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Properties of enteric coated sodium valproate pellets

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Abstract

The influence of subcoat application and micro-environmental pH on the dissolution properties of enteric coated sodium valproate pellets was investigated. The pellets were prepared by solution-layering or wet-mass extrusion-spheronization methods. In order to pass the USP enteric test, the solution-layered and wet-mass extruded pellets required 35 and 25% weight gain of Eudragit® L 30D-55, respectively. The application of a subcoat of either Methocel®-E5 (HPMC) or Opadry® AMB to the pellets resulted in a delay in sodium valproate release in 0.1N HCl. Further delay in drug release was observed when citric acid was present in a HPMC subcoat or when added to the core pellet formulation. The amount of drug released from coated pellets was a function of the level of citric acid in the pellet core or subcoat and subsequent micro-environmental pH of the pellets. Citric acid exerted a plasticizing effect on the enteric polymer film and improved film formation and polymer coalescence. When greater than 10% (w/w) citric acid was present in the pellets, a decrease in drug content was observed due to the conversion of sodium valproate to the volatile compound, valproic acid. Pellets containing less than 10% (w/w) citric acid maintained potency during processing.

Keywords: Eudragit® L 30D-55; Enteric polymer; Micro-environmental pH; Subcoat; Plasticizer; Organic acid

1. Introduction

Aqueous enteric polymeric dispersions are applied to solid oral dosage forms to facilitate targeted drug release to the upper GI tract as a result of the pH-dependent solubility of the polymeric acidic functional groups. Enteric polymeric coatings play an important role in protecting drugs that are susceptible to acidic or enzymatic degradation in the stomach. These coatings also function to protect the gastric mucosa from irritating compounds such as non-steroidal anti-inflammatory drugs (NSAIDS). The aqueous acrylic dispersion, Eudragit® L 30D-55, is an anionic copolymer based on methacrylic acid and ethyl acrylate, with free carboxyl groups in a ratio of 1:1 with the ester groups. The carboxylic groups begin to ionize in aqueous media at pH 5.5 and above, rendering the polymer resistant to acidic media but soluble in intestinal fluid. Aqueous enteric coatings consisting of methacrylic acid-based copolymers have been reported to be more gastric resistant than cellulose-based enteric polymers (Murthy et al., 1986; Garcia-Arieta et al., 1996). Gastric resistance varies from polymer to polymer, and applications of high polymer weight gains may be necessary to achieve resistance, even with acrylic-based systems (Murthy et al., 1986; Schmidt and Niemann, 1992; Garcia-Arieta et al., 1996; Thoma and Bechtold,

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1999). Factors such as processing conditions, additives in the film coating and substrate solubility have been reported to influence drug release from film coatings (Ghebre-Sellassie et al., 1987; Bianchini et al., 1991; Govender et al., 1995; Maul and Schmidt, 1995; Li et al., 1997).

The four mechanisms that control the rate of drug release of coated beads include the transport of drug through flaws or cracks in the matrix or uncoated system; transport of drug through media-filled pores in the coating; transport through a hydrated or swollen film; and transport of the drug through the nonporous coating due to permeability of the drug in the film (Zhang et al., 1991). Typically, highly water-soluble drugs will require a greater thickness of coating compared to water insoluble drugs, due in part to solubilization and partitioning of the drug in the aqueous polymer dispersion during film coating (Ghebre-Sellassie et al., 1987). The presence of drug in the coating can interfere with coalescence and film formation and result in a porous film structure during dissolution.

The application of polymeric subcoats to a solid dosage form prior to the application of an enteric film coating has been reported in the literature (Bianchini et al., 1991; Felton et al., 1995; Dangel et al., 2000c; Crotts et al., 2001). The subcoat can seal a water-soluble substrate to prevent migration of the active into the enteric polymer film and prevent degradation of acid labile compounds such as omeprazole (Lovgren et al., 1988). Subcoating, however, may not always be effective in improving gastric resistance, making it necessary to apply high weight gains of enteric coating. Subcoating also adds an additional step to dosage form manufacturing, increasing the cost and complexity of production.

In addition to subcoating, the composition of pellet and tablet formulations has been reported to influence the drug release properties of the film coated dosage form. Organic acids have been added to tablets containing noscapine HCl in order to maintain the drug in the soluble state inside the coated dosage form during dissolution testing in media pH 6.4 or greater (Thoma and Zimmer, 1990). A similar technique was used to achieve pH-independent release of verapamil HCl from uncoated matrix tablets where organic acids were added to maintain low pH values within the tablets in order to increase drug solubility (Streubel et al., 2000). Other authors have used organic acids as a method to sustain drug release in buffered media for colonic specific drug delivery (Ishibashi et al., 1998; Nykänen et al., 1999; Krogars et al., 2000).

The objectives of the current study were to investigate the influence of polymeric subcoats and organic acids on the dissolution properties of enteric coated sodium valproate pellets. The pellets were produced by either solution-layering or wet-mass extrusion processing and coated with Eudragit® L 30D-55. Organic acids were incorporated into the pellet matrices or into a subcoat prior to coating with the enteric polymer.

2. Materials and methods

2.1. Materials

Sodium valproate (2-propyl pentanoic acid sodium salt) and valproic acid were purchased from Sigma Aldrich Chemical Co., St. Louis, MO. Eudragit® L 30D-55 poly(methacrylic acid, ethyl acrylate) was donated by Röhm America, LLC Piscataway, NJ; Opadry® AMB (polyvinyl alcohol) was donated by Colorcon, Westpoint, PA; Methocel®-E5 (hydroxypropyl methylcellulose, HPMC) was donated by Dow Corning, Midland, MI; Kollidon® 90 and (polyvinyl pyrrolidone) were donated by BASF Corporation, Mount Olive, NJ; Avicel® PH 101 (microcrystalline cellulose) was donated by FMC Corp., Newark, DE; citric acid monohydrate, tartaric and succinic acids, acetonitrile (HPLC grade), and sodium phosphate tribasic were purchased from Spectrum Chemical, Gardena, CA. Talc, Altalc (500), was donated by Luzenac America, Alpine, AL; triethyl citrate (TEC) was donated by Morflex Inc., Greensboro, NC.

