

## Polyampholyte Acrylic Latexes for Tablet Coating Applications

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**ABSTRACT:** Polyampholyte latexes can exist within a certain pH range as low-viscosity aqueous dispersions, while upon a pH shift to the vicinity of the isoelectric point they undergo ionic coacervation. Three classes of coacervation latexes were synthesized and evaluated for their suitability for use in tablet coating applications. Pharmaceutical tablet coatings are commonly based on hydroxypropyl methyl cellulose, poly(vinyl alcohol), and acrylic polymers. Because of the high viscosity of their aqueous solutions, and to the consequent required low concentrations of the tablet coating polymers in the coating solutions to enable sufficiently low viscosity for effective spray application, the current commercial pharmaceutical tablet coating technology requires the removal of large amounts of water during the manufacturing process. In this work, films prepared from high-solids, low-viscosity coacervated acrylic latexes showed good hardness, very low tackiness, an excellent combination of optical properties, and very low water vapor permeability. © 2013 Wiley Periodicals, Inc. *J. Appl. Polym. Sci.* **2014**, *131*, 40049.

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### INTRODUCTION

Polyampholytes are charged macromolecules carrying both acidic and basic groups.<sup>1–3</sup> One example of synthetic polyampholytes is vinyl copolymers that possess charged acidic and basic groups on different monomer units.<sup>4–6</sup> These polymers can exist with extended storage stability in the form of low-viscosity aqueous solutions or dispersions, while upon a pH shift to the vicinity of the isoelectric point they undergo ionic coacervation.<sup>2,3,7–10</sup> There are several classes of polyampholytes based on the sensitivity of their ionic groups to neutralization upon change in pH.<sup>2</sup> Polyampholytes may contain weak acid groups (e.g., carboxylic) and strong base groups (e.g., quaternary ammonium). These polymers can form low-viscosity solutions or dispersions at acidic pH where the weak acid groups are not ionized. Upon increase in pH the weak acid groups deprotonate and ionically bind to the strong base groups, resulting in polymer coacervation (Figure 1a, Class A).<sup>9–12</sup> Another polyampholyte class includes polymers with strong acid groups (e.g., sulfonate) and weak base groups (e.g., amine). These polymers can form low-viscosity solutions or dispersions at basic pH where the weak base groups are not ionized. Upon decrease in pH the weak base groups become protonated and ionically bind to the strong acid groups, resulting in polymer coacervation (Figure 1b, Class B). Ionic coacervation can also occur with a mixture of two ionic polymers, anionic and

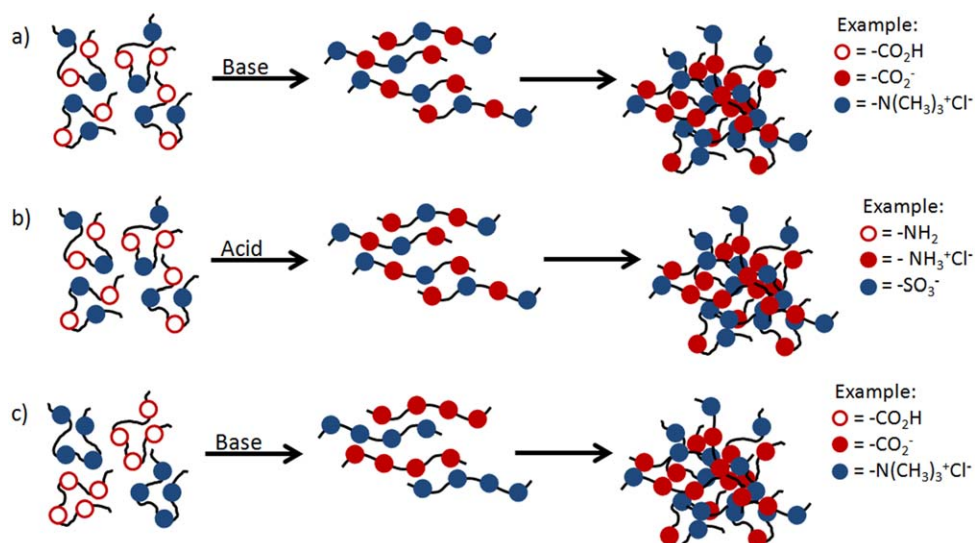
cationic, forming polyelectrolyte complexes (PEC) that exhibit amphoteric character.<sup>13–18</sup> When one polymer includes weak acid or base (e.g., carboxylate), while the other type includes strong acid or base functionality with the opposite charge (e.g., quaternary ammonium), the polymer mixtures can form low-viscosity solutions or dispersions in the pH range where the weak acid or base groups are not ionized. Upon pH shift, the ionization of the weak acid or base functionalities occurs, causing coacervation (Figure 1c, Class C).

Among the variables previously studied in PEC-forming polyelectrolytes were the charge density (the number of charged sites per unit length of the macromolecule), the distribution of these charged sites along the macromolecule, and the effect of polymer molecular architecture (including branching and crosslinking).<sup>14</sup> While those studies typically included complexes where at least one component was a water soluble macromolecule, in this work the coacervation occurred between anionic and cationic latexes that were dispersible, but insoluble in water.

