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Effect of Neutralization of Poly(Methacrylic Acid-co-ethyl Acrylate) on Drug Release From Enteric-coated Pellets Upon Accelerated Storage

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ABSTRACT The effect of neutralization of poly(methacrylic acid-co-ethyl acrylate) or poly(MA-EA) 1:1 (Eudragit® L 30 D-55) on drug release from enteric-coated pellets was studied upon accelerated storage. The dissolution rate of un-neutralized poly(MA-EA)-coated pellets decreased while the neutralized polymer-coated pellets maintained a constant drug release rate. Dynamic mechanical analysis showed that both un-neutralized and neutralized poly(MA-EA) films became rigid on aging. However, the un-neutralized films were affected more than those neutralized. Neutralization of poly(MA-EA) significantly changed the mechanical properties of coating films and improved the stability of poly(MA-EA) enteric-coated pellets upon accelerated storage at the studied conditions.

KEYWORDS Poly(methacrylic acid-co-ethyl acrylate), Eudragit® L 30 D-55, Neutralization, Enteric coating, Dissolution, Mechanical property, Stability

INTRODUCTION

Enteric coating of solid dosage forms has been widely employed to stabilize drugs susceptible to stomach acidic or enzymatic degradation, to prevent drug gastric mucosal irritation, as well as to target drug release in the lower gastrointestinal tract. Commonly used enteric-coating polymers, such as polymethacrylates (copolymer of methacrylic acid and methyl methacrylate or ethyl acrylate), cellulose derivatives (cellulose acetate phthalate, hydroxypropyl methylcellulose phthalate, hydroxypropyl methylcellulose acetate succinate), and vinyl derivatives (polyvinyl acetate phthalate), are primarily acidic in nature. These polymers are insoluble in gastric medium due to the un-ionized acidic functional groups, but become soluble in intestinal fluids by forming salts with alkalis or amines. Therefore, enteric polymers exhibit resistance to gastric fluids and maintain the integrity of coated solids in stomach. However, they do dissolve readily and release drugs in the mildly acidic to neutral pH environment of small intestine (Felton & McGinity, 2003; Chang et al., 2006).

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Partial neutralization of enteric polymers has been frequently used to minimize incompatibility between acid-labile drugs and acidic enteric polymers, to achieve aqueous-based enteric polymer coating solutions (Stafford, 1982; Chang, 1990) and sometimes to facilitate enteric polymer latex preparation, e.g., Eudragit® L 100-55 redispersion (Lehmann, 1989). However, limited work has been done on the effect of neutralization of enteric polymers on drug release (Béchard et al., 1995; Kim et al., 2003; Limmatvapirat et al., 2004), especially its effect on aging.

As one of the globally accepted gastroresistant-enterosoluble polymers, the anionic copolymer of methacrylic acid and ethyl acrylate or poly(MA-EA), in a molar ratio of 1:1 with a molecular weight of 250,000, is referred to as "Methacrylic Acid Copolymer, Type C" in USP XXI/NF XVI. This polymer is insoluble in acidic media, but dissolves readily at medium with pH above 5.5. As a commercially available, ready-to-use poly(MA-EA) 1:1 latex, Eudragit® L 30 D-55 has a 30% solid content with some emulsifier (Lehmann, 1989). The pH of Eudragit® L 30 D-55 dispersion is between 2.0 and 3.0 and can be increased by partially neutralizing the dispersion, i.e., neutralization of 6 mol% of the carboxylic groups, to a pH-value of approximately 5.0 (Eudragit®, Acrylic Polymers for Pharmaceutical Applications). Poly(MA-EA) 1:1 is also available as a spray-dried powder, Eudragit® L 100-55, produced by spray-drying of Eudragit® L 30 D-55. Eudragit® L 100-55 powder can be easily redispersed into water with the aid of small amounts of alkali or organic base, resulting in a redispersed latex with a final pH of ~5. It has been concluded that partial neutralization of Eudragit® L 100-55 during redispersion, which is in the order of 3–6 mol% ionization of the carboxylic group, does not have any remarkable effect on enteric coating properties (Lehmann, 1989). However, little knowledge is currently available on the effect of neutralization of poly(MA-EA) 1:1 on drug release under the influence of accelerated stability storage.

In the present study, partially neutralized and un-neutralized Eudragit® L 30 D-55 based poly(MA-EA) enteric-coating systems were evaluated for the impact of neutralization on drug release, especially under accelerated stability storage conditions. Effect of neutralization on the physicochemical properties of poly(MA-EA) latex, as well as the morphological and mechanical properties of poly(MA-EA) films and coated pellets, particularly under the aging influence, were investigated and correlated with the observed dissolution phenomena.

MATERIALS AND METHODS

Materials

Poly(MA-EA) 1:1 in the form of 30% aqueous dispersion or Eudragit® L 30 D-55 was provided by Röhm America LLC. (Piscataway, NJ). Triethyl citrate was purchased from Morflex Inc. (Greensboro, NC) and talc was acquired from Barretts Minerals Inc. (Dillon, MT). Size #0 empty hard gelatin capsule shells were provided by Capsugel (Greenwood, SC). Desiccant canister was obtained from Süd-Chemie Inc., Performance Packaging (Colton, CA).

Partial Neutralization of Poly(MA-EA)

Partially neutralized poly(MA-EA) was prepared by slowly adding 1.0 N NaOH in a thin stream into the Eudragit® L 30 D-55 aqueous dispersion under continuous mixing. The weight ratio of NaOH to poly(MA-EA) was about 0.5:99.5 and the resulting poly(MA-EA) latex had a pH value of approximately 5.0 (ThermoOrion pH Meter, Model 420, Thermo Electron Corp., Waltham, MA). The partially neutralized poly(MA-EA) latex was screened through a #30 (600 μm) mesh sieve (Gilson Company, Inc., Lewis Center, OH) to remove any coarse agglomerates prior to use.

The Eudragit® L 30 D-55 aqueous dispersion filtered through a #30 (600 μm) mesh screen was used as the un-neutralized poly(MA-EA). The pH value for un-neutralized poly(MA-EA) latex was about 2.9.

Preparation of Poly(MA-EA) Enteric-Coated Pellet-Filled Capsules

Preparation of Drug Pellet Cores

An acid-labile, water-soluble compound was chosen as a model drug. The drug is a white-colored, nonhydroscopic, crystalline material with an average particle size of 10 μm. It is stable at neutral or slightly alkaline pH, but is unstable at acidic pH. Highly drug-loaded pellets (~90% w/w) were prepared through a series of operations of mixing, wet granulation, extrusion, spheronization, and fluid-bed drying.

The drug and other inert pharmaceutical excipients, in a weight ratio of approximately 90 to 10 and a batch size of 3 kg, were screened through a #20 (850 μm) mesh sieve. The de-lumped drug and excipients were added dry into the bowl of a Collette Gral 25 Liter High Shear Mixer/Granulator (Niro Inc., Columbia, MD) and mixed for 5 min with the mixer speed maintained at the low setting. Granulation was achieved by spraying an aqueous neutral polymeric granulating solution into the drug blend in the granulator. The granulating solution (~1 kg) was added using a peristaltic pump and a hydraulic nozzle at a spray rate of 200 g/min. During granulation the chopper was activated at low speed and the mixer speed was kept at the low setting. The total mixing time during granulation was 8 min. The moisture content of wet granules was approximately 30% (w/w) (Mettler Moisture Analyzer HR73, Mettler-Toledo, Inc., OH).

The wet cohesive granules were then passed through a NICA™ E140 Extruder (Niro Inc., Columbia, MD) for extrusion with a screen size of 1.0 mm. The feed rate for extrusion was approximately 1 kg/min at a feeder speed of 50 rpm and an impeller speed of 50 rpm. The cylindrical extrudates were immediately placed in a NICA™ S450 Spheronizer (Niro Inc., Columbia, MD) for spheronization. The feed rate for spheronization was about 1.0 kg/allotment and the disc speed was 900 rpm. The spheronization time for each allotment was maintained at 30 ± 10 s. The wet spheronized pellets were subsequently dried to a moisture content of about 1.5% (w/w) in a fluid bed drier (Glatt GPCG-5, Glatt Air Techniques, Inc., Ramsey, NJ) at an inlet air temperature of 50 ± 2°C. The dried drug pellets were screened through a #16 (1180 μm) and a #20 (850 μm) mesh sieve.

Seal-Coating of Drug Pellet Cores

To avoid direct contact of the acid-labile drug with the acidic poly(MA-EA) enteric-coating system, the screened drug pellet cores were primarily coated with a protective neutral polymeric seal-coat with 5% seal-coating weight gain. Seal-coat can physically separate acid-labile drug from acidic enteric-coating and, thereby, prevent drug decomposition (Lofgren et al., 1988). The aqueous polymeric seal-coat solution was sprayed tangentially onto the drug pellets in a fluid bed with a rotor insert (Glatt GPCG-3, Glatt Air Techniques, Inc., Ramsey, NJ). After prewarmed at an exhaust air temperature of 35 ± 2°C, the drug pellets were sprayed with the required amount of aqueous polymeric solution with the exhaust air temperature maintained at 32 ± 2°C. The neutral polymer seal-coated pellets were then dried for 30 min at an exhaust air temperature of 40 ± 2°C. The dried seal-coated drug pellets, with 5% seal-coating weight gain, were then sieved through a #16 (1180 μm) and a #20 (850 μm) mesh sieve.