2.2. Methods

2.2.1. Preparation of sodium valproate pellets using the layering technique

Non-pareils 800–1000 μm were layered with a 2% (w/w) solution of HPMC containing sodium valproate until 20% drug loading was achieved. The solution was applied to the non-pareils by a top spray technique in a fluidized bed coater (Glatt WSG-2, Germany) using an inlet temperature of 60 °C and an outlet temperature of 50 °C. The solution was sprayed at a rate of 1 g/min with a 1 mm size nozzle diameter at 2 bar atomization

pressure. Pellets were stored in a desiccator following preparation and content of active was assayed by high performance liquid chromatography (HPLC) prior to coating with Eudragit® L 30D-55 to ensure the pellets contained 20% drug loading.

2.2.2. Preparation of sodium valproate pellets by wet-mass extrusion

Sodium valproate and Avicel® PH 101 were mixed in a twin-shell blender for 15 min. The material was then transferred to a planetary mixer and a solution of Kollidon® K 90 (3%, w/w of total pellet formulation) was added to prepare a wet-mass. Citric acid 1, 5, 10, 15, and 20% (w/w) amounts were included in the pellet core to lower the micro-environmental pH. The citric acid amounts were blended with the sodium valproate and Avicel® PH 101 in a twin-shell V-blender, followed by the addition of the binder solution to the powder blend using a planetary mixer. The wet-mass was then extruded using a LCI Benchtop Granulator (LCI Corp., Charlotte, NC) with a 1.2 mm screen and the extrudates were spheronized for 4 min in a Caleva model 120 spheronizer (G. B. Caleva Ltd., Dorset, England). The beads were dried at 40 °C for up to 48 h and then sized, using 14–20 mesh screens and assayed by HPLC for drug content.

2.2.3. Preparation of film coatings

A 30% (w/w) dispersion of Eudragit® L 30D-55 was diluted to a final solids content of 15% (w/w) based on dry polymer weight. TEC, 15% (w/w) based on the dry polymer content, was added to the dispersion and equilibrated for at least 30 min with the Eudragit® L 30D-55 prior to coating. Talc, 50% (w/w) based on dry polymer weight was dispersed in water using a Polytron® mixer (Brinkmann Instruments, Westbury, NY) and combined with the Eudragit® L 30D-55.

2.2.4. Preparation of subcoats

Subcoating layers of hydrophilic polymers were applied to the sodium valproate pellets. The subcoat applied to the solution-layered pellets consisted of a 10% (w/w) solution of HPMC prepared by adding the polymer to water and dissolving 10% (w/w) citric acid in the solution after it was cooled to room temperature.

The wet-mass extruded pellets were subcoated with Opadry® AMB. The coating solution was prepared by adding the polymer to water (10%, w/w solids content) and agitating with a Lightnin™ variable speed mixer (Mixing Equipment Co., Rochester, NY) for 45 min prior to coating.

2.2.5. Film coating conditions

Eudragit® L 30D-55 was applied to a 300 g charge of wet-mass extruded pellets using a Strea 1 fluidized bed coater (Strea I, Niro Inc., Columbia, MD) with bottom spray and a Wurster column insert. The coating conditions consisted of an inlet temperature of 40 °C, an outlet temperature maintained between 32 and 34 °C, sprayed at a rate of 4 g/min using a 1 mm nozzle and 2 bar atomization pressure. Similar parameters were used to coat a 1000 g charge of the solution-layered pellets in a GPCG-1 (Glatt, Germany) with Eudragit® L 30D-55. A subcoat of HPMC was applied to the solution-layered pellets using the same parameters as outlined in Section 2.2.1. The Opadry® AMB subcoat was applied to the extruded pellets at an inlet temperature of 60 °C maintaining an outlet temperature of 50 °C, at a rate of 1 g/min with a 1 mm nozzle diameter and 2 bar atomization pressure.

2.2.6. Scanning electron microscopy studies

The surface morphology of the layered pellets was examined using a scanning electron microscope (SEM Joel model JSM-840A, Germany), while a Hitachi model S-4500 (Hitachi Instruments Inc., San Jose, CA) was used to examine the surface of the wet-mass extruded pellets. The pellets were sputter coated using either a Hammer or a Pelco Gold-Palladium coater (TED Pella Inc., Tustin, CA).

2.2.7. Drug release studies

The drug release properties of the enteric coated wet-mass extruded and solution-layered pellets were determined according to USP 24, delayed-release articles, method A, apparatus 2 at 100 rpm and 37 °C using either a model DT 80 (Erweka, Germany) or a Van Kel 600 (Van Kel, Cary, NC) dissolution apparatus. Samples were removed from the dissolution media at various intervals during the first 2 h in 750 ml of 0.1N HCl. After 2 h, the pH was increased to 6.8 with the addition of 250 ml of 0.20 M sodium phosphate triphosphate to dissolve the enteric coating. After 3 h, the pellets were homogenized using a Polytron® mixer and the final drug content of the

pellets was determined. The percent drug released during dissolution from the pellets was calculated from the actual drug content of each dosage form.

2.2.8. Sodium valproate analysis

The sodium valproate content of the solution-layered pellets was measured using a HPLC system (Thermo Separation Products, Germany) with an injection volume of 20 μl using a reversed-phase isocratic method with a flow rate of 2.0 ml/min. The mobile phase consisted of 63% (w/v) 25 mM sodium phosphate monobasic and 37% (w/v) acetonitrile. The pH of the mobile phase was adjusted to 2.3 using phosphoric acid. The ionized form of the drug was converted to the free acid at this pH during the HPLC analysis. The resultant valproic acid was separated using a stainless steel column (7 μm Machery-Nagel, C8) with dimensions of 125 mm × 4.6 mm. The ultra-violet absorbance detector was set at 210 nm. Reference standards were prepared in the mobile phase using the same bulk sodium valproate USP material used in the preparation of pellets.