Polyampholytes have found application in areas such as lithographic film,<sup>19</sup> drag reduction,<sup>20</sup> membranes,<sup>21</sup> water-based coatings,<sup>22</sup> papermaking,<sup>23</sup> skin care,<sup>24</sup> and controlled drug release.<sup>25</sup> In addition, polyampholyte latexes have been developed for various types of fast-setting industrial coatings (on cement, metal, glass, wood, and other surfaces).<sup>10,26</sup>

Additional Supporting Information may be found in the online version of this article.

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**Figure 1.** Schematic representations of polymer coacervation: (a) Class A: Amphoteric polymer having weak anionic and strong cationic groups; (b) Class B: Amphoteric polymer having strong anionic and weak cationic groups; (c) Class C: A combination of two ionic polymers, anionic and cationic. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

In this work, polyampholyte acrylic latexes were evaluated for their potential to be used as pharmaceutical tablet coatings. Tablets are by far the most popular dosage form for delivery of active pharmaceutical ingredients (APIs) to the human body. Most tablets on the market today are coated for various reasons using a wide variety of materials.<sup>27,28</sup> The tablet coating materials are primarily based on hydroxypropyl methyl cellulose (HPMC), poly(vinyl alcohol) (PVOH), and acrylic polymers.<sup>29</sup> Because of the high viscosity of their aqueous solutions,<sup>30,31</sup> and to the consequently required low concentrations of the tablet coating polymers in the coating solutions to enable sufficiently low viscosity for effective spray application, the current commercial pharmaceutical tablet coating technology requires the removal of large (>75% of the applied solution is water) amounts of water during the tablet coating process. Development of tablet coating technology that minimizes the amount of water required to be removed during the drying step would be advantageous since it would significantly reduce coating manufacturing time and energy, resulting in customer cost savings. For example, the process time could be reduced by 43% if the solids level of coating systems were increased from 15 to 25 wt %.<sup>32</sup> The industry is looking for new coating materials that can be applied at high solids. The objective of our study was to evaluate polyampholyte latexes for their potential to be used as novel high-solids, low-viscosity tablet coatings with a pH-tunable formation and dissolution. These coatings could be useful in pH-tunable release of active pharmaceutical ingredients in different stages of the digestion process (i.e., gastric release vs. intestinal release).

## EXPERIMENTAL

### Materials

Butyl acrylate (BA), methyl methacrylate (MMA), methacrylic acid (MAA), [2-(methacryloyloxy)ethyl]-trimethylammonium chloride (QMA), 2-acrylamido-2-methyl-1-propanesulfonic acid

(AMPS), 2-(dimethylamino)ethyl methacrylate (DMAEMA), *t*-butyl hydroperoxide, sodium 1-hydroxymethanesulfonate (sodium formaldehyde sulfoxylate) and sodium lauryl sulfate were purchased from Sigma–Aldrich. Arquad 18-50 (octadecyl-trimethylammonium bromide) was obtained from Akzo Nobel. Eudragit™ L100 copolymer of methyl methacrylate and methacrylic acid) was obtained from Evonik. HPMC E6 and HPMC VLV are Dow Chemical products. All of these chemicals were used as received. The structures of acrylate monomers used in the synthesis of latexes are shown in Figure 2. In all latex syntheses in this study, AMPS was predominantly in the ionized form (as shown in the Figure 2). The abbreviation “AMPS” is used in this article for both the nonionized and ionized form of this monomer. The following pH reference buffers from Fisher Scientific were used: SB96-500 (pH 2.00; potassium chloride–hydrochloric acid), SB98-500 (pH 4.00; potassium hydrogen phthalate, 0.05 M), SB104-500 (pH 6.00; potassium dihydrogen phosphate, 0.05 M), SB108-500 (pH 7.00; potassium phosphate monobasic–sodium hydroxide, 0.05 M), SB112-500 (pH 8.00; potassium phosphate monobasic–sodium hydroxide, 0.05 M), and SB116-500 (pH 10.00; potassium carbonate–potassium borate–potassium hydroxide, 0.05 M). Other pH buffers from this work (with pH values of 5.00, 5.50, 6.50, 7.50, 8.50, 9.00, and 9.50) were prepared by mixing the above Fisher Scientific at the ratios calculated and measured to give the target pH values.

### Synthesis of Polyampholyte Latexes

The polyampholyte latexes were prepared using a previously described two-step process.<sup>10,24,26</sup> The first step included synthesis of a polystyrene latex seed stabilized with either Arquad 18-50 (a cationic surfactant) or with sodium lauryl sulfate (an anionic surfactant). In the subsequent emulsion polymerization synthesis of the latexes, the latex seed stabilized with a cationic surfactant was used to prepare weak acid/strong base polyampholyte latexes and cationic latexes, while the latex

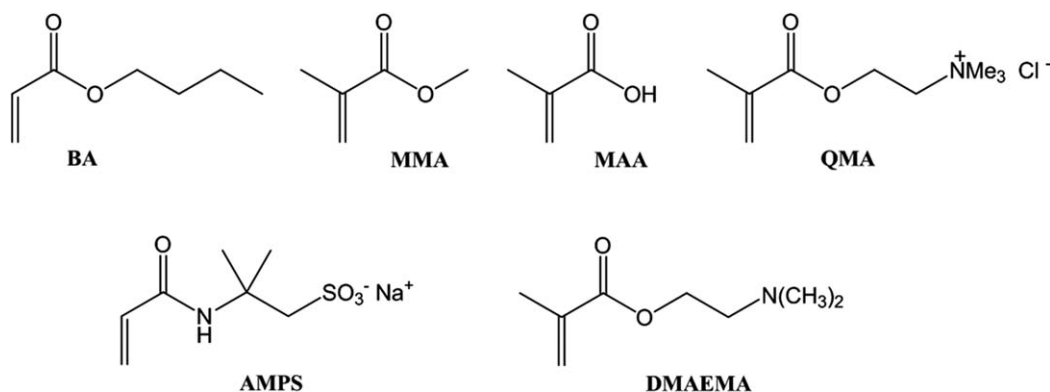


Figure 2. Structures of monomers used in latex syntheses.