Poly(MA-EA) Enteric-Coating of Sealed Drug Pellets

Triethyl citrate was selected as a plasticizer and talc was used as an anti-tacking agent to prepare the poly(MA-EA) enteric-coating dispersion. Partially neutralized or un-neutralized enteric-coating dispersion was prepared by plasticizing the partially neutralized or un-neutralized poly(MA-EA) latex with triethyl citrate for at least 30 min, followed by mixing the plasticized polymeric dispersion with talc and diluting the dispersion with purified water to reach a total solid content of 20% (w/w). Due to the negligible amount of NaOH added, the weight ratio of poly(MA-EA):triethyl citrate:talc was approximately the same for partially neutralized and un-neutralized enteric-coating dispersions. To avoid sedimentation of talc, the coating dispersion was under continuous mixing throughout the coating process.

The poly(MA-EA) enteric-coated drug pellets, with 20% enteric-coating weight gain, were obtained by film-coating the partially neutralized or un-neutralized poly(MA-EA) coating dispersion onto the seal-coated drug pellets in a fluid bed coater with a rotor insert (Glatt GPCG-3, Glatt Air Techniques, Inc., Ramsey, NJ). After prewarmed at an exhaust air temperature of 35 ± 2°C, the seal-coated drug pellets were sprayed tangentially with the partially neutralized or un-neutralized poly(MA-EA) dispersion with the exhaust air temperature maintained at 32 ± 2°C. Once the required amount of enteric-coating dispersion had been sprayed, the enteric-coated pellets were dried and cured for 30 min at an exhaust air temperature of 40 ± 2°C. The dried poly(MA-EA) enteric-coated drug pellets were subsequently screened through a #14 (1400 μm) and a #20 (850 μm) mesh sieve.

Encapsulation

The screened poly(MA-EA) enteric-coated drug pellets were mixed with talc in a weight ratio of 99.5:0.5

in a 0.25 cu. ft. V-blender (P-K Cross Flow®, Patterson-Kelley, East Stroudsburg, PA) for 5 min. Talc, used as an antiadherent, was screened through a #30 (600 μm) mesh sieve prior to use. The final poly(MA-EA) enteric-coated pellets blend was encapsulated into size #0 hard gelatin capsule shells with an intermittent motion capsule-filling machine (Zanasi 12F, IMA North America Inc., Bristol, PA). The encapsulator was equipped with size #0 tooling and size #0 dosators for pellets. The capsule-filling speed was approximately 75 capsules/min.

Physical Evaluation of Poly(MA-EA) Enteric-Coated Pellets and Pellet-Filled Capsules

The size and distribution of poly(MA-EA) enteric-coated pellet blend were determined by sieve analysis using a Gilsonic GA-6 Sonic Sifter (Gilsonic Auto Siever, Dual Tapper Model, Gilson Company, Inc., Lewis Center, OH). The assembled sieves consisted of, from top to bottom, numbers 12 (1700 μm), 14 (1400 μm), 16 (1180 μm), 18 (1000 μm), 20 (850 μm), 25 (710 μm), and 30 (600 μm). About 5 g of the pellet blend were placed on top of the largest opening sieve (#12) and sieved at a maximum amplitude of 10 with a ramp-up, run, and ramp-down time of 0.5, 10.0, and 0.3 min. The percentage of pellets retained on each sieve was recorded and the mean particle size was estimated. The results reported were the average of three measurements.

Poly(MA-EA) enteric-coated pellet-filled capsules were weighed using a Mocon automatic balance (Mocon, Inc. Minneapolis, MN) and a sample of 100 readings was used for calculating the average and %CV of fill weight. The empty size #0 hard gelatin capsule shells weighed approximately 95 mg. The data are expressed as percentage of target-fill weight. The results reported were the average of two replicates.

Preparation of Poly(MA-EA) Films

Preliminary trial experiments showed that poly(MA-EA) films, generated with the same plasticizer content (w/w) as in the drug pellets enteric-coating dispersion or with less than 40% (w/w) plasticizer content, were fragile and easy to break upon peeling off from the substrate. Thus, partially neutralized or un-neutralized poly(MA-EA) films were cast from the partially neutralized or un-neutralized poly(MA-EA) latex plasticized with 40% (w/w) triethyl citrate (based on the total solid mass).

The poly(MA-EA) latex was mixed or equilibrated with triethyl citrate for at least 30 min and then the plasticized polymer dispersion was poured onto a 10 cm diameter Teflon plate. The cast polymer latex was allowed to dry in a vacuum drying oven (DP32, Ultra-Tech Inc., Woodbridge, VA) at 50°C for 1 day followed by 1 day drying at room temperature. The dried films were peeled off and cut to dimensions of around 8 × 4 cm with a stainless steel sharp blade. The film thickness (~0.3 mm) was measured with an electronic digital caliper (Pro-max S 225, Fred V. Fowler Company, Newton, MA). Cast films were stored in a silica gel desiccator at room temperature prior to testing.

Packaging and Accelerated Storage Condition

Poly(MA-EA) enteric-coated pellet-filled capsules were packaged in 120 cc HDPE bottles. Each bottle contains 30 capsules and a 2-g silica gel desiccant canister. Similarly, poly(MA-EA) cast films were stored in 120 cc HDPE bottles with one piece of film and a 2-g silica gel desiccant canister in each bottle. All bottles were induction (foil) sealed and subjected to accelerated stability testing at 60°C (Lunaire Environmental's Temperature/Humidity Chamber, Thermal Product Solutions, Williamsport, PA) for 2 weeks.

Capsule Assay and Drug Release Studies

The drug assay was performed with a robust extraction procedure followed by a validated HPLC analysis. The contents of 20 capsules were ground with a glass pestle and mortar. A portion of the triturated fine powder was subsequently soaked with 0.01 N NaOH and shaken at high speed on a mechanical shaker (Eerbach, Surplus Lab, Inc., Muskegon, MI) for 30 min followed by sonication (Branson 8510, Kell-Strom Tool Co., Wethersfield, CT) for 20 min. The drug extraction mixture was then centrifuged and the clear supernatant was used for analysis. The validated HPLC method utilized a mobile phase comprising of aqueous solution of triethylamine, methanol, and

acetonitrile, a Waters SymmetryShield RP8 15-cm C8 column and a Waters Alliance HPLC System equipped with a 2487 Dual Wavelength Absorbance Detector (Waters Corporation, Milford, MA). Assays were performed in triplicates.

The drug release studies were performed using a USP apparatus I (baskets) (VK7000 Dissolution Tester, Varian, Inc., Palo Alto, CA) at 100 rpm rotation speed and 37 ± 0.5°C. A two-stage (acid and pH 6.8 buffer) dissolution test was designed for this enteric-coated product. Capsules were placed into 900 mL of 0.1 N HCl for 2 hr, then transferred into 900 mL of pH 6.8, 0.05 M phosphate buffer for an additional 2 hr. At each predetermined sampling point, an aliquot of 5 mL was withdrawn manually from each vessel. The samples were filtered through 0.45 μm syringe filters (Whatman Inc., Florham Park, NJ) and analyzed by a validated UV spectrophotometric method (2487 Dual Wavelength Absorbance Detector, Waters Corporation, Milford, MA). The results reported were the average of six capsules.

Physicochemical Characterization of Poly(MA-EA) Latex

Viscosity-pH Profile of Poly(MA-EA) Latex

The un-neutralized poly(MA-EA) latex was titrated with 1.0 N NaOH and the dynamic viscosity of the resulting dispersion or solution at predetermined pH conditions was measured with a controlled-stress Rheometer (AR 1000, TA Instruments, New Castle, DE). The measurement was performed at constant temperature (25°C) with parallel-plate geometry. The stainless steel parallel plate diameter was 40 mm and the plate-plate gap was set at 500 μm for all tests. The apparent viscosity at each pH condition was evaluated at three different shear rates (10, 100, and 1000 1/sec). Each titration and viscosity measurement was performed three times.

Particle Size and Zeta Potential Analyses of Poly(MA-EA) Latex

The average particle size and zeta potential of poly(MA-EA) latex were determined with Brookhaven's ZetaPlus (Brookhaven Instruments Limited, Redditch, Worcestershire, UK). ZetaPlus combines zeta potential measurement with particle sizing in one comprehensive particle characterization system. A portion of the freshly prepared poly(MA-EA) latex was extemporaneously diluted with purified water prior to testing. The submicron particle size distribution data were acquired by dynamic light scattering. The zeta potential values were determined via measurement of electrophoretic mobility of dispersed particles in a charged field. The mean particle size and zeta potential values of six replicates were reported.

Morphology and Mechanical Evaluation of Poly(MA-EA) Enteric-Coated Drug Pellets

Scanning Electron Microscope Analysis

Cross-sections of poly(MA-EA) enteric-coated drug pellets were made with a stainless steel scalpel and the cross-sectioned pellets were mounted with double-sided carbon tape on aluminum stubs. The pellets' cross-sections were viewed and photographed at 10 kv at appropriate magnification with a JSM-5610LV Scanning Electron Microscope (SEM) (JEOL USA, Inc., Peabody, MA).