The sodium valproate content of the dissolution samples of wet-mass extruded pellets was determined using a reversed-phase isocratic HPLC method on a Waters model 501 pump and a 996 PDA detector equipped with an Alltech 571 autosampler with a 50 μl loop. The mobile phase was the same as described in the previous paragraph. The ionized form of the drug was converted to the free acid during the HPLC analysis. The resultant valproic acid was separated using a Phenomenex Luna C18(2) column 150 mm × 4.6 mm, 3 μm, 1 ml/min and detected at 210 nm.

2.2.9. Measurement of pellet pH

The pH of the uncoated wet-mass extruded pellets was measured using a Corning® pH meter model 220. The pellets were ground into fine particles using a mortar and pestle and 2 g of the pulverized material was then added to 20 ml of de-ionized water. The slurry was mixed for 5 min prior to pH measurement.

2.2.10. Thermal analysis of polymeric films

The effect of citric acid on the thermal properties of Eudragit® L 30D-55 was determined by preparing films containing 0, 5, 10, 20, and 40% (w/w) citric acid, based on dry polymer weight. Two film sample sets were prepared for MDSC analysis containing the citric acid, with and without the incorporation of the 15% (w/w) (based on dry polymer weight) TEC that was included in the Eudragit® L 30D-55 coating dispersion used in preparing the pellets. The films were prepared by equilibrating the Eudragit® L 30D-55 polymeric dispersion for 2 h with the added ingredients by continual stirring, then cast in aluminum pans and placed in a 35 °C oven for 72 h. After drying, the films were stored in a desiccator at 0% RH for 72 h prior to analysis using modulated differential scanning calorimetry (MDSC model 2920, TA Instruments, Newcastle, DE). A 10–20 mg sample was sealed in an aluminum pan. The samples were heated at a rate of 5 °C/min with a modulation temperature amplitude of ±1 °C and a modulation period of 1 min (Coleman and Craig, 1996) ramping from −20 to 140 °C or −20 to 120 °C for samples containing TEC. Three measurements were performed on each film sample and the average of the glass transition temperature values was calculated and reported. The glass transition temperature was calculated as the midpoint of the step transition. The MDSC was calibrated by scanning an indium and a sapphire standard. Control samples consisting of Eudragit® L 30D-55 films containing no plasticizer were prepared in order to ensure that the selected parameters for MDSC analysis were adequate to determine accurately the glass transition temperature of the polymer. The glass transition temperature values measured were comparable to the reported values in the literature.

2.2.11. Thermogravimetric analysis of sodium valproate/valproic acid

A Thermogravimetric Analyzer (TGA) (Perkin-Elmer Corp., Shelton, CT) was used to evaluate the thermal stability of sodium valproate and valproic acid. A 2–5 mg sample was heated from 50 to 500 °C. The weight percent of sample remaining was plotted as a function of time. Additionally, a sample of valproic acid was held under isothermal conditions at 40 °C for 16 h and the weight percent of valproic acid was plotted as a function of time.

2.2.12. Stability of sodium valproate wet-mass extruded pellets

Sodium valproate 10% (w/w) drug-loaded wet-mass extruded pellets were prepared to contain 0, 5, 10, and 20% (w/w) citric acid. The moisture content of

the pellets was determined using a Karl Fischer titrator immediately after preparation and after storage in open containers for 24 and 48 h at 25 °C/60% RH, 40 °C/30% RH, and 60 °C/20% RH conditions. Three samples of pellets were dispersed into 1000 ml of de-ionized water to dissolve the sodium valproate. The mixtures were filtered using a 0.45 μm Gelman Acrodisc® syringe filter and analyzed by HPLC for sodium valproate content before and after storage. The moisture content of the pellets was included in the potency determination. The amount of drug in the pellets was plotted as a function of citric acid content for each temperature and storage time.

Sodium valproate 10% (w/w) wet-mass extruded pellets containing 5% (w/w) citric acid were prepared as previously described in Section 2.2.2 with the exception that the pellets were dried at 25 °C for 24 h. The pellets were enteric coated with 15% weight gain Eudragit® L 30D-55. The initial drug release properties of the pellets was determined before storing the pellets in sealed HDPE bottles for 4 months at 25 °C/60% RH and 40 °C/75% RH conditions. The drug content of the uncoated pellets was measured prior to coating as described in the preceding paragraph. The coated pellets were assayed by transferring a sample ($n = 3$) into a volumetric flask and diluting to 1000 ml with 0.05 M, pH 6.8 phosphate buffer solution in order to dissolve the enteric coating. The mixtures were filtered using a 0.45 μm Gelman Acrodisc® syringe filter and analyzed by HPLC. A Karl Fischer analyzer was used to determine the amount of moisture contained in the pellets after storage in order to calculate pellet drug content.

2.2.13. Mass spectrometry

Mass spectrometry (Finnigan TSQ 70, Thermoquest, San Jose, CA) consisting of direct chemical ionization (DCI) with methane gas as the ionizing agent and a solids probe, was used as a qualitative method to confirm the presence of valproic acid in wet-mass extruded pellets. The pellets contained 10% (w/w) sodium valproate and 0, 5, and 20% (w/w) citric acid. A single pellet was placed inside a glass capillary tube and inserted into the tip of the probe. Each pellet analyzed was approximately of the same size and fit snuggly inside the capillary tube. 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. The mass spectrometer chamber was maintained at a pressure of 3 Torr and a temperature of 150 °C. The intensity or abundance (%) of valproic acid was plotted versus temperature. Valproic acid was detected in the pellets and corresponded to 145 *m/z* (mass to charge ratio) in the mass spectrometer.

