluble compounds [22,23]. Drug crystallinity within the extruded formulations was shown to be less extensive, inferring partial drug solubilization within the polymeric tablet matrix. Interestingly, physically mixed formulations containing citric acid displayed additional peaks (19.33°, 25.08 and 33.60°, Fig. 1d) that were not evident in the corresponding extruded formulations. One of the principal reasons for the exclusion of these peaks in the extruded systems may be attributed to citric acid being solubilized in the extruded matrix, again providing further evidence for the solid-state plasticization which took place during processing.

Given that the aim of this investigation was to investigate the properties of a matrix tablet capable of providing gastro-resistance, the *in vitro* drug release characteristics of the extruded tablets were determined. Initially the drug release properties of five HME formulations (A–E) in pH 1.2 acidic media for 2 h followed by exposure to pH 6.8 phosphate buffer for 10 h were examined. The results obtained from drug dissolution studies on formulations A–C confirmed a biphasic, pH dependent release of 5-ASA that was significantly influenced by the percentage of plasticizer and the incorporation of citric acid (Fig. 2a). Formulations A, B and C (devoid of PVP K30 or Carbopol 971P) released less than 5% w/w of the total drug loading within the first 2 h of dissolution under acidic conditions. There was no significant difference in the release properties of formulations A and B during the first 2 h in acidic media; however the addition of 17% w/w citric acid (comparing formulation B to C) significantly increased the percentage of drug released in acid media (pH 1.2), although the dosage form retained high gastric resistance releasing less than 5% of total loading within this time period (Table 2). It is also worth noting that formulation C including citric acid contained a significantly lower amount of Eudragit® L100-55 within the tablet matrix, which may additionally increase tablet erosion in pH 1.2 media.

At pH 6.8, formulations A, B and C displayed a burst effect and, after 8 h at this elevated pH, all formulations had released more than 85% of the total drug loading. Increasing the concentration of TEC within the extruded matrix from 10 to 20% w/w significantly increased the percentage drug release ($f_2 = 43$ between formulations A and B). For example, at 4 h formulation A (10% w/w TEC) had released 30.22 ± 2.49 % of 5-ASA whereas formulation B (20% TEC) had released 43.33 ± 1.20%. The incorporation of an acidic solid-state plasticizer (citric acid) into the Eudragit® L100-55 matrix significantly reduced the percentage release of drug as expected (Fig. 2). In essence, the drug release properties exhibited by formulation C at pH 6.8 were characteristic of formulation A containing only 10% w/w TEC (similarity factor f_2 was = 61). This may be attributed to the delayed erosion and solubilization of the Eudragit® L100-55 matrix as a result of decreased microenvironment pH surrounding the matrix [24]. Increased plasticizer (TEC) concentration resulted in a decrease in the rigidity of network structure within the matrix and hence an increase in water ingression and drug diffusion/solubilization [25] Moreover, the inclusion of citric acid aided manufacture, increased the percentage of drug released at pH 1.2 (although not beyond 5%) and retarded drug release at pH 6.8.

Hydrophilic polymers have been used extensively to retard drug release from matrix systems through the formation of a gel layer at the tablet-dissolution fluid interface [26]. In this study we investigated the effect of two hydrophilic polymers on the drug release properties of HME tablets. The drug release profile obtained for HME tablets containing either 20% w/w Carbopol 971P or 20% w/w