Texture Analysis

The mechanical strength of poly(MA-EA) enteric-coated drug pellets was determined, in compression mode, as the cracking force needed to break the pellets with a TA.XTplus Texture Analyzer (Texture Technologies Corp., Scarsdale, NY/Stable Micro Systems, Godalming, Surrey, UK). The load cell was 5 kg with 1 g increment sensitivity. The probe was a stainless steel cylinder with a bottom diameter of 8 mm. A single pellet was compressed with the probe at a pretest, test and posttest speed of 1.0, 0.1, and 10.0 mm/second. The compression force was 100.0 g. The auto trigger force was set at 10.0 g. The hold time was 10.0 s. The maximum peak force in compression was recorded as cracking force in grams and an average cracking force of 20 pellets was reported.

Dynamic Mechanical Analysis of Poly(MA-EA) Films

The mechanical analysis of poly(MA-EA) films were performed using a Dynamic Mechanical Analyzer (DMA Q800, TA Instruments, New Castle, DE). Rectangular samples (~7 × 5.3 mm) were cut from the

cast films with a DMA 5.3 mm film cutter. The dimensions of films were measured with an electronic digital caliper (Pro-max S 225, Fred V. Fowler Company, Newton, MA). The sample film was placed between parallel-plate compression clamps. The film mechanical properties were evaluated through a creep-recovery and a stress-strain test. In creep-recovery test, after being equilibrated at predetermined temperature for 5 min, the film was subjected to a constant stress of 1.0 MPa for 10 min. The response of film to applied constant stress or film vertical deformation was measured over time. Following removal of the applied stress, the film recovery or progressive decrease of deformation was monitored for 20 min. Characteristic deformation (creep) of films as a function of time was recorded. To perform the stress-strain test, the test sample was equilibrated at predetermined temperature for 5 min, then a dynamic stress, i.e., a continuously increasing ramp force from 1.0 to 18.0 N, was applied to the sample at a rate of 1.0 N/min and the resulting deformation was measured. The results reported were the average of four replicates.

Statistical Analysis

Experimental data are expressed as mean ± SD where appropriate analysis of the significance of difference were performed using a Student's *t*-test run on SigmaPlot 9.0 (Systat Software, Inc., Point Richmond, CA). Statistical significant difference was accepted at $p < 0.05$.

A similarity factor f2 test was employed for dissolution profile comparison. The factor f2 measures the closeness between two dissolution profiles (Moore & Flanner, 1996). When two profiles are identical the similarity factor is 100. As the dissimilarity increases the similarity factor decreases. An f2 value of 50 indicates an average difference of 10% at all measured time points. As per the FDA guideline for industry, an f2 value between 50 and 100 indicates similarity between two dissolution profiles (Guidance for Industry, 1995).

RESULTS AND DISCUSSION

Physical Evaluation of Poly(MA-EA) Enteric-Coated Pellets and Pellet-Filled Capsules

The size and distribution of poly(MA-EA) enteric-coated pellet blend characterized by sieve analysis are illustrated in Fig. 1. For both partially neutralized and un-neutralized poly(MA-EA)-coated pellet systems, the majority of pellets was retained on the #20 (850 μm) and #18 (1000 μm) mesh sieves (Fig. 1). The estimated average pellet size was 955.6 ± 3.5 μm for the partially neutralized poly(MA-EA)-coated pellets and 960.2 ± 5.1 μm for the un-neutralized polymer-coated pellets. Statistical analysis showed that there was no significant difference in size and distribution between neutralized and un-neutralized poly(MA-EA)-coated pellets.

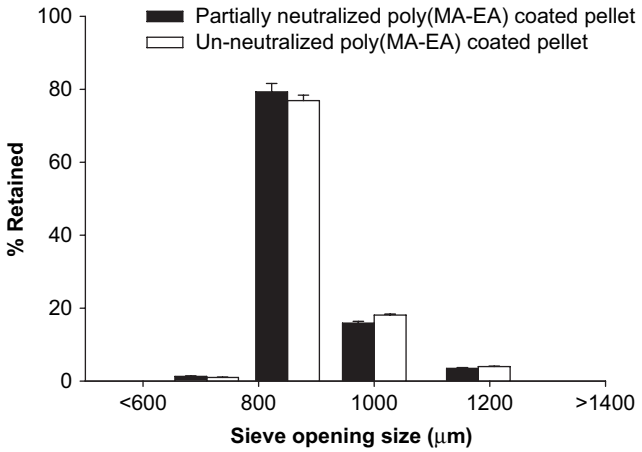


FIGURE 1 **Particle Size Distribution of Poly(MA-EA) Enteric-Coated Pellet Blend.**

The average capsule-fill weight, expressed as percentage of target-fill weight, was 100.0% (CV%, 1.2%) for the partially neutralized poly(MA-EA)-coated pellet-filled capsules and 100.1% (CV%, 1.5%) for the un-neutralized polymer-coated pellet-filled capsules, indicating a good encapsulation process in both cases.

Drug Assay and Release Properties of Poly(MA-EA) Enteric-Coated Pellet-Filled Capsules

The poly(MA-EA) enteric-coated pellet-filled capsules, initial samples, as well as finished products stored at 60°C for 1 and 2 weeks, were tested for both drug assay and release profiles. The drug was chemically stable in both partially neutralized and un-neutralized poly(MA-EA)-coated pellet-filled capsules as indicated by the consistent assay values upon accelerated storage tabulated in Table 1. The neutral polymeric seal-coat, with 5% coating weight gain, demonstrated its effectiveness in preventing the

TABLE 1 **Drug Assay Values Upon Accelerated Storage at 60°C**

Drug assay (% Recovery ± SD)	Partially neutralized poly (MA-EA)-coated pellet-filled capsules	Un-neutralized poly(MA-EA)-coated pellet-filled capsules
Initial	98.0 ± 1.7	96.6 ± 0.1
1 Week	95.7 ± 1.2	97.2 ± 1.3
2 Weeks	98.3 ± 0.6	96.3 ± 1.5

potential incompatibility between the acid-labile drug and acidic un-neutralized poly(MA-EA) enteric-coating system.

The percent drug release in both acid and buffer stages from partially neutralized and un-neutralized poly(MA-EA)-coated pellet-filled capsules upon storage at 60°C are depicted in Figs. 2 and 3. The calculated f2 values between various dissolution profiles are tabulated in Table 2. At the initial time of stability study, consistent with the previously reported results (Lehmann, 1989), partially neutralized and un-neutralized poly(MA-EA)-coated pellet-filled capsules did not exhibit significant difference in their release profiles in both acid and buffer stages (Table 2). Both coating systems effectively inhibited drug release in acidic media and exhibited comparable dissolution profiles in buffer exposure phase.

However, upon accelerated storage at 60°C, a significant retardation in drug release was observed for the un-neutralized poly(MA-EA)-coated pellet-filled capsules in pH 6.8 buffer stage (Fig. 3). This aging

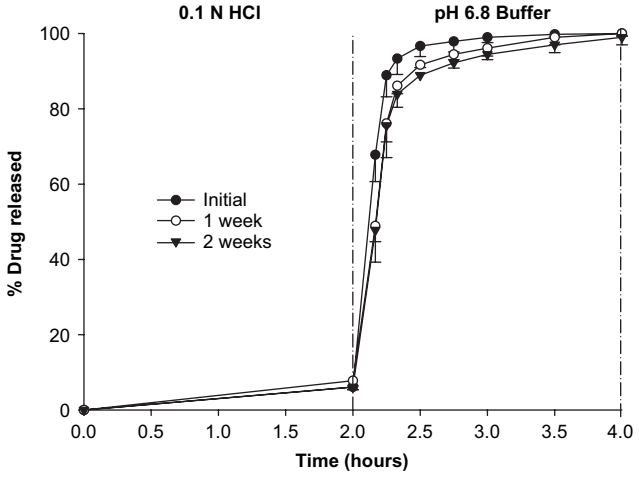


FIGURE 2 **Percent Drug Release in Acid and Buffer Stages from Partially Neutralized Poly(MA-EA) Enteric-Coated Pellet-Filled Capsules Stored at 60°C.**