3. Results and discussion

3.1. Drug release properties of sodium valproate pellets

The amount of Eudragit® L 30D-55 coating applied to pellets prepared by both wet-mass extrusion and solution-layering methods influenced the sodium valproate release rate in acidic media, as demonstrated in Figs. 1 and 2, respectively. The wet-mass extruded pellets required a 25% weight gain of enteric polymer to pass the USP enteric test, whereas the solution-layered pellets required a 35% weight gain of Eudragit® L 30D-55. The higher levels of film coating required for

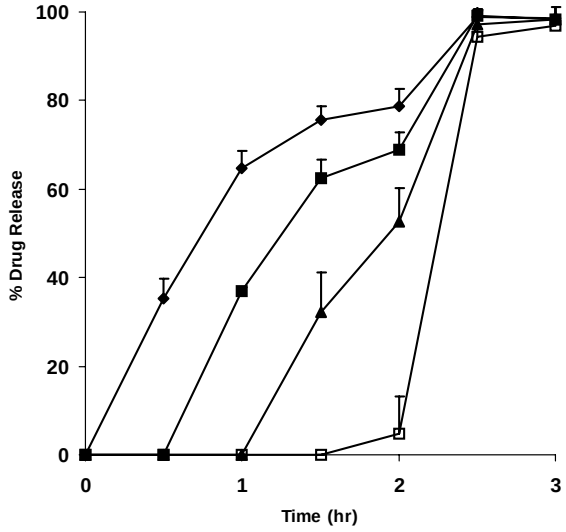

Fig. 1. Influence of Eudragit® L 30D-55 coating levels on the release of sodium valproate 10% (w/w) loaded pellets prepared by wet-mass extrusion. Media consisting of 0.1N HCl, pH 1.2 during first 2 h of dissolution and 0.05 M phosphate buffer, pH 6.8 from 2 to 3 h, 37 °C, 100 rpm ($n = 3$). (◆) 10% polymer weight gain, (■) 15% polymer weight gain, (▲) 20% polymer weight gain, (□) 25% polymer weight gain.

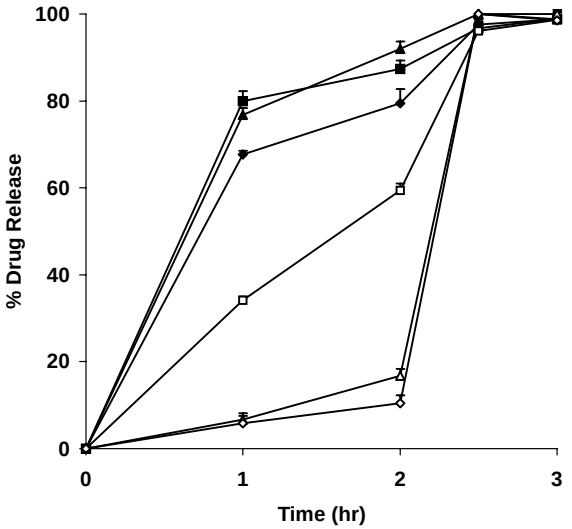

Fig. 2. Influence of Eudragit® L 30D-55 coating levels on the release of sodium valproate 20% (w/w) loaded pellets prepared by solution-layering. Media consisting of 0.1N HCl, pH 1.2 during first 2 h of dissolution and 0.05 M phosphate buffer, pH 6.8 from 2 to 3 h, 37 °C, 100 rpm ($n = 3$). (■) 10% polymer weight gain, (▲) 15% polymer weight gain, (◆) 20% polymer weight gain, (□) 25% polymer weight gain, (△) 30% polymer weight gain, (◇) 35% polymer weight gain.

the solution-layered pellets compared to the wet-mass extruded pellets to achieve gastric resistance was attributed to the higher drug loading, and to the higher concentration of the water-soluble drug on the surface of the solution-layered pellet in intimate contact with the enteric polymeric film. Enhanced surface contact between the drug and the polymer increases the possibility for drug migration into the film as well as the potential for drug–polymer interaction. Sodium valproate is a charged drug and flocculates the pseudolatex dispersion. A flocculation interaction during coating application could interfere with film formation and affect the drug release properties of the pellets (Bodmeier and Wong, 1996). After examining the coated surface of both pellet types using SEM, it was observed that as the amount of enteric polymer applied to the pellet surface was increased, the film appeared smoother. The roughness of the pellet surfaces at the lower coating levels suggested the water-soluble drug particles may have migrated into the film, or that a drug–polymer interaction occurred causing incomplete film formation at lower coating levels. Water-soluble compounds have been reported to migrate into film coatings during processing (Yang and Ghebre-Sellassie, 1990). Drug release rate is thereby increased due to pores and defects resulting from solubilization and leaching of soluble components in the film. Higher coating levels are then required to fill in the pores and defects to delay drug release (Zhang et al., 1991).

3.2. Influence of subcoating on pellet drug release properties

A subcoat was applied to both the solution-layered and wet-mass extruded pellets in order to act as a barrier between the water-soluble drug and the enteric film coating. The subcoat also increases the diffusional path length between the pellet core and the dissolution medium. Subcoating the solution-layered pellets with 3% weight gain of HPMC and the wet-mass extruded pellets with 3% Opadry® AMB delayed the release of sodium valproate in acidic media. The subcoated pellets, however, still failed the USP enteric test conditions resulting in the requirement for increased enteric polymer application. The drug release profiles of wet-mass extruded pellets subcoated with Opadry® AMB are shown in Fig. 3. The slight delay in drug release rates observed for the pellets suggests that the subcoat did act as a barrier to prevent contact between the soluble drug and the enteric polymer, but it was insufficient thickness to preclude premature drug release.