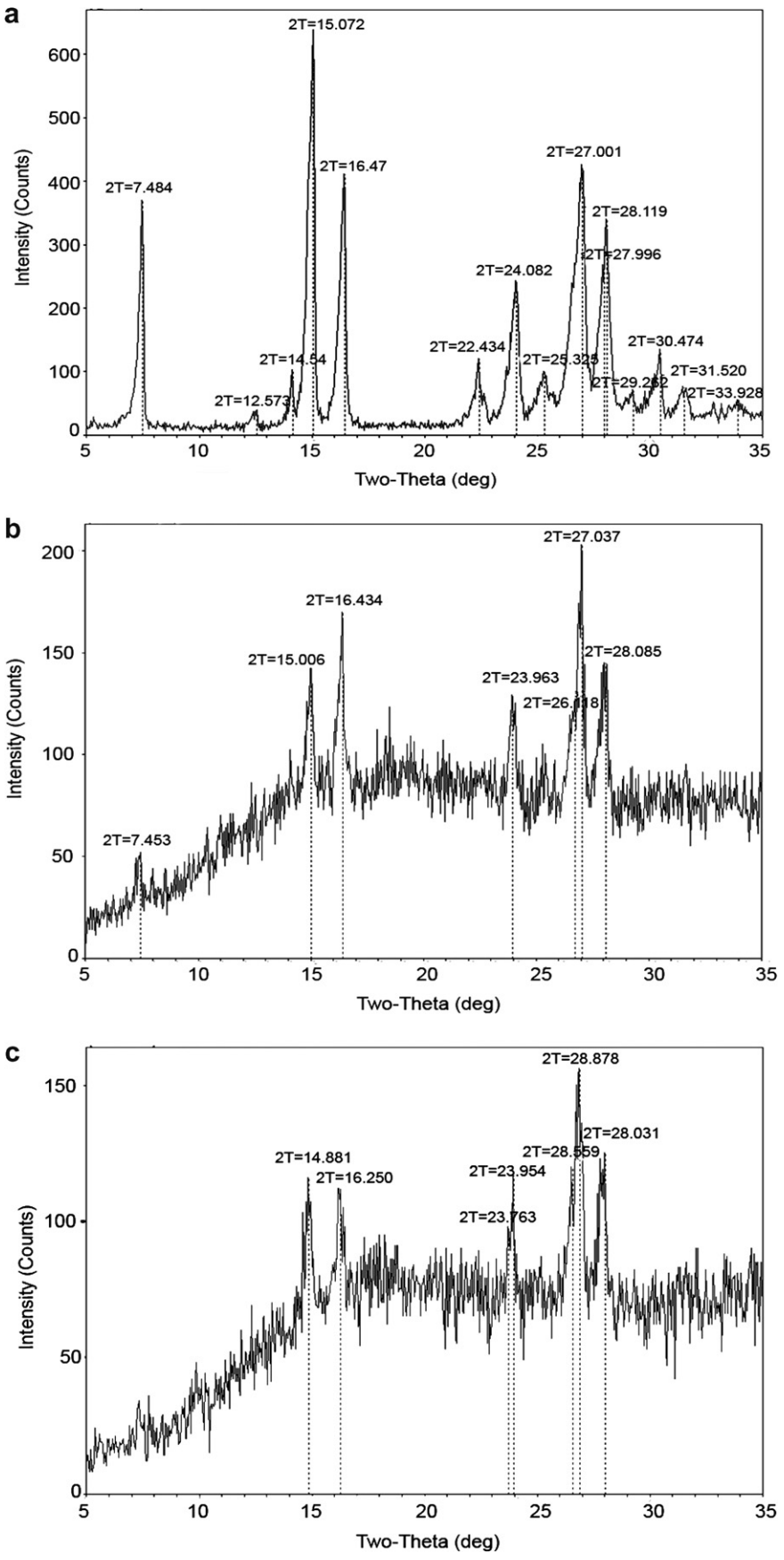

Fig. 1. X-ray powder diffractions of (a) 5-ASA; (b) formulation A (physical mix); (c) formulation A (extruded); (d) formulation C (physical mix); (e) formulation C (extruded).