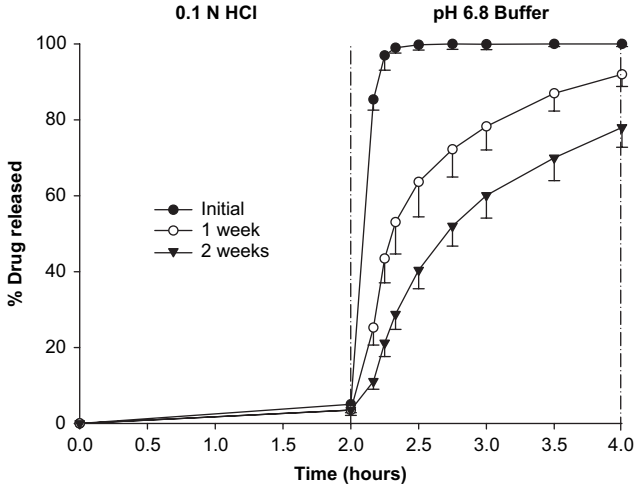


FIGURE 3 **Percent Drug Release in Acid and Buffer Stages from Un-Neutralized Poly(MA-EA) Enteric-Coated Pellet-Filled Capsules Stored at 60°C.**

effect on drug release was not shown for the neutralized polymer-coated pellet-filled capsules (Fig. 2). The neutralized polymer-coated pellet-filled capsules maintained similar enteric dissolution profiles to the initial release profiles in both acid and buffer stages, indicating a stable drug release rate over 2 weeks upon storage (Fig. 2 and Table 2). In comparison, the un-neutralized poly(MA-EA)-coated pellet-filled capsules exhibited significantly slower dissolution rates in buffer exposure stage (Fig. 3 and Table 2), even though the enteric property was satisfactorily maintained after storage. The percent drug release from un-neutralized poly(MA-EA)-coated pellet-filled capsules at the end of 2-hr buffer stage decreased significantly from the initial 100 to 92% at 1 week and 78% at 2 weeks. The dissolution data suggested that the pellets coated with un-neutralized poly(MA-EA) might have experienced more aging than those coated with neutralized polymer when stored at 60°C. Neutralization of poly(MA-EA) enteric-coating system improved the stability of poly(MA-EA) enteric-coated pellets when stored at the studied conditions.

To elucidate the fundamental difference between partially neutralized and un-neutralized poly(MA-EA) enteric-coating systems and to interpret the observed drug release characteristics in more detail, the physicochemical properties of poly(MA-EA) latex, the morphological and mechanical properties of poly(MA-EA) films and coated pellets, along with the changes thereof upon exposure to accelerated stability storage at 60°C, were investigated.

TABLE 2 **Calculated f2 Values between Various Dissolution Profiles**

Comparison of dissolution profiles	f2 value	
	Dissolution profile in both acid and buffer stages	Dissolution profile in buffer stage
Partially neutralized poly(MA-EA)-coated pellet-filled capsules and un-neutralized poly(MA-EA)-coated pellet-filled capsules, initial samples	59.1	59.1
Partially neutralized poly(MA-EA)-coated pellet-filled capsules, initial samples and capsules stored at 60°C for 1 week	55.0	55.0
Partially neutralized poly(MA-EA)-coated pellet-filled capsules, capsules stored at 60°C for 1 and 2 weeks	85.0	85.8
Un-neutralized poly(MA-EA)-coated pellet-filled capsules, initial samples and capsules stored at 60°C for 1 week	23.6*	23.6*
Un-neutralized poly(MA-EA)-coated pellet-filled capsules, capsules stored at 60°C for 1 and 2 weeks	37.9*	37.9*

*f2 < 50, f2 test.

Effect of Degree of Neutralization on Viscosity of Poly(MA-EA) Latex

The apparent viscosity versus pH profiles of poly(MA-EA) latex at various shear rates are illustrated in Fig. 4. The decrease in viscosity with increasing shear rate at each evaluated pH condition indicated that the poly(MA-EA) latex colloidal coating dispersion exhibited a shear thinning (non-Newtonian) behavior regardless of degree of neutralization. The partially neutralized poly(MA-EA) at pH 5.0 showed minimal shear dependence (Fig. 4). However, the consistent low apparent viscosity values (~0.07 poises) of poly(MA-EA) dispersion below pH 5.0 measured at high shear rates (100 and 1000 1/sec) suggested that partial neutralization of poly(MA-EA) to pH 5.0, i.e., the ionization of about 6 mol% of the carboxylic groups (Eudragit®, Acrylic Polymers for Pharmaceutical Applications), did not cause any significant change in apparent viscosity at high shear rates. Above pH 5.0, the polymer became very pH-sensitive, a slight increment in pH resulted in a dramatic increase in apparent viscosity at all shears rates. At pH 5.5, the apparent viscosity of poly(MA-EA) dispersion reached 426 poises at a shear rate of 100 1/sec.

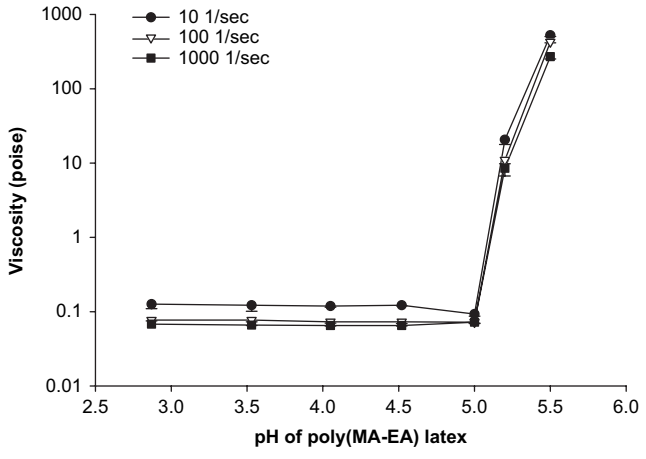


FIGURE 4 **Apparent Viscosity versus pH Profiles of Poly(MA-EA) Latex at Various Shear Rates.**

The hypothesized diagram of poly(MA-EA) network dissociation during neutralization is depicted in Fig. 5. Initially at acidic pH, the poly(MA-EA) probably existed primarily as tightly entangled polymer coils (a), maintained most likely through the Van del Waals forces, especially the H-bonding between un-ionized carboxylic acid groups. Along with the neutralization process the exposed carboxylic acid groups –COOH on polymer side chains probably became ionized into hydrophilic sodium salts $–COO^{-}Na^{+}$ (b) and the polymer chains started hydrating and swelling. To certain neutralization extent, the repulsive forces generated between negatively charged ionized carboxylic acid groups became dominated, playing an essential role in further uncoiling the polymer network into an extended structure (c). The polymer network dissociation as well as polymer solubilization probably contributed together to the dramatic viscosity increase of neutralized poly(MA-EA) latex at pH above 5.0.

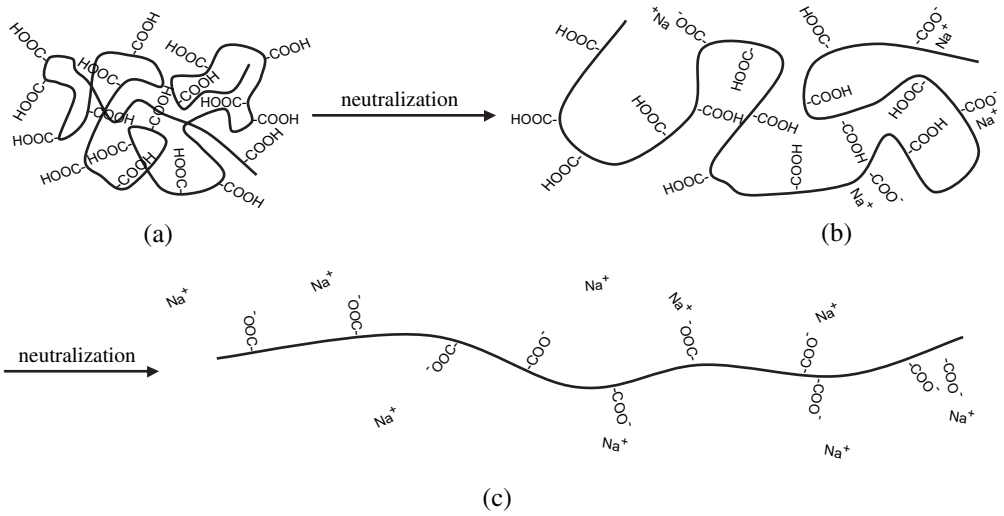


FIGURE 5 **Hypothesized Diagram of Poly(MA-EA) Network Dissociation during Neutralization.**

Effect of Neutralization on Particle Size and Zeta Potential of Poly(MA-EA) Latex

The average particle size and zeta potential of partially neutralized and un-neutralized poly(MA-EA) latex are listed in Table 3. The mean particle size of un-neutralized poly(MA-EA) latex was increased from 145.1 nm by partial neutralization to 171.0 nm. As illustrated in Fig. 5, neutralization of poly(MA-EA) latex initiated the ionization of carboxylic acid group –COOH into the hydrophilic dissociated form $–COO^–$, resulting in the hydration and swelling of polymer network. The larger particle size of neutralized system could be attributed to the hydrated and swelled polymer chains in the colloidal dispersion.

Zeta potential is an important physicochemical characteristic of colloidal dispersion and can be used to predict stability of colloidal suspensions or emulsions. The greater the zeta potential (absolute value), the higher the repulsive forces between charged particles will be and the more likely the dispersion is to be deflocculated or to be stable (Lieberman et al., 1989). As shown in Table 3, the zeta potential (absolute value) of partially neutralized poly(MA-EA) latex (51.5 mV) was slightly larger than that of un-neutralized system (49.1 mV), possibly due to the partially ionized carboxylic acid groups $–COO^–$ on polymer side chains via neutralization (Fig. 5). It has been reported that the redispersed Eudragit® L 100-55 latex at pH 5 is to some extent more stable than the commercial Eudragit® 30D-55 latex at pH 3 (Lehmann, 1989), which could be explained by the observed slightly higher zeta potential value for the partially neutralized poly(MA-EA) latex at pH 5.0 as compared to the un-neutralized system at pH 2.9.