seed stabilized with anionic surfactant was used to prepare strong acid/weak base polyampholyte latexes and anionic latexes. In one approach, latexes were prepared in a glass reactor using a literature procedure.<sup>10</sup> In an alternative approach, latexes were prepared in a high-throughput mode using semi-continuous parallel pressure reactor (ScPPR) manufactured by Freeslate.<sup>33</sup> This reactor enables simultaneous synthesis of 24 latexes. In this work, JMP design-of-experiment (DOE) methodology<sup>34</sup> was used to investigate structure–property relationship of weak acid/strong base polyampholyte latexes. A D-optimal design algorithm<sup>34</sup> was used to design a library of 24 weak acid/strong base polyampholyte latexes with 20 different compositions, and the whole library was run twice. The monomer compositions for the library of these latexes are shown in the Supporting Information Table S1. JMP software<sup>34</sup> was applied to develop statistical models for several latex properties and to propose a latex composition with a desirable balance of properties.

#### Particle Size Determination

Particle sizes were determined by dynamic light scattering using a Brookhaven 90Plus Particle Size Analyzer (Brookhaven Instruments). A polystyrene standard (0.1  $\mu\text{m}$ ) was used to calibrate the instrument. The sample was diluted in DI water prior to measurement to avoid saturating the detector. The average count rate was in the range of 400–500 kcps.

#### Viscosity of Latexes

The viscosity of the latexes was determined using a Brookfield DV-II+ viscometer using the RV1 spindle at 100 rpm.

#### Differential Scanning Calorimetry

The glass transition temperature ( $T_g$ ) of latexes was determined by differential scanning calorimetry (DSC) using an Autosampling DSC 2920 differential scanning calorimeter (TA Instruments). In a typical procedure, the wet latex sample was placed in preweighed aluminum DSC pan. The pan with the latex sample was stored at ambient temperature for 2–3 days in a box equipped with a flow of dry nitrogen. The mass of the DSC pan with dry latex samples was recorded to determine the amount of dry latex sample. In DSC analysis aluminum pans with dry latex samples are heated from  $-50^\circ\text{C}$  to  $120^\circ\text{C}$  at  $10^\circ\text{C min}^{-1}$  under nitrogen.

#### Screening of Setting Efficiency

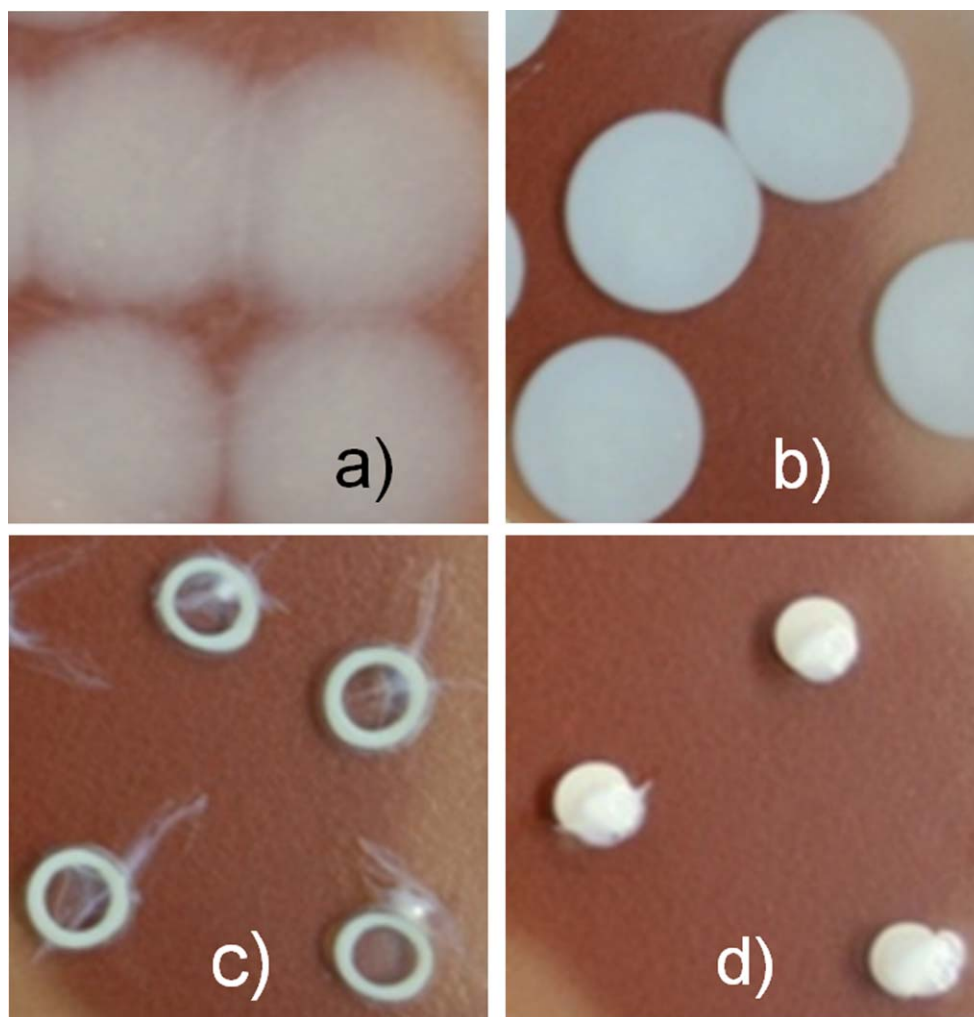
A series of buffers with pH from 2.0 to 10.0 were used in this screening. In a typical procedure, about 7 mL of buffer were placed in a Petri dish ( $60 \times 15 \text{ mm}^2$ ), then small droplets of the polyampholyte latex were carefully added with a pipette (Eppendorf 10–100  $\mu\text{L}$ ) onto the buffer surface, and the extent and rate of latex agglomeration was observed. Figure 3 shows representative examples of different coacervate setting efficiencies. In the absence of setting, the buffer droplets quickly dispersed throughout the buffer. If the latex droplets started to disperse through the buffer, but then agglomerated, the setting was categorized as weak. If only minor spreading of a latex droplet through the buffer occurred, followed by intensive latex agglomeration at the latex/buffer interface that stopped further droplet spreading, the setting was categorized as strong. In that case, predominant latex agglomeration at the latex/buffer interface typically resulted in a ring-like morphology. If the latex droplets agglomerated almost instantaneously after the contact with a buffer (with a negligible spreading of the latex droplet) to give small balls of quick-set latex, the setting was categorized as fast and strong.