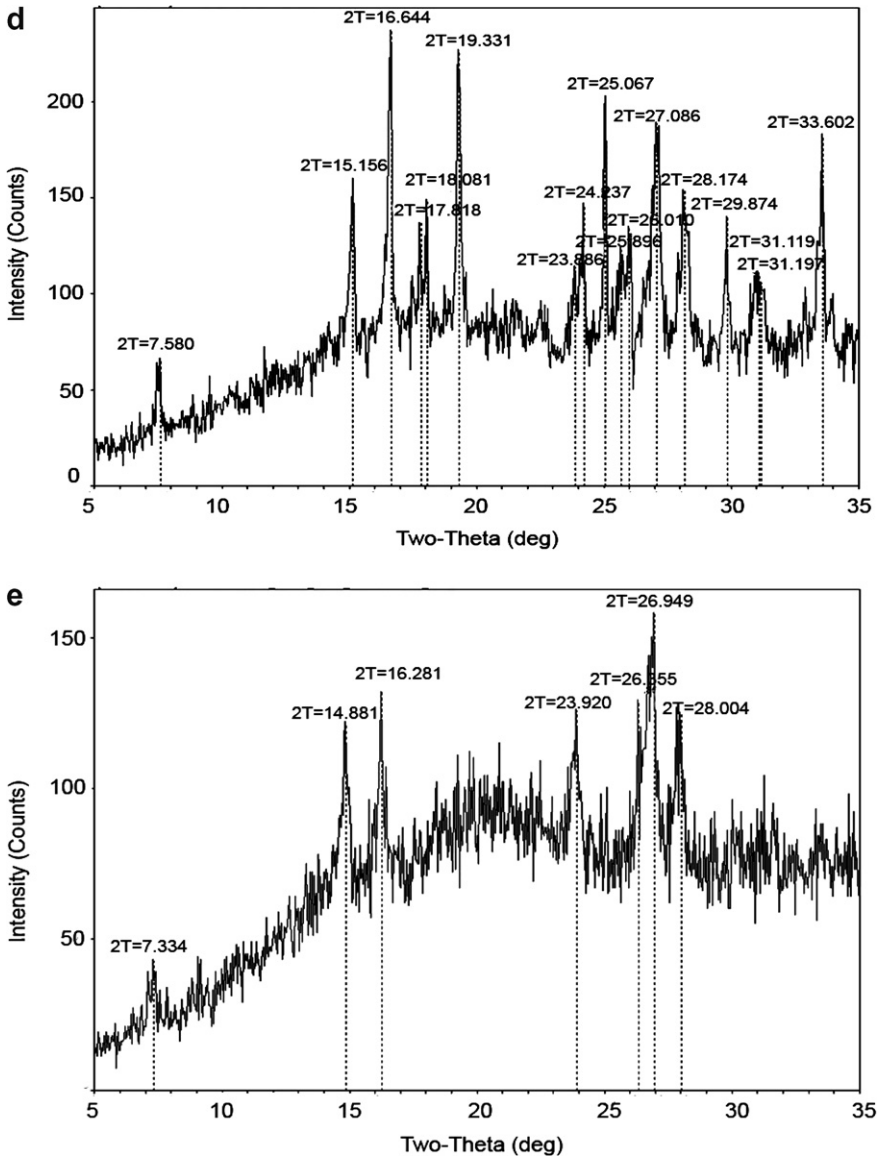

Fig. 1 (*continued*)

PVP K30 is illustrated in Fig. 2b. At pH 1.2 the incorporation of either hydrophilic polymer (PVP or Carbopol) significantly increased the release of 5-ASA with no significant difference in the release of 5-ASA from formulations containing these polymers. The similarity factor (f_2) values determined for formulations C and D or C and E were less than 50 ($f_2 = 19$ and 20, respectively), whereas the f_2 value calculated for formulation D and E was greater than 50 ($f_2 = 91$). Eudragit® L100-55 is insoluble in acidic conditions whereas both hydrophilic polymers will become dispersed/solubilized. The increase in the amount of 5-ASA released in acidic media may be attributed to an increase in diffusivity in the matrix due to the formation of a low viscosity viscoelastic fluid and subsequently channels/pores in the matrix through which the dissolution media could travel, aiding drug dissolution. At pH 6.8, the inclusion of hydrophilic polymers significantly retarded the release of 5-ASA. Furthermore, there was no significant difference between the release of 5-ASA between formulations D and E. During dissolution testing in pH 6.8 media, the tablets containing either 20% w/w Carbopol 971P or PVP K30 formed a visible gel layer on the exterior of the tablet. Matrix tablets containing hydrophilic polymers are well known to form highly viscous gel barriers that significantly retard drug release [27]. Consequently the formation of such a highly viscous gel layer on the surface of the HME tablets decreased drug diffusion and additionally retarded ingress of dissolution fluid into the core of the tablet [28].