TABLE 3 **Average Particle Size and Zeta Potential of Partially Neutralized and Un-Neutralized Poly(MA-EA) Latex**

	Average particle size (nm ± SD)	Zeta potential (mV ± SD)
Partially neutralized poly(MA-EA) latex	171.0 ± 0.9	–51.5 ± 1.5
Un-neutralized poly(MA-EA) latex	145.1 ± 3.4**	–49.1 ± 1.2*

*$p < 0.05$, Student's *t*-test.
**$p < 0.01$, Student's *t*-test.

Effect of Neutralization on Morphology of Poly(MA-EA) Enteric-Coating Systems

The SEM micrographics of cross-sections of partially neutralized and un-neutralized poly(MA-EA)-coated pellets stored at 60°C for 1 and 2 weeks are shown in Figs. 6 and 7. The cross-sectional images of pellets at the initial time of stability test showed that there was no observable morphological difference between two coating films. Continuous dense films were formed around the pellet cores from both neutralized and un-neutralized poly(MA-EA) enteric coating systems, indicating that the fluid-bed coating

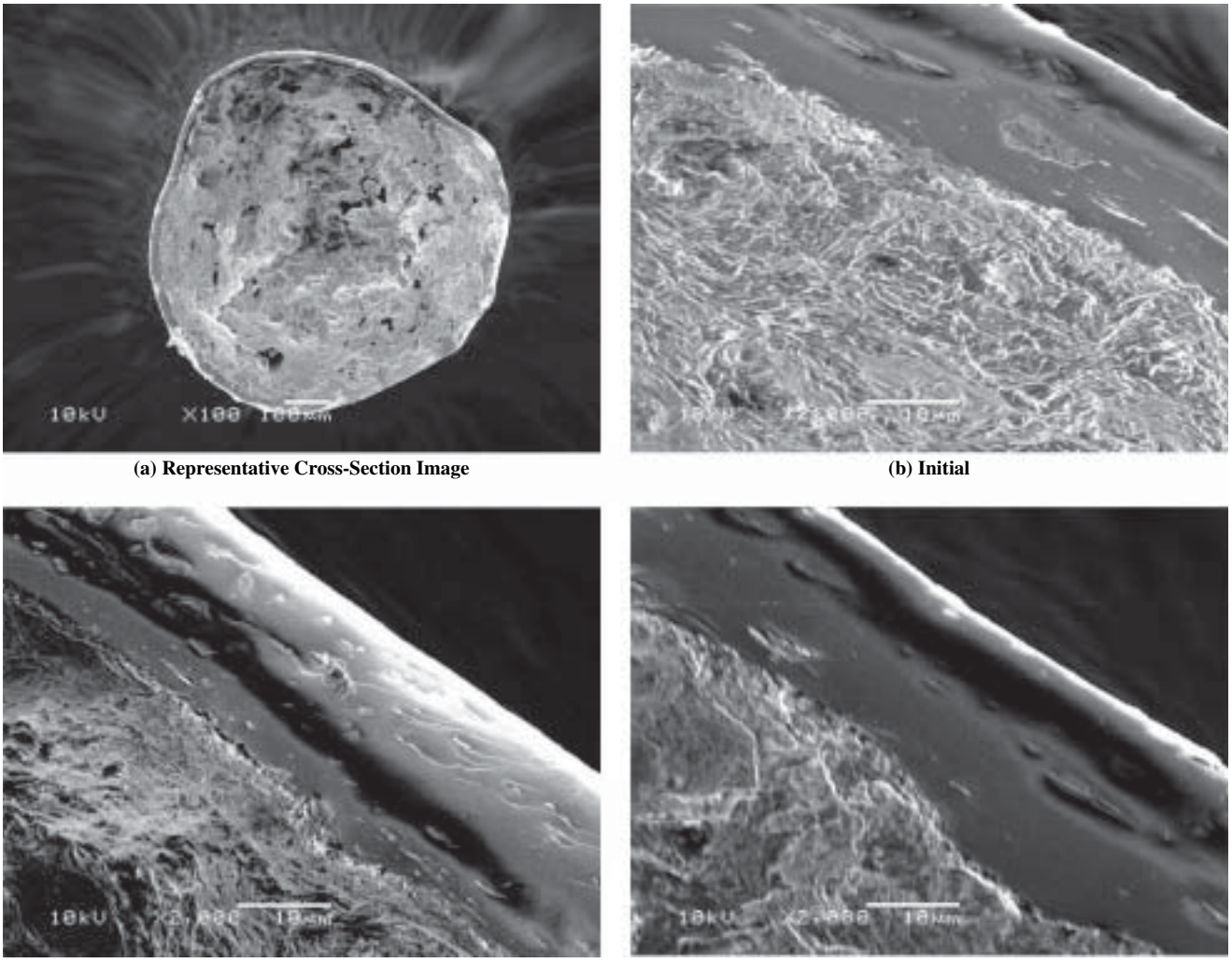
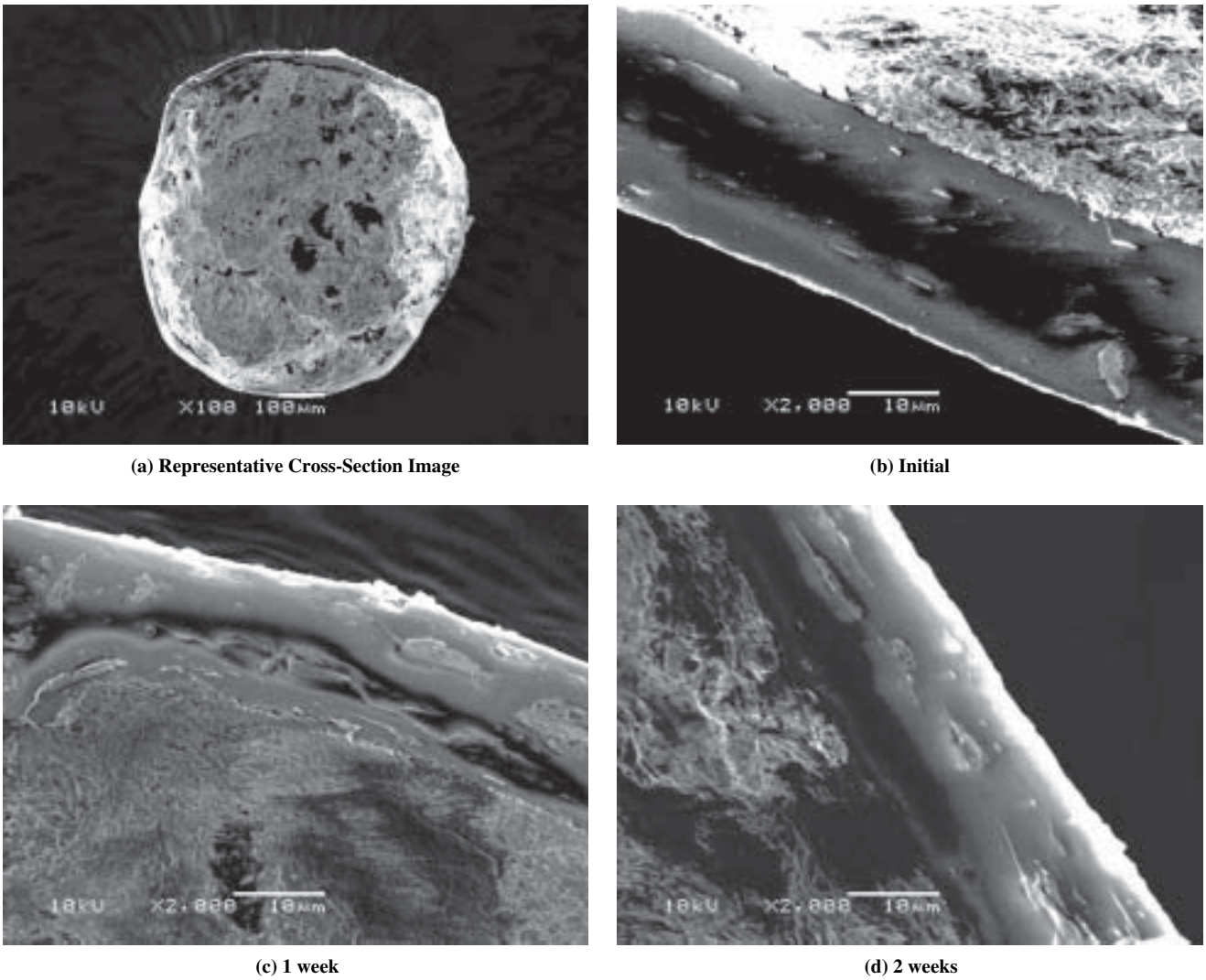


FIGURE 6 SEM Micrographics of Cross-Sections of Partially Neutralized Poly(MA-EA) Enteric-Coated Pellets Stored at 60°C.

conditions were optimal for both coating operations. Furthermore, there was no significant change in coated-film appearance among the initial, 1 and 2 weeks pellets for both neutralized and un-neutralized polymer-coated pellets. It seemed that SEM micrography was not an ideal method to be correlated with the findings from dissolution study.