#### Film Casting

Latexes were cast onto glass plates using a 2.5"  $\times$  2.5" square draw-down bar. The resulting latex films were dried at ambient temperature for 2 days and the films were then removed from the glass plates using a stainless steel scraper. The typical thickness of the resulting films was in the range from 130 to 170  $\mu\text{m}$  for all latex types. In the determination of water vapor transmission rate and the puncture force, all values were normalized for the film thickness. Therefore, small variations in the thickness of prepared films did not have a major influence of the reported values.

#### Pendulum Hardness Measurement

Hardness of the latex films was measured using a Pendulum Hardness Tester (König method, BYK Gardner) with a digital counter. The instrument was calibrated by measuring the pendulum hardness of a standard prior to use. The procedure as per König is based on the measurement of the damping of a pendulum oscillating on the film. The time in seconds for the pendulum deflection to slow down to a specific value is measured, and it is considered proportional to the hardness of film.



**Figure 3.** Examples of different latex setting efficiencies: (a) no setting; (b) weak setting; (c) strong setting; (d) fast, strong setting. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

At least five measurements on different areas of the film were made for each film and an average was taken.

#### Tackiness Measurement

The tackiness data were generated using TA-XTplus Texture Analyzer (Texas Instruments) equipped with a 5-kg load cell. A glass plate coated with a latex film was placed on a custom made stainless steel holder. The principle of operation for the instrument involves a probe (model TA-57R) moving to contact the film surface at a fixed rate of  $0.01 \text{ mm s}^{-1}$ . A constant force (100.0 g) is applied to the contact surface for 2.0 s; the instrument then removes the probe from the film surface at a fixed rate of  $5.00 \text{ mm s}^{-1}$ . The force needed to remove the probe is recorded as a function of time. The peak force of removal is defined as tack, or adhesive strength. At least ten measurements were made on different spots on each film and an average value was taken.

#### Clarity Measurement

A PG-5500 digital photometric unit (Gardner Laboratory) was used to quantify film clarity. Clarity measurements were made

at four different spots on each film. The average value was then recorded.

#### Transmission and Haze Measurement

Transmission and haze of prepared films were measured by a Haze-Gard Plus (BYK Gardner, Cat No. 4725). The transmission was measured between the wavelengths of 400–700 nm, according to the procedure in the equipment manual. Both haze and transmission are reported as percentages.

#### Water Vapor Transmission Rate Measurement

Water vapor transmission rates were measured using the “dry cup” method. Calcium chloride (2.0 g) was weighed into a 4 oz jar and allowed to sit at 50 % relative humidity ( $73^\circ\text{C}$ ) with a closed cap for 1 h. Next, a small amount of vacuum grease was placed around the edge of the jar’s mouth. Films were cut into  $\sim 1.3''$  diameter circles using a metal punch. The film samples were placed on top of the jar and a  $1''$  diameter open hole lid was placed on top. The lid was tightened down to form a seal, while making sure not to crack the film. Vials were then placed into a temperature-humidity chamber equipped with an Environ-Cab controller (Lab-Line Instrument) set to 75% relative