3.3. Influence of pellet core pH on pellet drug release properties

Both alkaline and acidic drug substances have been observed to influence the functionality of methacrylic acid copolymer film coatings (Dangel et al., 2000a,b). Dangel and co-workers found that film coated diclofenac sodium tablets (an alkaline drug) required a higher weight gain of polymer compared to tablets containing indomethacin (an acidic drug) to achieve gastric resistance. Sodium valproate, like diclofenac sodium, has alkaline properties and is very water-soluble. Studies were conducted with the sodium valproate enteric coated pellets to investigate the influence of micro-environmental pH on the drug release properties of pellets in 0.1N HCl. During dissolution testing, the enteric-coating was observed to swell,

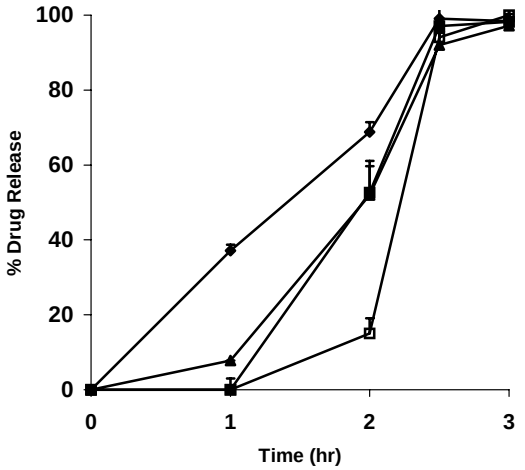

Fig. 3. Influence of Opadry® AMB subcoat on the release properties of 10% (w/w) sodium valproate wet-mass extruded pellets enteric coated with Eudragit® L 30D-55. Media consisting of 0.1N HCl, pH 1.2 during first 2 h of dissolution and 0.05 M phosphate buffer, pH 6.8 from 2 to 3 h, 37 °C, 100 rpm ($n = 3$). (◆) No subcoat and 15% weight gain enteric polymer, (▲) 3% Opadry® AMB subcoat and 15% weight gain enteric polymer, (■) no subcoat and 20% weight gain enteric polymer, (□) 3% Opadry® AMB subcoat and 20% weight gain enteric polymer.

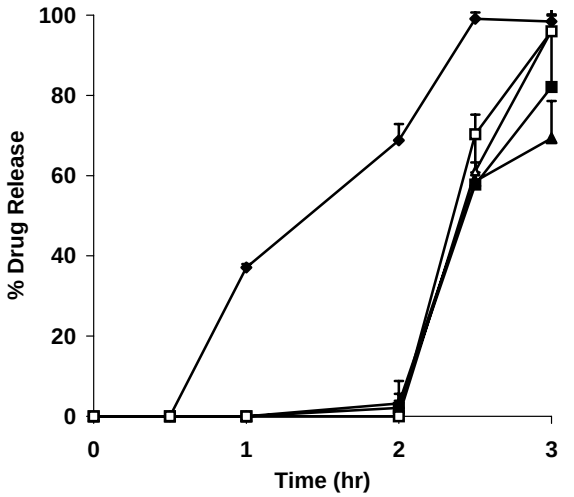

Fig. 4. Drug release properties of 10% (w/w) sodium valproate wet-mass extruded pellets containing 5, 10, 15, and 20% (w/w) citric acid and enteric coated with 15% weight gain of Eudragit® L 30D-55. Media consisting of 0.1N HCl, pH 1.2 during first 2 h of dissolution and 0.05 M phosphate buffer, pH 6.8 from 2 to 3 h, 37 °C, 100 rpm ($n = 3$). (◆) No citric acid, (□) 5% citric acid, (△) 10% citric acid, (■) 15% citric acid, (▲) 20% citric acid.

indicating permeation of dissolution medium into the film coating. Permeation of the dissolution medium into the pellet core would dissolve the sodium valproate, increasing the pellet core micro-environmental pH at the pellet core/film coating interface. A solution (10%, w/v) of sodium valproate has a slightly alkaline pH value of 7.4. When the pellet core micro-environmental pH exceeds pH 5.5, the enteric polymer will ionize and dissolve prematurely resulting in a more permeable membrane. To test this theory, the micro-environmental pH of the pellet was lowered by the addition of an organic acid to the HPMC subcoat and to the pellet core. Both pellet core pH and sodium valproate release were measured after including citric acid in the formulation.

For the solution-layered pellets containing 20% (w/w) sodium valproate, 10% (w/w) citric acid was included in the HPMC solution and the polymer subcoat was applied to yield a 3% weight gain. A 15% weight gain of Eudragit® L 30D-55 was applied to the pellets. The amount of sodium valproate released in 2 h from the solution-layered pellets was 92% (no subcoat), 71% (HPMC subcoat), and 40% (HPMC subcoat with citric acid). The subcoat containing citric acid was the most effective in delaying drug release. The acid acted as an acidic diffusion barrier surrounding the pellet retarding the ionization of the enteric polymer.

Addition of 5% (w/w) citric acid to the wet-mass extruded pellet core formulation followed by application of 15% weight gain of Eudragit® L 30D-55, dramatically decreased the amount of sodium valproate released in 0.1N HCl from 68% (without citric acid) to 0% (Fig. 4). The amount of enteric polymer required to pass the USP enteric test was shown to decrease as a function of the level of citric acid in the pellet cores. The pellets passed the USP test releasing only 5.3% sodium valproate with the application of a 10% weight gain of Eudragit® L 30D-55 when 10% (w/w) citric acid was added to the pellet formulation as demonstrated in Fig. 5. The uncoated pellet pH and the resultant micro-environmental pH of the pellet core also decreased as a result of the addition of citric acid. A correlation between uncoated pellet core pH and drug release is shown in Fig. 6. The soluble citric acid dissolves when dissolution medium penetrates into the pellet core, lowering the core micro-environmental