Effect of Neutralization on Mechanical Properties of Poly(MA-EA) Enteric-Coated Pellets

The effect of neutralization on mechanical properties of poly(MA-EA) enteric-coated pellets was investigated by measuring the cracking force needed to break the pellets with a TA.XTPlus texture analyzer, for both partially neutralized and un-neutralized poly(MA-EA)-coated pellets, initial samples, as well as pellets stored at 60°C. As shown in Fig. 8, at the initial time of stability study, the cracking force needed to break the partially neutralized poly(MA-EA)-coated pellets was comparable to that required for the un-neutralized polymer-coated pellets, suggesting that neutralization of poly(MA-EA) did not change the mechanical strength at a 20% poly(MA-EA) enteric-coating weight gain. However, when stored at 60°C for 1 week and 2 weeks, the cracking force increased for both neutralized and un-neutralized poly(MA-EA)-coated pellets, indicating that both coating films became rigid during storage at the studied conditions. However, there was no significant difference in cracking force between neutralized and un-neutralized polymer-coated pellets after storage. It appeared that the cracking force data



(a) Representative Cross-Section Image

(b) Initial

(c) 1 week

(d) 2 weeks

FIGURE 7 SEM Micrographics of Cross-Sections of Un-Neutralized Poly(MA-EA) Enteric-Coated Pellets Stored at 60°C.

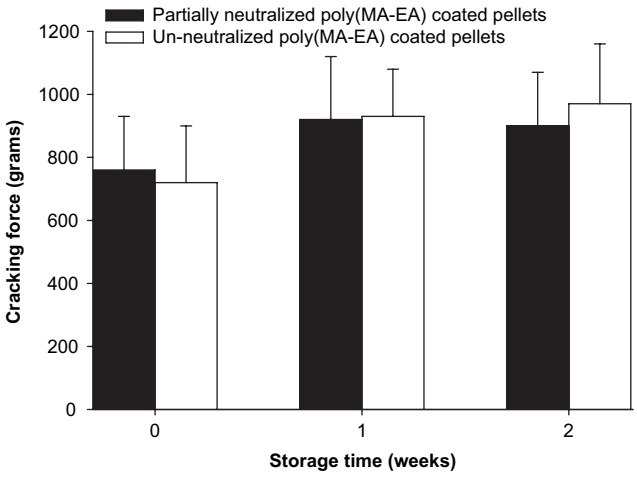


FIGURE 8 Cracking Force of Partially Neutralized and Un-Neutralized Poly(MA-EA) Enteric-Coated Pellets Stored at 60°C.

were unlikely to provide an explanation for the observed dissolution phenomena.

Effect of Neutralization on Mechanical Properties of Poly(MA-EA) Films

Successful coating requires that polymer solution or dispersion be applied to substrate surface and solvent fluid carrier is removed by application of heat. In the case of polymer aqueous dispersion, film formation depends on the coalescence of polymer latex particles driven by water evaporation and the resultant capillary forces (Bindschaedler et al., 1983). The mechanical properties of free films would be useful information to assess the performance of film-forming formulations. Dynamic mechanical analysis (DMA) has been demonstrated to

be a powerful tool to characterize the viscoelastic properties of materials (Jones, 1999; Lafferty et al., 2002a; Bashaiwoldu et al., 2004).

To further understand the observed dissolution difference between partially neutralized and un-neutralized poly(MA-EA)-coated pellet-filled capsules upon accelerated stability storage at 60°C, polymer films from these two enteric-coating systems were prepared and exposed to the same accelerated stability storage condition. DMA in creep-recovery and stress-strain modes was chosen to characterize the viscoelasticity of polymeric films. For partially neutralized and un-neutralized poly(MA-EA) films, initial samples as well as films stored at 60°C, the typical creep-recovery curves as seen from DMA Q800 are depicted in Figs. 9 and 10. The representative creep-recovery test results are summarized in Table 4.

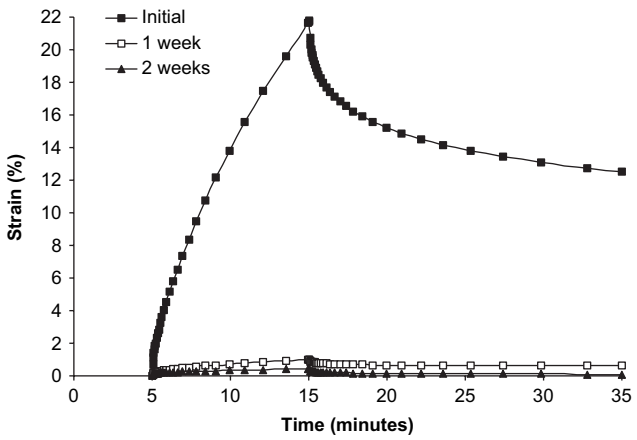


FIGURE 9 **Typical Creep-Recovery Curves of Partially Neutralized Poly(MA-EA) Films Stored at 60°C (Tested at 25°C).**

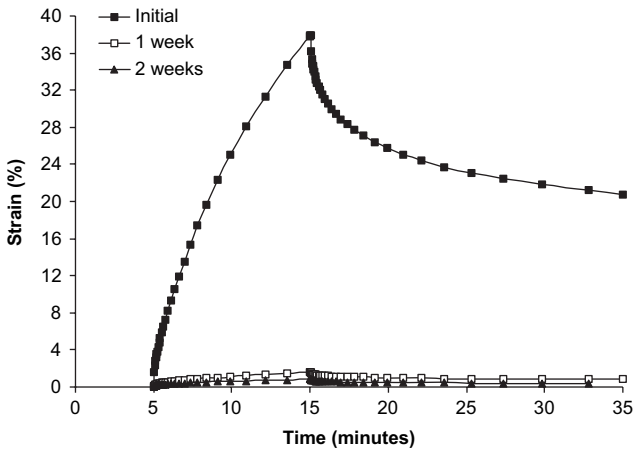


FIGURE 10 **Typical Creep-Recovery Curves of Un-Neutralized Poly(MA-EA) Films Stored at 60°C (Tested at 25°C).**

For the initial film samples, subjected to the same constant stress (1 MPa) for the same period of time (10 min), the un-neutralized poly(MA-EA) films underwent more vertical deformation or elongation (% strain) than those neutralized as shown in Figs. 9 and 10. Both deformation extent or maximum strain and elongation rate were much higher for the un-neutralized poly(MA-EA) films (38.0% and 2.55%/min) than for those neutralized (21.7 and 1.51%/min) when tested at 25°C (Table 4), suggesting that the un-neutralized poly(MA-EA) films were more flexible or softer than those neutralized at the initial time of stability study. In addition, for both the initial neutralized and un-neutralized poly(MA-EA) films, the observed maximum strain and elongation rate were much higher when tests were performed at 37°C than at 25°C (Table 4). This indicated that both poly(MA-EA) films became more flexible or softer at higher temperature. However, at both high and low testing temperatures, the un-neutralized poly(MA-EA) films were more pliable or softer than those neutralized as demonstrated by the significantly greater maximum strain and elongation rate of the un-neutralized systems in each case (Table 4).

Upon accelerated storage at 60°C, both partially neutralized and un-neutralized poly(MA-EA) films became more rigid and stiffer as indicated by the significant reduced maximum strain and elongation rate over time, especially within the first week of storage (Figs. 9, 10 and Table 4). Upon 1-week storage at 60°C, the maximum strain decreased from 21.7 to 0.9% with a change rate of –20.8% per week for the neutralized poly(MA-EA) films, while for the un-neutralized systems, the maximum strain decreased from 38.0% to 1.6% with a change rate of –36.4% per week. Similarly, the elongation rate reduced from 1.51 to 0.06%/min with a change rate of –1.45%/min per week for the neutralized films, while for the un-neutralized systems, the elongation rate reduced from 2.55 to 0.09%/min with a change rate of –2.46%/min per week (Table 4, 5 and Fig. 11). This indicated that, although the maximum strain and elongation rate of both partially neutralized and un-neutralized poly(MA-EA) films significantly decreased, their change magnitude and rate (absolute value) were much greater for the un-neutralized films (36.4%, 36.4%/week, 2.46%/min and 2.46%/min/week) than for those neutralized (20.8%, 20.8%/week, 1.45%/min and 1.45%/min/week) upon 1 week storage at 60°C (Table 5 and Fig. 11).