**Table I.** The Composition and Characterization of Weak Acid/Strong Base Polyampholyte Latexes

Latex <sup>a</sup>	Monomers (wt %)				Molar ratio	$T_g$ (°C)	Setting at pH 7.0
	BA	MMA	MAA	QMA	MAA/QMA		
1	55.54	41.40	1.19	1.87	1.54	5.4	Strong
2	56.62	39.73	1.78	1.87	2.30	2.5	Fast, strong
3	53.79	40.09	2.38	3.74	1.54	4.1	Weak
4	50.00	46.35	1.78	1.87	2.30	8.1	Fast, strong
5	45.00	51.35	1.78	1.87	2.30	15.6	Strong
6	40.00	56.35	1.78	1.87	2.30	25.5	strong

<sup>a</sup>Latexes 1, 2, and 3: The effect of MAA and QMA; Latexes 4, 5, and 6: The effect of BA level.

humidity and 25°C. The total weight of the jar, lid, films, and calcium chloride was recorded and measured again every 24 h for 5 days. A linear regression of the mass gain ( $m$ ) plotted against time ( $t$ ) was used to obtain a mass transfer rate. The mass transfer rate was divided by the area of the exposed film to provide the water vapor transmission (WVT) rate ( $\text{g cm}^{-2} \text{h}^{-1}$ ),

$$\text{WVT} = \frac{m_t}{A},$$

where  $m_t$  is the change in mass with time ( $\text{g h}^{-1}$ ) and  $A$  is the exposed film area in  $\text{cm}^2$ . The film permeability was calculated according to the following equation:

$$\text{Permeability} = \frac{\text{WVT} \times l}{S(\text{RH}_2 - \text{RH}_1)},$$

where  $l$  is the film thickness,  $S$  is the saturated vapor pressure of water at 25°C,  $\text{RH}_2$  is 0.75 (75% relative humidity) and  $\text{RH}_1$  is 0. The  $S(\text{RH}_2 - \text{RH}_1)$  term gives the driving force for mass transfer of water through the film. The average water vapor permeation is reported in gram per Pascal hour meter.

#### Puncture Strength Measurement

The mechanical strength of films was measured using a TA-XT2i Texture Analyzer (Texas Instruments) equipped with a 25-kg load cell. The rupture force and elongation distance were recorded by piercing the films with a probe (model TA-57R) and film extensibility fixture (TA-108S5) with 9-mm round openings (modified from the original 10 mm openings). The fixture was aligned under the probe, and the films were compressed until failure with 10 g of force at a speed of  $2.1 \text{ mm s}^{-1}$ . The normalized puncture force was calculated using the following equation:

$$\text{Normalized puncture force} = \frac{[\text{film rupture strength (g)}]}{[\text{thickness of film (mm)} \times 5000]}$$

The puncture force measurements were normalized for the film thickness, compensating for small variations in thickness of film samples.

#### Preparation of Tablet Coatings

Tablet coatings were prepared over substrate G placebo tablets that contained 67.5% fast-flow lactose (FFL), 30.0% microcrystalline cellulose, 2.0% talc, and 0.5% Mg-stearate. Polyampholyte latexes were sprayed over these tablets using either a tablet

coater (LDCS Vector Laboratory Development Coating System) or an airbrush gun. For preparation of a coating from a combination of anionic and cationic latex, placebo tablets were adhered to a glass slide using a double-sided tape and the cationic latex 22 was sprayed over them using an airbrush gun. After this, anionic latex 18 that was adjusted to pH 8 and contained carmine (1.42 wt % based on latex) and SDS (0.14 wt % based on latex) was sprayed over the coated tablets in a second step while the cationic latex was still wet.

## RESULTS AND DISCUSSION

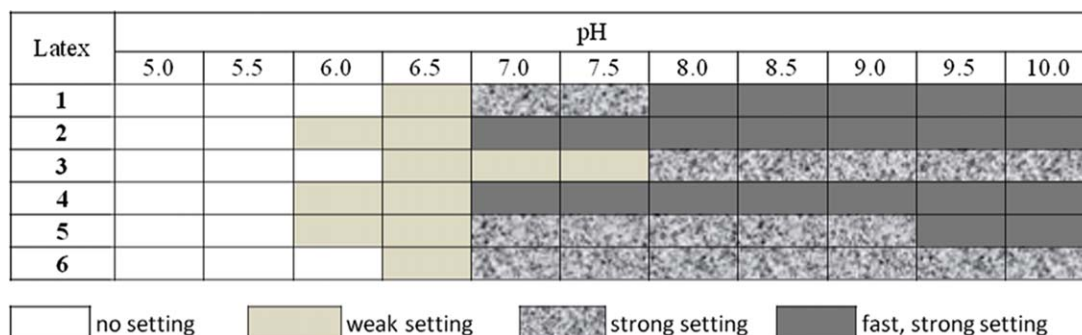
Three classes of polyampholytes were studied in this work: latexes with weak acid and strong base groups (Figure 1, Class A), latexes with strong acid and weak base groups (Figure 1, Class B), and mixtures of oppositely charged latexes (Figure 1, Class C). Latexes from the Class A were studied in some detail, while in the screening of latexes from the Classes B and C the objective was less intensive and done solely to perform a preliminary demonstration of the potential suitability of these polyampholyte classes for tablet coating applications, and not to determine which latex structures were optimal for this application.