Drug release data obtained for the HME tablets at pH 1.2 and 6.8 (Fig. 3) were fitted to a general Power law expression described by Korsmeyer et al. [15]. Using this relationship the release exponent, n, may be used to determine the mechanism of release from a dosage form, particularly when the mechanism of release is not well known or when a combination of release phenomena is involved [29].

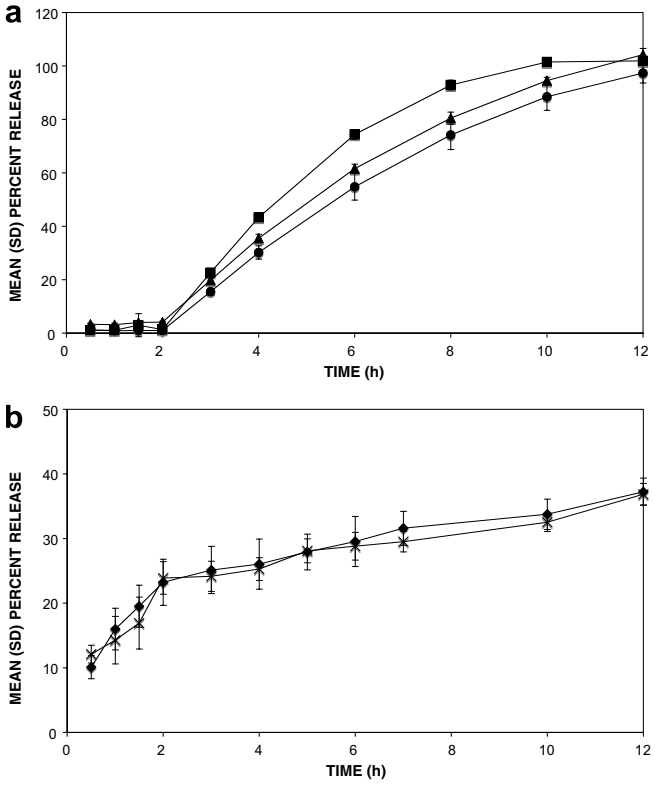

Fig. 2. 5-ASA release from hot-melt extruded tablets containing TEC and citric acid. (a) (●) Formulation A, 8.5% w/w TEC; (■) formulation B, 17% w/w TEC; (▲) formulation C, 17% w/w TEC/17% w/w citric acid. (b) (X) Formulation D, 17% w/w TEC/17% w/w citric acid/17% w/w PVP K30; (◆) formulation E, 17% w/w TEC/17% w/w citric acid/17% w/w Carbopol 971P. Dissolution experiments were conducted at 37 °C in 0.1 M HCl (pH 1.2) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 12 h. The values shown are the average ± standard deviation of six replicates.