TABLE 4 **Representative Creep-Recovery Test Results for Partially Neutralized and Un-Neutralized Poly(MA-EA) Films Stored at 60°C for 1 and 2 Weeks**

Sample	Storage period	Creep-recovery test temperature (°C)	Maximum strain (% ± SD)	Elongation rate (%/min ± SD)	Elastic recovery (% ± SD)
Partially neutralized poly(MA-EA) films	Initial	25	21.7 ± 4.2	1.51 ± 0.24	41.1 ± 3.9
		37	54.0 ± 6.4**[(b)]	2.25 ± 0.46*[(b)]	39.8 ± 5.6
	1 week	25	0.9 ± 0.3**[(d)]	0.06 ± 0.03**[(d)]	32.4 ± 4.5
	2 week	25	0.4 ± 0.2	0.02 ± 0.01	47.7 ± 6.3
Un-neutralized poly(MA-EA) films	Initial	25	38.0 ± 4.7**[(a)]	2.55 ± 0.51*[(a)]	44.2 ± 6.2
		37	68.5 ± 7.6**[(b)], *[(c)]	5.37 ± 1.13**[(b)], **[(c)]	40.9 ± 6.9
	1 week	25	1.6 ± 0.4**[(d)]	0.09 ± 0.02**[(d)]	47.8 ± 5.4
	2 week	25	0.7 ± 0.2	0.05 ± 0.01	49.7 ± 7.8

*$p < 0.05$, Student's *t*-test.
**$p < 0.01$, Student's *t*-test.
[(a)]Maximum strain or elongation rate comparison of the initial partially neutralized and un-neutralized poly(MA-EA) films tested at 25°C.
[(b)]Maximum strain or elongation rate comparison of the initial partially neutralized or un-neutralized poly(MA-EA) films tested at 25°C and 37°C.
[(c)]Maximum strain or elongation rate comparison of the initial partially neutralized and un-neutralized poly(MA-EA) films tested at 37°C.
[(d)]Maximum strain or elongation rate comparison of the partially neutralized or un-neutralized poly(MA-EA) films tested at 25°C, initial samples and films stored at 60°C for 1 week.

TABLE 5 **Change Magnitude and Rate of Maximum Strain and Elongation Rate for Partially Neutralized and Un-Neutralized Poly(MA-EA) Films Stored at 60°C for 1 and 2 Weeks (Tested at 25°C)**

		Maximum strain (%)		Elongation rate (%/min)	
Sample	Storage period	Change magnitude (%)	Change rate (%/week)	Change magnitude (%/min)	Change rate (%/min/week)
Partially neutralized poly(MA-EA) films	Initial 1 week	–20.8	–20.8	–1.45	–1.45
	1 – 2 week	–0.5	–0.5	–0.04	–0.04
Un-neutralized poly (MA-EA) films	Initial 1 week	–36.4	–36.4	–2.46	–2.46
	1 – 2 week	–0.9	–0.9	–0.04	–0.04

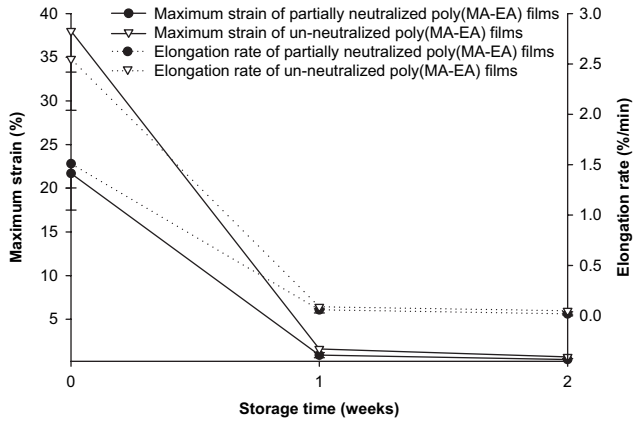


FIGURE 11 **Influence of Accelerated Storage at 60°C on Maximum Strain and Elongation Rate of Poly(MA-EA) Films (Tested at 25°C).**

Furthermore, the initial partially neutralized and un-neutralized poly(MA-EA) films had similar elastic recovery values (Table 4), suggesting that neutralization of poly(MA-EA) did not have remarkable impact on the elastic recovery property of polymeric films. In addition, for both the initial partially neutralized and un-neutralized poly(MA-EA) films there was no remarkable difference between elastic recovery values when tests were performed at different temperatures (25 and 37°C). Lafferty et al. have also reported similar phenomena (Lafferty et al., 2002b). This might provide an explanation for the observed nearly unchanged elastic recovery values for both neutralized and un-neutralized films after storage at 60°C for 1 and 2 weeks.

Similar results were found from the stress-strain tests of partially neutralized and un-neutralized poly(MA-EA) films, initial samples as well as films stored at 60°C for 1 and 2 weeks, as presented in Figs. 12 and 13 and shown in Table 6. For the initial film samples, under the same dynamic stress, i.e., the continuously increasing ramp force from 1.0 to 18.0 N at the rate of 1.0 N/min, a smaller Young's modulus accompanied with a larger elongation rate was

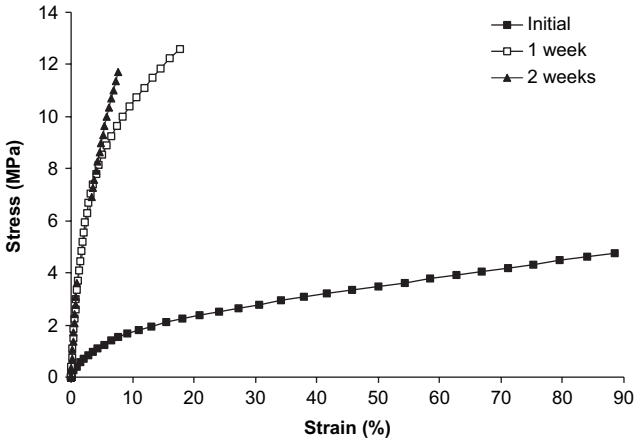


FIGURE 12 **Typical Stress-Strain Curves of Partially Neutralized Poly(MA-EA) Films Stored at 60°C (Tested at 25°C).**

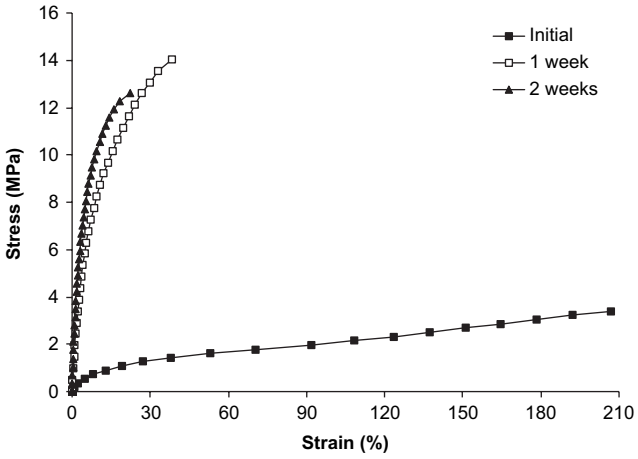


FIGURE 13 **Typical Stress-Strain Curves of Un-Neutralized Poly(MA-EA) Films Stored at 60°C (Tested at 25°C).**

observed for the un-neutralized poly(MA-EA) films (1.3 MPa and 45.5%/min) as compared to those neutralized (3.3 MPa and 12.3%/min; Table 6). This further indicated that the un-neutralized films were more flexible or pliable than those neutralized at the initial time of stability test. Similarly, an increase in softness or pliability was demonstrated for both the initial neutralized and un-neutralized poly(MA-EA) films when tests were performed at 37°C than measured at 25°C, as indicated by the decreased Young's modulus and increased elongation rate when tested at 37°C for each polymeric film system. However, at both high and low testing temperatures, the un-neutralized poly(MA-EA) films were more pliable or softer than those neutralized as demonstrated by the significantly smaller Young's modulus and larger elongation rate of the un-neutralized systems in each case (Table 6).

Upon accelerated storage at 60°C, the obvious changes of stress-strain curves from a typical ductile behavior to a more brittle behavior, together with the increased Young's modulus and decreased elongation rate for both partially neutralized and un-neutralized poly(MA-EA) films, further confirmed that both films became more brittle and harder or lost their flexibility especially during the first week of storage (Figs. 12, 13 and Table 6). Upon one week storage at 60°C, the Young's modulus increased from 3.3 to 25.1 MPa with a change rate of 21.8 MPa per week for the neutralized poly(MA-EA) films, while for the un-neutralized systems, the Young's modulus increased from 1.3 to 24.8 MPa with a change rate of 23.5 MPa per week. Similarly, the elongation rate reduced from 12.3%/min to 4.7%/min with a change rate of –7.6%/min per week for the neutralized films, while for the un-neutralized systems, the elongation rate reduced from 45.5 to 9.2%/min with a change rate of –36.3%/min per week (Tables 6, 7 and Fig. 14). This indicated that, although the Young's modulus and elongation rate of both partially neutralized and un-neutralized poly(MA-EA) films significantly changed, their change magnitude and rate were much greater for the un-neutralized films (23.5 MPa, 23.5 MPa/week, 36.3%/min and 36.3%/min/week) than for those neutralized (21.8 MPa, 21.8 MPa/week, 7.6%/min and 7.6%/min/week) upon one week storage at 60°C (Table 7 and Fig. 14).