#### Latexes with Weak Acid Groups and Strong Base Groups

Several polyampholyte latexes with weak acid and strong base groups were synthesized. Their composition and properties are shown in Table I and Figure 4. These latexes have compositions similar to polyampholyte latexes that were previously synthesized at the Dow Chemical.<sup>10,24,26</sup> Latexes 1 through 6 had 38 to 40 wt % solids, pH of 2.2 to 2.5, and particle size of 125–137 nm. At strongly acidic pH the carboxylic groups were not ionized and these latexes were stable as low-viscosity dispersions. Increase in pH resulted in deprotonation of carboxylic groups, and their ionic binding to quaternary ammonium groups causing latex setting.

The setting of coacervation latexes at a certain pH is controlled by the effect of ionic charges at that pH and by the latex  $T_g$ . To better understand each of these effects, two composition variables were studied in this work: the level of ionic monomers MAA and QMA (the control of ionic charges), and the level of BA (the control of  $T_g$ ).

The level of ionic (or ionizable) monomers MAA and QMA showed a dramatic effect on setting at pH 7.0. Latex 1 showed strong setting at pH 7, while fast and strong setting was



**Figure 4.** Setting efficiency of weak acid/strong base latexes. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

observed at pH 8 and above. In the synthesis of latex 2 the level of MAA was increased by 50% relative to that in the latex 1, while the level of QMA was kept the same as in the latex 1. The setting efficiency of this latex increased relative to that of latex 1, and fast/strong setting was observed even at pH 7. However, in the synthesis of latex 3 the levels of both MAA and QMA were doubled relative to the levels in latex 1, and the setting efficiency decreased. This latex showed weak setting at pH 7, and it did not exhibit fast/strong setting even at pH 10. These results demonstrate that for the desired level of setting (fast and strong) the level and balance of ionic groups should be carefully selected. Methacrylic acid is weak acid with  $pK_a \sim 4.5$ ,<sup>35</sup> while QMA is strong base ionizable over the whole pH range (the quaternary ammonium functionalities are not pH-responsive.<sup>36</sup> To balance this difference in ionizability of functionalities for effective setting, the level of carboxylate groups must be in excess relative to the level of trimethylammonium groups. In this study, a desirable level of setting was observed in latexes 2 and 4 with the molar ratio MAA/QMA = 2.30, while at the lower molar ratio MAA/QMA = 1.54 (in latexes 1 and 3) the setting was less effective.

The effect of pH on the setting of weak acid/strong base polyampholyte latexes has been studied.<sup>10</sup> Zeta potential measurements were used to characterize the electrostatic properties of the latex. Upon pH change of the latex the zeta potential changes, and at the pH where it is close to zero the latex particles rapidly undergo the setting process. For weak acid/strong base latexes, at low pH latex particles are cationic and the zeta potential is positive. Upon increase in the pH, the charge of latex particles monotonically decreases until pH 7–8, where the zeta potential is essentially zero. At this isoelectric point (IEP) the latex particles undergo ionic coacervation, and the latex setting occurs. The level of MAA and QMA in the latex can influence the IEP and the pH at which the latex setting occurs.

Another factor that has critical effect on setting is the  $T_g$  of the latex. According to the Gordon–Taylor equation<sup>37</sup> and Fox equation,<sup>38</sup> the  $T_g$  of A/B copolymer can be calculated from the  $T_g$  values of the corresponding homopolymers A and B at the respective weight fractions of polymers A and B in the A/B copolymer. The glass transition temperatures of poly(BA), poly(MMA), and poly(MAA) are listed as 219, 378, and 501K, respectively.<sup>39</sup> Therefore, the  $T_g$  of a latex increases with decrease in the BA level. In the synthesis of latexes 2, 4, 5, and

6 the same levels of MAA and QMA were used, while the ratio of BA and MMA was gradually reduced. Latexes 2 and 4 have high BA levels and  $T_g$  below ambient temperature, and upon setting they give “soft” agglomerates that enable fast, strong and irreversible setting at pH 7. Latexes 5 and 6 have lower BA levels and higher  $T_g$  values, and upon setting they give “hard” agglomerates that still exhibit strong setting, but at a slower setting rate. For the latex 5 the fast and strong setting was observed for the latex 5 at pH 9.5 and above, while for the latex 6 it was not seen even at pH 10. Slightly reduced level of MAA and QMA in latexes 1 and 3 resulted in a decrease in the setting efficiency (as described above), but they did not have a major effect on  $T_g$ .

The effect of BA level on the mechanical properties of the latex films was also studied (Table II). Films from latexes 2 and 4 (prepared with high BA levels) had  $T_g$  values below ambient temperature and therefore showed substantial tackiness<sup>40</sup> that is detrimental for the tablet coating application. Films from latexes 5 and 6 (prepared with lower BA levels) had  $T_g$  values above ambient temperature and showed very low tackiness. The film from latex 6 had nil tackiness, but its hardness was too high and this film was brittle. A balance of properties is sought from polymers suitable for use in tablet coating applications.

A desirable latex composition would enable fast and strong setting and have excellent mechanical properties (high hardness and nil tackiness). In this initial set of weak acid/strong base latexes 1–6, two latexes (2 and 4) exhibited fast and strong setting, but also undesirable tackiness. The latexes 5 and 6 showed very low tackiness, but their setting efficiency was lower than for latexes 2 and 4. Therefore, it seems impossible to design a latex composition that would show optimal performance in all testing methods critical for tablet coating applications. Instead, our goal was to identify

**Table II.** Mechanical Properties of Weak Acid/Strong Base Latex Films

Latex	$T_g$ (°C)	Hardness <sup>a</sup> (König)	Tackiness <sup>a</sup> (g)
2	2.5	0	609
4	8.1	4	101
5	15.6	12	3
6	25.5	46	0

<sup>a</sup>Reported values are averages of five to seven measurements.