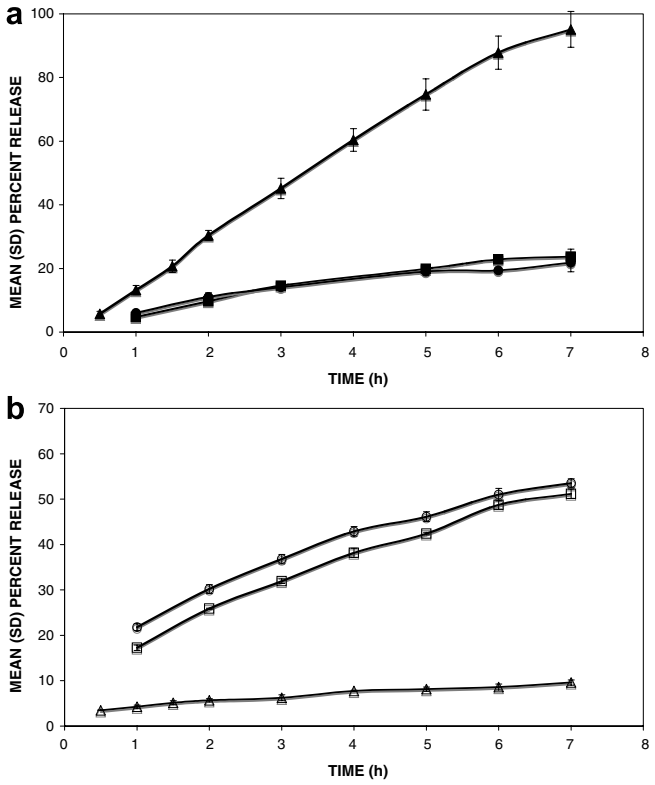

Fig. 3. 5-ASA release from hot-melt extruded tablets containing 17% w/w TEC and 17% w/w citric acid. (a) (▲) Formulation C, no optional hydrophilic polymer in phosphate buffer (pH 6.8); (●) formulation D, 17% w/w PVP in phosphate buffer (pH 6.8); (■) formulation E, 17% w/w Carbopol in phosphate buffer (pH 6.8). (b) (△) Formulation C, no optional hydrophilic polymer in 0.1 N HCl (pH 1.2); (○) formulation D, 17% w/w PVP in 0.1 N HCl (pH 1.2); (□) formulation E, 17% w/w Carbopol in 0.1 N HCl (pH 1.2). The values shown are the average ± standard deviation of six replicates.

A release exponent approximately equal to 0.5 indicates Fickian diffusion, $n \approx 1$ indicates zero-order release (case-II), whereas values in the range $0.5 < n < 1$ are indicative of anomalous non-Fickian release. As shown in Table 3, the HME tablets devoid of PVP or Carbopol (formulation C) approached a Fickian release mechanism in 0.1 N HCl (pH 1.2) whereas in phosphate buffer (pH 6.8) the release exponent was approximately zero-order (case-II). At low pH, Eudragit® L100-55 is insoluble and the release of 5-ASA was governed by diffusion whereas at higher pH the matrix becomes soluble and release of 5-ASA was governed by solubilization of the Eudragit® L100-55 polymer. The incorporation of a hydrophilic polymer (in this case PVP or Carbopol) significantly increased the release exponent value obtained from pH 1.2 dissolution data, however the values obtained from this model were indicative of diffusion controlled release. Interestingly, at pH 6.8 the inclusion of a hydrophilic polymer significantly retarded drug release and decreased the release exponent in comparison to formulation C, devoid of these hydrophilic polymers. Therefore, whilst formulation C had a release exponent close to unity, indicative of case-II transport, the calculated exponents for those formulations containing hydrophilic polymer were in the range 0.6–0.8, suggesting a combination of matrix erosion and diffusion.

Table 2
Percent release of 5-ASA from formulations A–C at defined time periods

Formulation	Time (min)					
	30	60	90	120	360	600
A	1.12 ± 0.32	0.89 ± 0.08	0.97 ± 0.07	1.02 ± 0.08	54.78 ± 4.99	88.45 ± 5.10
B	1.11 ± 0.07	1.07 ± 0.07	1.20 ± 0.15	1.29 ± 0.10	74.35 ± 1.77	101.46 ± 1.65
C	3.35 ± 0.42	3.19 ± 0.52	3.99 ± 0.36	4.15 ± 0.33	61.58 ± 1.66	94.49 ± 1.24

Dissolution experiments were conducted at 37 °C in 0.1 M HCl (pH 1.2) from 0 to 2 h and phosphate buffer (pH 6.8) from 2 to 12 h.
Each value is the average ± standard deviation of six replicates.

Table 3
Korsmeyer–Peppas model fitting of dissolution data from HME tablets

Formulation	Release exponent (n)	
	pH 1.2 (0.1 N HCl)	pH 6.8 (PBS)
C	0.39 ± 0.01	1.14 ± 0.07
C_1	0.71 ± 0.04	—
C_2	0.72 ± 0.06	—
D	0.47 ± 0.01	0.67 ± 0.05
E	0.57 ± 0.03	0.72 ± 0.06

The values presented are the average ± standard deviation of six replicates and the correlation coefficient (r^2) for the Korsmeyer–Peppas model was $\geqslant 0.98$.