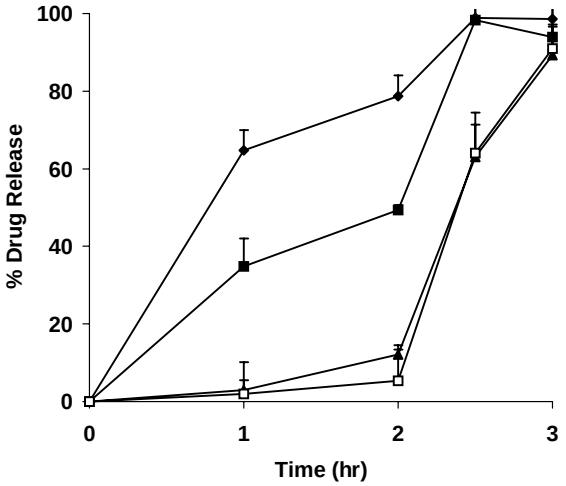

Fig. 5. Drug release properties of 10% (w/w) sodium valproate wet-mass extruded pellets containing 1, 5, and 10% (w/w) citric acid and enteric coated with 10% weight gain of Eudragit® L 30D-55. Media consisting of 0.1N HCl, pH 1.2 during first 2 h of dissolution and 0.05 M phosphate buffer, pH 6.8 from 2 to 3 h, 37 °C, 100 rpm ($n = 3$). (◆) No citric acid, (■) 1% citric acid, (▲) 5% citric acid, (□) 10% citric acid.

pH, suppressing the ionization of the enteric polymer, thus reducing membrane permeability. Further evidence of suppression of polymer ionization is demonstrated in Figs. 4 and 5 as a delay in the release of the sodium valproate after the dissolution medium pH is increased to 6.8. The citric acid also converts the sodium valproate to valproic acid. This compound contributes to lowering the pellet micro-environmental pH and pellet core solubility, subsequently retarding drug release. In addition, the uncharged valproic acid does not interact with the enteric polymer to cause flocculation, thus promoting better film formation. As a result, less enteric polymer is required for acid resistance.

3.4. Influence of acid solubility and pK_a on matrix pellet drug release properties

Additional organic acids including succinic and tartaric acid (10%, w/w) were incorporated in the core of wet-mass extruded pellets to further investigate the effect of acid solubility and pK_a on drug release properties of the coated pellets. The amount of drug released after 2 h in 0.1N HCl was compared after coating

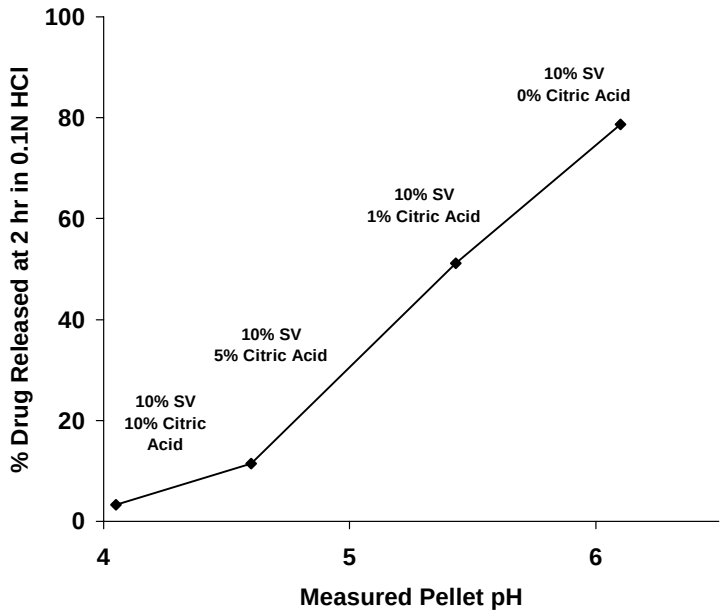

Fig. 6. Influence of citric acid content and pellet core pH on the release of 10% (w/w) sodium valproate (SV) wet-mass extruded pellets coated with a 10% weight gain of Eudragit® L 30D-55 after 2 h in 0.1N HCl, 37 °C, 100 rpm ($n = 3$).

Table 1
Physicochemical properties of organic acids used in pellet formulations

Organic acid (molecular weight, g/mol)	Solubility (g/ml)[a,b]	pK_a at 25 °C[a,b]
Citric acid monohydrate (210 g/mol)	0.592 g in 1 ml at 20 °C	pK_{a1} = 3.12 pK_{a2} = 4.76 pK_{a3} = 6.39
Tartaric acid (150 g/mol)	1 g in 0.75 ml at 20 °C	pK_{a1} = 2.93 pK_{a2} = 4.23
Succinic acid (118 g/mol)	1 g in 20 ml at 15 °C	pK_{a1} = 4.20 pK_{a2} = 5.63

[a] Merck Index (2001).
[b] Thoma and Zimmer (1990).

with a 10% weight gain of Eudragit® L 30D-55. The coated pellets containing tartaric and citric acid both passed the USP enteric test, releasing 3 and 5% drug after 2 h in 0.1N HCl, respectively, whereas 26% drug was released after 2 h from pellets containing succinic acid. The higher aqueous solubility and lower pK_a values of tartaric and citric acid (shown in Table 1) resulted in more rapid ionization and dissolution of the acids in the core to retard polymer ionization and reduce permeability within the 2-h period of dissolution testing.