**Table III.** The Composition and Characterization of Strong Acid/Weak Base Polyampholyte Latexes

Latex	Monomers (wt %)				Molar ratio		$T_g$ (°C)	Setting at pH 4.0
	BA	MMA	AMPS	DMAEMA	AMPS/DMAEMA			
8	57.50	40.57	0.51	1.42	0.25	1.4	Fast, strong	
9	52.50	45.57	0.51	1.42	0.25	5.8	Strong	
10	47.50	50.57	0.51	1.42	0.25	20.5	Strong	
11	42.50	55.57	0.51	1.42	0.25	21.6	Strong	
12	57.50	38.64	1.03	2.83	0.25	3.0	Fast, strong	
13	52.50	43.64	1.03	2.83	0.25	9.9	Fast, strong	
14	47.50	48.64	1.03	2.83	0.25	15.3	Fast, strong	
15	42.50	53.64	1.03	2.83	0.25	24.2	Fast, strong	

a monomer composition that would give a polyampholyte latex with a desirable balance of properties (at least a strong setting efficiency at pH 7.0, minimal film tackiness, and at least moderate hardness that would not lead to a brittle film). To determine such a latex composition, a design-of experiment (DOE) methodology<sup>34</sup> was applied. The following limits of monomer levels (wt %) were used: BA, 35–55; MMA, 0–64; MAA, 0.5–5.0; QMA, 0.5–5.0. The following constraints on MAA/QMA ratios were used:  $1.2 < (MAA/QMA)_{\text{molar}} < 6.0$ ;  $0.5 < (MAA/QMA)_{\text{wt}} < 2.5$ . These levels were chosen in order to test the effect of polymer  $T_g$ , the charge level, and the ratio of anionic and cationic charge on film properties, because they were already established to be key factors in film setting and performance. A library of 24 polyampholyte latexes with 20 different compositions was established based on D-optimal design algorithm. The monomer composition for these 24 latexes is shown in the Supporting Information Table S1. This 24-latex library was prepared in a high-throughput mode using semicontinuous parallel pressure reactor (ScPPR) manufactured by Freeslate<sup>33</sup> and the whole library was duplicated once. The properties of all latex samples were characterized, including  $T_g$ , setting efficiency, and tackiness of films prepared from these latexes. JMP statistical discovery software (version 9) from SAS<sup>34,41</sup> was used to analyze the DOE results. In the first stage, this software was used to develop three statistical models for three individual latex properties:  $T_g$  (linear regression), setting efficiency (logistic regression), and tackiness (linear regression). All three models are statistically significant. The graphical “Prediction Profiler” was used to predict impact of each monomer on latex properties ( $T_g$ , setting efficiency, and film tackiness), and for each of these properties the prediction formula was generated. The properties of latexes predicted by statistical models showed good agreement with experimental results, suggesting good predictive abilities of statistical models. For example, the statistical model for  $T_g$  predicted strong correlation of this property with the level of BA and MMA, and suggested that the low levels of MAA and QMA do not appear to be an important factor for the latex  $T_g$ . The second stage of DOE included multiple-response optimization of latex composition using a three-response prediction profiler (or “Multiple Profiler”).<sup>34,41</sup> All three prediction formulas (for  $T_g$ , setting efficiency, and tackiness) were simultaneously included in the generation of this three-response prediction profiler, in order to predict the latex composition with the desired balance of target

properties (maximal setting efficiency and minimal tackiness). This methodology predicted that the maximal desirability is reached for latex 7 with the following monomer composition (wt %): BA, 47.50; MMA, 47.8; MAA, 2.50; QMA, 2.20 (the molar ratio MAA/QMA = 2.73). It should be emphasized that this DOE methodology did not include actual synthesis of latex 7, and therefore it is not included in the Table S1 (in the Supporting Information). In our follow-up work, the latex 7 was synthesized in a bench-top reactor using a standard literature procedure.<sup>10</sup> This latex had  $T_g$  of 18.6°C, it showed strong setting at pH 7.0, and a film prepared with this latex showed a pendulum hardness (König) of 23 and nil tackiness. All these properties are close to the predicted values.

#### Latexes with Strong Acid Groups and Weak Base Groups

For our second class of polyampholytes, the objective was to develop latexes that contain sulfonate groups (strong acid) and amine groups (weak base) within the same latex. While the weak acid/strong base latexes from the Class A were studied in some detail, in the screening of strong acid/weak base latexes the primary objective was to demonstrate their potential suitability for tablet coating applications. For this class of polyampholyte latexes, our goal was not to determine an optimal latex composition for these applications, nor to undertake a detailed characterization of their films and coatings. In this study, 2-acrylamido-2-methyl-1-propanesulfonic acid (AMPS) was selected as a strong acid monomer. In the pH range used in this study, the sulfonic group of AMPS is fully ionized and therefore the sulfonate group is not pH-responsive.<sup>36,42</sup> 2-(dimethylamino)ethyl methacrylate (DMAEMA) was selected as a weak base monomer. It has  $pK_a$  of 8.4,<sup>43,44</sup> while the  $pK_a$  of its homopolymer is 7.0.<sup>45</sup> To balance this difference in ionizability of the sulfonate and the amine group for effective latex setting, the level of amine groups must be in excess relative to the level of sulfonate groups. Our preliminary screening of latexes from this class indicated that for latexes with an AMPS/DMAEMA molar ratio of 0.25, fast, strong setting can be obtained, while latexes with higher molar ratio of these monomers showed weak setting or no setting at all. Eight latexes were synthesized as copolymers of four monomers: BA, MMA, AMPS, and DMAEMA, and for all these latexes AMPS/DMAEMA molar ratio was 0.25. Their