The drug release properties of compressed tablets produced from milled extrudates were compared to those of HME extruded tablets to assess whether compressed tablets could produce a similar enteric effect. Given that formulation C was the most suitable candidate in respect to processing, milled powders representing this formulation were pressed into tablets and the drug release properties were examined at pH 1.2. Compressed tablets maintained the majority of their initial mass and possessed reasonably low friability values (<1%). In all cases, solid dosage forms prepared either by HME or compression had friability values within pharmaceutically acceptable levels. Tablets were compressed using different punch settings to achieve variable tablet hardness and density values to assess the effect on drug release properties. As illustrated in Fig. 4 compressed tablets released a significantly greater percentage of 5-ASA than the melt-extruded tablets at each time point during dissolution testing at pH 1.2. Interestingly, HME tablets released less than 10% of the API within 2 h and provided a suitable enteric effect whereas the tablets prepared by physical compression released more than 10% of total drug loading within 2 h. Compressed tablets manufactured from milled extrudate produced similar release profiles in pH 1.2 media irrespective of the tablet hardness or density. The difference observed between the compressed tablets manufactured from milled extrudate and those produced directly from the HME process may be attributed to destruction of a continuous, highly dense network. During milling, extreme forces are generated that fracture the melt extrudate, reducing the material to a fine powder ($(d_p)_{am} = 264$ μm). The compression of this powder into a tablet requires plastic deformation and cohesion between the particles. Inevitably compression of such particles will result in tablets with a significantly lower density (higher porosity) than produced by a HME process (Table 1), wherein the polymeric carrier is melted and compacted under extremely high pressure within the extruder barrel. Consequently ingress of the dissolution fluid into the compressed tablets may be more rapid, promoting drug dissolution and diffusion and in this case negating the desired enteric effect. This was further confirmed upon examination of the release mechanism calculated using the Korsmeyer–Peppas equation. Compressed tablets had a significantly higher release exponent (Table 3) than those that were hot-melt extruded ranging from 0.5 to 1.0, indicative of an anomalous transport mechanism.

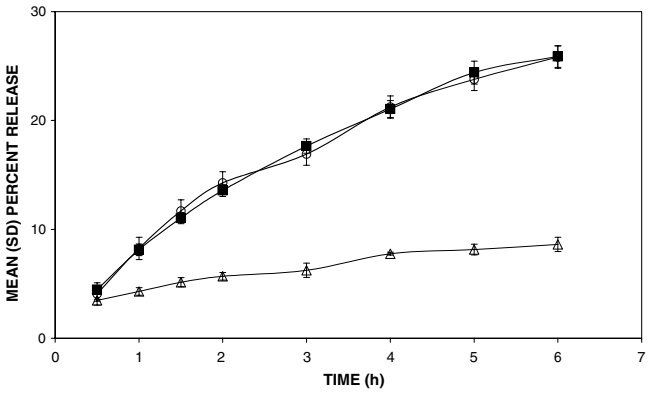

Fig. 4. Influence of method of manufacture on the release of 5-ASA from Eudragit L100-55 tablets in 0.1 N HCl dissolution media (pH 1.2). (△) HME tablet; (■) compressed tablet with hardness value of 62 ± 2 N; (○) compressed tablet with hardness value of 230 N ± 12 N. Each result shows means ± SD ($n = 6$).

4. Conclusion

In this study, HME was successfully used to manufacture gastro-resistant matrix tablets consisting of Eudragit® L100-55, demonstrating that HME techniques may be used as an alternative to conventional enteric film-coating processes. Extruded tablets provided a continuous matrix of low porosity resulting in a dosage form with effective enteric protection against acid media. The data illustrate that extruded Eudragit® L100-55 matrix tablets plasticized with TEC and citric acid provide pH dependent dissolution as expected due to the neutralization of the polymer matrix in neutral media. Interestingly, compressed tablets (from milled extrudates) released more than 10% w/w of API loading in acidic media whereas HME tablets showed excellent gastro-resistance. This is most likely due to poor plastic deformation of the extruded material during direct compression, leading to reduced tablet strength and faster disintegration times. Moreover, drug release from HME tablets during dissolution testing was dependent upon the concentration of TEC, the presence of citric acid, PVP® K30, and Carbopol® 971P, and the pH of the release media. Inclusion of an optional gelling agent was found to significantly reduce drug release at pH 6.8 by preventing drug diffusion from the tablet core. Future studies are necessary to further optimize HME formulations for gastro-resistant enteric tablets to improve processing parameters and controlled release rates.

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