3.5. Thermal analysis of polymeric films

Plasticizers are added to polymers to increase flexibility and distensibility by decreasing cohesive forces between the polymer chains, thereby increasing segmental mobility, as demonstrated by a reduction in the polymer glass transition temperature (T_g). This allows the polymer particles to soften and promotes polymer particle coalescence and film formation. A material can act as a plasticizer if the molecule is small enough and has structural and functional groups that are miscible with and capable of interacting with the polymer chains. Non-traditional compounds such as methylparaben and drugs such as ibuprofen and chlorpheniramine maleate have been cited in the literature as having a plasticizing effect on pharmaceutical polymers, resulting in a reduction in drug release from film coated dosage forms (Wu and McGinity, 1999). Citric acid is a small molecule similar in structure to triethyl citrate, allowing it to function as a plasticizing agent for the enteric film coating. Polymeric films of Eudragit® L 30D-55 were prepared containing citric acid both with and without TEC to quantify polymer plasticization by the organic acid. Citric acid was shown to plasticize the polymeric films (Table 2), reducing the polymer T_g by 26 °C when incorporated

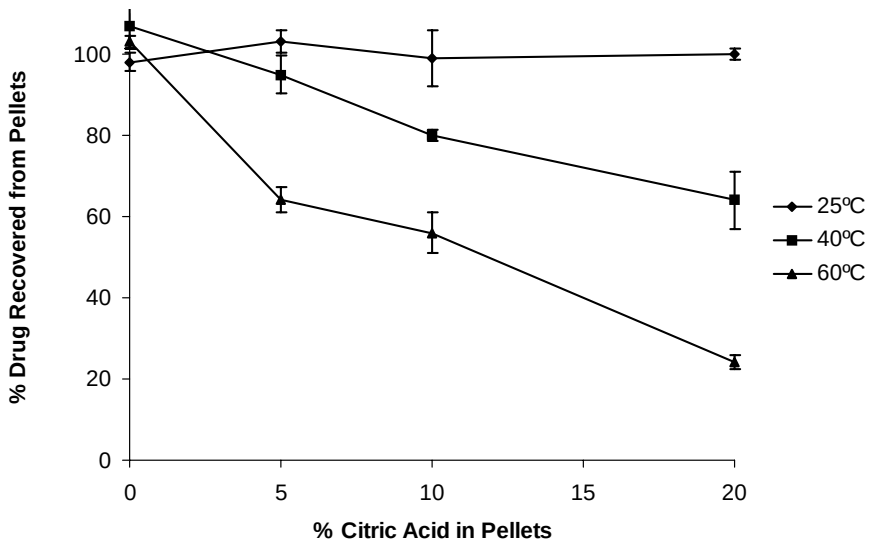

Fig. 7. Stability of 10% (w/w) sodium valproate wet-mass extruded pellets containing 5, 10, and 20% (w/w) citric acid after storage in open containers for 48 h at 25 °C/60% RH, 40 °C/30% RH, and 60 °C/20% RH temperature conditions ($n = 3$).

Table 2
Average glass transition temperature values of Eudragit® L 30D-55 cast films containing varying levels of citric acid ($n = 3$)

Citric acid (% based on dry polymer)	Film T_g (°C) without TEC	Film T_g (°C) with 15% TEC
0	110 ± 4.2	84 ± 1.0
5	112 ± 2.0	76 ± 2.2
10	84 ± 2.5	69 ± 1.8
20	88 ± 4.0	62 ± 2.8
40	80 ± 2.3	65 ± 1.3

at 10% (w/w), based on polymer dry weight. The T_g of films containing 10% (w/w) citric acid was further reduced an additional 15 °C when 15% (w/w) TEC, based on dry polymer weight, was incorporated. The plasticizing effect of citric acid on the enteric film coating helps to further explain the reduction in pellet drug release.

3.6. Sodium valproate/valproic acid thermal stability

Sodium valproate is reported to be a very stable compound in the presence of heat, light and strong aqueous alkali or acids (Florey, 1979). Although sodium valproate is stable, the potency of the coated pellets was found to decrease when the level of citric acid present in the pellet core was greater than 10% (w/w).

To understand the mechanism of pellet drug loss, the effects of processing and storage conditions on the potency of the wet-mass extruded pellets were