Both creep-recovery and stress-strain tests suggested that the un-neutralized poly(MA-EA) films were more flexible and pliable compared to those partially neutralized at all studied conditions. As illustrated in Fig. 5, for the partially neutralized poly(MA-EA) at pH 5.0, certain percentage of the carboxylic acid groups had been ionized to the negatively-charged COO^- along polymer side chains. In comparison, the un-neutralized poly(MA-EA) at pH 2.9 existed mainly with the un-ionized carboxylic acid functional groups COOH. During the polymer chain network re-arrangement at the stage of film formation or during accelerated stability storage, for the un-neutralized poly(MA-EA), the predominant Van del Waals forces, especially the H-bonding between un-ionized carboxylic acid groups, might have facilitated the polymer interpenetration and assisted the entanglement of polymer chains. As discussed by Lecomte et al. (2004), H-bonding could be expected to promote the polymer chain miscibility. The promoted polymer chain miscibility or facilitated polymer chain interaction suggested a higher polymer

TABLE 6 **Stress-Strain Test Results for Partially Neutralized and Un-Neutralized Poly(MA-EA) Films Stored at 60°C for 1 and 2 Weeks**

Sample	Storage period	Stress-strain test temperature (°C)	Young's modulus (MPa ± SD)	Elongation rate (%/min ± SD)
Partially neutralized poly(MA-EA) films	Initial	25	3.3 ± 0.4	12.3 ± 1.9
		37	1.4 ± 0.2**[b]	29.7 ± 3.4**[b]
	1 week	25	25.1 ± 6.1**[d]	4.7 ± 0.8**[d]
	2 week	25	24.3 ± 7.3	3.5 ± 0.6
Un-neutralized poly(MA-EA) films	Initial	25	1.3 ± 0.2**[a]	45.5 ± 7.2**[a]
		37	0.6 ± 0.1*[b], *[c]	85.5 ± 11.3**[b], **[c]
	1 week	25	24.8 ± 4.6**[d]	9.2 ± 2.3**[d]
	2 week	25	24.2 ± 3.9	10.1 ± 1.7

*$p < 0.05$, Student's *t*-test.
**$p < 0.01$, Student's *t*-test.
[a]Young's modulus or elongation rate comparison of the initial partially neutralized and un-neutralized poly(MA-EA) films tested at 25°C.
[b]Young's modulus or elongation rate comparison of the initial partially neutralized or un-neutralized poly(MA-EA) films tested at 25°C and 37°C.
[c]Young's modulus or elongation rate comparison of the initial partially neutralized and un-neutralized poly(MA-EA) films tested at 37°C.
[d]Young's modulus or elongation rate comparison of the partially neutralized or un-neutralized poly(MA-EA) films tested at 25°C, initial samples and films stored at 60°C for 1 week.

TABLE 7 **Change Magnitude and Rate of Young's Modulus and Elongation Rate for Partially Neutralized and Un-Neutralized Poly(MA-EA) Films Stored at 60°C for 1 and 2 Weeks (Tested at 25°C)**

		Young's modulus (MPa)		Elongation rate (%/min)	
Sample	Storage period	Change magnitude (MPa)	Change rate (MPa/week)	Change magnitude (%/min)	Change rate (%/min/week)
Partially neutralized poly(MA-EA) films	Initial 1 week	21.8	21.8	–7.6	–7.6
	1 – 2 week	–0.8	–0.8	–1.2	–1.2
Un-neutralized poly(MA-EA) films	Initial 1 week	23.5	23.5	–36.3	–36.3
	1 – 2 week	–0.6	–0.6	0.9	0.9

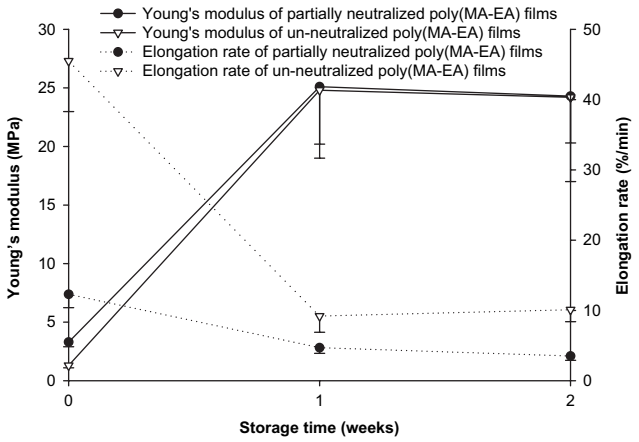


FIGURE 14 **Influence of Accelerated Storage at 60°C on Young's Modulus and Elongation Rate of Poly(MA-EA) Films (Tested at 25°C).**

chain mobility and might contribute to the flexibility or softness of un-neutralized poly(MA-EA) films. While for the partially neutralized poly(MA-EA), the possible repulsive force generated from the negatively-charged polymer side chains might have limited or restricted the polymer chain miscibility or polymer chain interpenetration and entanglement, i.e., the polymer chain mobility. Therefore, the partially neutralized poly(MA-EA) films was found to be more rigid and stiffer than those un-neutralized. However, at the initial time, there was no significant difference between dissolution profiles of partially neutralized and un-neutralized poly(MA-EA)-coated pellet-filled capsules (Table 2, Figs. 2 and 3), suggesting that the physical difference between neutralized and un-neutralized poly(MA-EA) coating films did not have any significant impact on drug release at the initial time of stability study.

In addition, both creep-recovery and stress-strain tests indicated that both partially neutralized and un-neutralized poly(MA-EA) films became more rigid and stiffer upon storage at 60°C, suggesting that both neutralized and un-neutralized polymer particles had experienced further coalescence and formed more densely packed network during storage. In pharmaceutical

manufacturing, the further coalescence of polymer coating films is the so-called curing process (Williams & Liu, 2000) and, from a stability point of view, it is also an aging phenomenon. Similar physical aging of acrylic polymer films has been previously reported (Gutierrez-Rocca & McGinity, 1993). However, the magnitude and rate of mechanical changes or physical aging were much more for the un-neutralized poly(MA-EA) films than for those neutralized (Tables 5, 7 and Figs. 11, 14). Mechanical data also showed that the higher the temperature, the higher the softness or mobility of polymer chains. Therefore, upon accelerated stability storage at 60°C, the higher softness or mobility of un-neutralized polymer chains, probably driven by the strong H-bonding, might have promoted more polymer-polymer interpenetration or polymer chain re-arrangement and led to the formation of a more densely packed network and less permeable coating lacquer. This extensive physical curing or aging effect experienced by the un-neutralized poly(MA-EA) coating films might contribute to the significantly retarded drug dissolution rates of un-neutralized polymer-coated pellets upon accelerated storage at 60°C (Table 2 and Fig. 3). In comparison, the less flexibility or mobility of partially neutralized polymer chains, possibly caused by the repulsion of negatively charged COO^-, might have limited the polymer-polymer interpenetration and entanglement and resulted in a limited or restricted coalescence or network formation for the neutralized systems upon storage. Therefore, the partially neutralized poly(MA-EA)-coated pellet-filled capsules could maintain a constant drug release rate over 2 weeks upon accelerated stability storage at 60°C (Table 2 and Fig. 2).

CONCLUSION

The effect of neutralization of poly(methacrylic acid-co-ethyl acrylate) on drug release from enteric-coated pellets under accelerated stability storage at 60°C was investigated. Drug-loaded pellets were enteric-coated with partially neutralized (pH 5.0) or un-neutralized (pH 2.9) poly(MA-EA). Drug release evaluation in 0.1 N HCl/pH 6.8 buffer indicated that neutralization of poly(MA-EA) did not exhibit any significant effect on drug dissolution except for in the stability samples. A significantly retarded drug release rate was observed for the un-neutralized poly(MA-EA)-coated pellet-filled capsules when stored at 60°C while no aging effect on drug release was shown for the partially neutralized polymer-coated pellet-filled capsules. Effect of neutralization on the physicochemical properties of poly(MA-EA) latex, as well as the morphological and mechanical properties of poly(MA-EA) films and coated pellets, particularly the aging influence, were investigated and correlated with the observed dissolution phenomena.

Dynamic mechanical analysis (DMA) showed that the un-neutralized poly(MA-EA) films were more flexible and pliable than those partially neutralized at all studied conditions. However, the difference in film mechanical properties caused by neutralization of poly(MA-EA) did not exhibit any significant impact on drug dissolution at the initial time of stability study. Upon accelerated storage at 60°C, both partially-neutralized and un-neutralized poly(MA-EA) films became more rigid and stiffer. However, the un-neutralized films were affected more than those neutralized. The higher flexibility or mobility of un-neutralized polymer chains, probably driven by the strong H-bonding, might have led to a denser and less permeable network formation upon storage, therefore, resulting in a significant slower dissolution rate over time for the un-neutralized poly(MA-EA)-coated pellet-filled capsules. In comparison, the less flexibility or mobility of partially neutralized polymer chains, possibly caused by the repulsion of negatively charged COO^-, might have resulted in a limited or restricted dense network formation upon storage, therefore, exhibiting no remarkable effect on drug dissolution over time for the partially neutralized poly(MA-EA)-coated pellet-filled capsules. In conclusion, neutralization of poly(MA-EA) improved the stability of poly(MA-EA) enteric-coated pellets upon accelerated stability storage at the studied conditions.

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