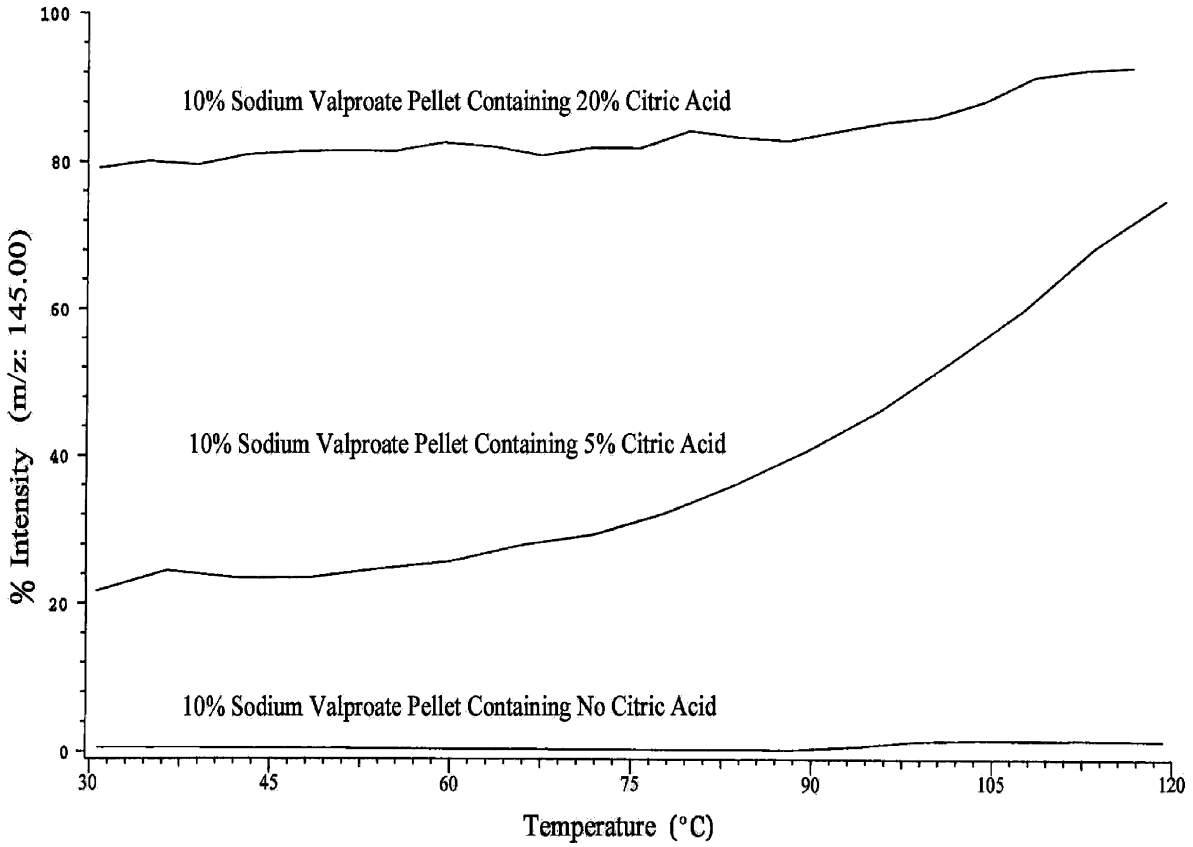

Fig. 8. Detection of valproic acid in 10% (w/w) sodium valproate wet-mass extruded pellets containing 0, 5, and 20% (w/w) citric acid using solids probe mass spectrometry with direct chemical ionization. The relative intensity/abundance of valproic acid detected increased as a function of citric acid content in the pellet and with exposure to increased temperature conditions.

investigated. Following preparation, pellets containing 5, 10, and 20% (w/w) citric acid were stored in open containers in ovens at 25 °C/60% RH, 40 °C/30% RH, and 60 °C/20% RH. The drug content of the pellets was determined immediately after preparation and after storage. The sodium valproate content decreased in pellets as a function of citric acid content and storage time as shown in Fig. 7; however, potency was maintained in all pellets stored at 25 °C/60% RH during the 48-h period of testing. The decrease in pellet potency is explained by the conversion of sodium valproate to the volatile compound valproic acid due to the presence of citric acid in the pellet core. Thermogravimetric analysis of pure valproic acid held isothermal at 40 °C for 16 h demonstrated a 30% loss in weight confirming pellet drug loss due to volatilization. Sodium valproate demonstrated no loss in weight at the same conditions.

3.7. Valproic acid identification

Mass spectrometry was used to identify and further confirm that converted valproic acid was released from the uncoated wet-mass extruded pellets during exposure to heat. Valproic acid has a molecular weight of 144 g/mol and after chemical ionization can be identified in the mass spectra as having a mass to charge (m/z) ratio of 145. The pellets analyzed contained 10% (w/w) sodium valproate, with citric acid contents of 0, 5, and 20% (w/w). The relative intensity or abundance (%) of valproic acid identified during the analysis of the pellets was plotted versus temperature as shown in Fig. 8. Minimal levels of valproic acid were detected in the pellet containing 10% (w/w) sodium valproate and 0% (w/w) citric acid. This analytical technique, although qualitative, clearly demonstrated that the sodium valproate was converted to valproic acid as a function of the amount of citric acid present in the pellet core. These results also demonstrated that the valproic acid volatilized from the pellet core upon exposure to increasing temperature conditions during the pellet drying process. The loss of pellet potency was prevented by maintaining a low level (5%, w/w) of citric acid in the pellet core, and by drying the pellets at 25 °C. The drug content of the 5% (w/w) citric acid containing pellets coated with 15% weight gain of Eudragit® L 30D-55 remained unchanged and passed the USP enteric test after 4 months storage at 25 °C/60% RH and 40 °C/75% RH in sealed HDPE containers.

4. Conclusions

Sodium valproate pellets prepared by either solution-layering or wet-mass extrusion required high weight gains of Eudragit® L 30D-55 in order for the pellets to pass the USP enteric test. A reduction in drug release from the coated pellets in acidic media was observed when citric acid was added to the subcoat polymer applied to solution-layered pellets or to the core of wet-mass extruded pellets. High polymer weight gains, however, were still required for pellets to pass the USP enteric test. The incorporation of citric acid in a subcoat of HPMC or into the core of matrix pellets reduced the release of sodium valproate in 0.1N HCl. Addition of 5% (w/w) amount of citric acid to wet-mass extruded pellet cores coated with a 15% weight gain of Eudragit® L 30D-55 decreased sodium valproate release in acid from 68 to 0% after 2 h. The reduction in drug release was shown to be a function of pellet pH due to the amount of citric acid added to the pellet cores. Tartaric and succinic acid were also included in the pellet core. Citric and tartaric acids (10%, w/w) were both effective in delaying drug release in acidic media with only 10% weight gain of Eudragit® L 30D-55 and this was attributed to acid pK_a and solubility. Citric acid was shown to delay drug release by lowering the pellet micro-environmental pH, preventing premature ionization of the enteric polymer. The citric acid also functioned to plasticize the Eudragit® L 30D-55 film coating. Plasticization increased the film elastic modulus, thus improving the gastric resistance of the coated pellets. Delay in drug release was also due to reduced pellet core solubility as a result of conversion of the sodium valproate to valproic acid. When lower levels of citric acid were present in the pellet core, less sodium valproate was converted to valproic acid, preventing drug loss due to valproic acid volatilization. The pellet drug content was maintained by limiting the amount of citric acid incorporated into the pellet and by reducing the pellet drying time and temperature. Sodium valproate pellets containing 5% (w/w) citric acid and enteric coated with 15% weight gain Eudragit® L 30D-55 passed the USP enteric test

after storage at 25 °C/60% RH and 40 °C/75% RH conditions for 4 months.

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