Latex	pH					
	1% HCl	2.0	4.0	6.0	7.0	8.0
8	fast, strong setting	fast, strong setting	fast, strong setting	strong setting	strong setting	no setting
9	fast, strong setting	fast, strong setting	strong setting	strong setting	weak setting	no setting
10	fast, strong setting	fast, strong setting	strong setting	strong setting	weak setting	no setting
11	fast, strong setting	strong setting	strong setting	strong setting	weak setting	no setting
12	fast, strong setting	fast, strong setting	fast, strong setting	fast, strong setting	strong setting	no setting
13	fast, strong setting	fast, strong setting	fast, strong setting	strong setting	strong setting	no setting
14	fast, strong setting	fast, strong setting	fast, strong setting	strong setting	weak setting	no setting
15	fast, strong setting	fast, strong setting	fast, strong setting	strong setting	weak setting	no setting

fast, strong setting   
  strong setting   
  weak setting   
  no setting

**Figure 5.** Setting efficiency of strong acid/weak base latexes. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

composition and properties are shown in Table III and Figure 5. All latexes 8 through 15 had pH of 7.0–7.4. In this pH range the dimethylamino groups were not protonated, and these latexes were stable as low-viscosity dispersions. Decrease in pH resulted in the protonation of the dimethylamino groups and their ionic binding to the sulfonate groups, causing latex setting.

Latexes 12–15, prepared with high level of AMPS (1.03 wt %) and DMAEMA (2.83 wt %), showed, at pH 4.0, fast and strong setting. Among latexes prepared with low level of AMPS (0.51 wt %) and DMAEMA (1.42 wt %), only the low- $T_g$  latex 8 showed fast and strong setting at pH 4.0, while the latexes 9, 10, and 11 showed strong, but not fast setting. These results suggest that a high level of ionic groups is required for effective setting of latexes from this class. Also, these results are in agreement with the observed effect of  $T_g$  on the setting efficiency of weak acid/strong base latexes, where low- $T_g$  latexes 2 and 4 enabled fast and strong setting while latexes 5 and 6 with higher  $T_g$  values exhibited a slower setting rate. Films from latexes 8–15 were prepared and their mechanical properties was studied (Table IV). In this set of amphoteric latexes, latex 14 showed a desirable balance of properties. At pH 4.0 its setting is fast and strong. The film from this latex has very low tackiness and it is sufficiently hard without resulting in brittle character. Therefore, it was selected as the primary candidate from this set for further application tests.

**Table IV.** Mechanical Properties of Strong Acid/Weak Base Latex Films

Latex	$T_g$ (°C)	Hardness (König)	Tack force (g)
8	1.4	6.2 ± 3.8	170 ± 90
9	5.8	12.5 ± 3.1	8.8 ± 7.0
10	20.5	40.1 ± 9.9	0.3 ± 0.1
11	21.6	66 ± 15	0.3 ± 0.1
12	3.0	3.0 ± 0.0	315 ± 118
13	9.9	11.5 ± 1.6	29 ± 23
14	15.3	18.5 ± 1.6	0.3 ± 0.1
15	24.2	33.4 ± 7.8	0.3 ± 0.1

### Combination of Anionic and Cationic Latex

Development of tablet coatings from polyampholyte latexes with acid and base functionalities within the same latex could include several problems. Synthesis of polyampholyte latexes is more complicated and more expensive than the synthesis of common anionic and cationic latexes. Regulatory approval for latexes that simultaneously contain acid and base functionalities could be complicated. Therefore, instead of using single polyampholyte latex, separate anionic and cationic latexes were prepared and their mixtures were evaluated in tablet coating formulations. Similar to our approach in the study of strong acid/weak base latexes (Class B), the primary objective in the study of a combination of anionic and cationic latex was to demonstrate their potential suitability for tablet coating applications. Our goal was not to determine the optimal latex composition for these applications, nor to run a detailed characterization of their films and coatings. All anionic and cationic latexes from this study were synthesized from the same set of monomers as in the synthesis of weak acid /strong base polyampholyte latexes, but each contained only MAA or only QMA as the ionic monomer. The compositions of anionic latexes 16–19 and cationic latexes 20–23 made in this study are shown in Table V. The combinations of monomers in these latexes are similar to those in commercially available Eudragit polymers.

**Table V.** The Composition of Anionic and Cationic Latexes

Latex	Monomer (wt %)			
	BA	MMA	MAA	QMA
16	47.50	50.50	2.00	
17	47.50	49.50	3.00	
18	47.50	48.50	4.00	
19	47.50	47.50	5.00	
20	47.50	50.50		2.00
21	47.50	49.50		3.00
22	47.50	48.50		4.00
23	47.50	47.50		5.00



For example, Eudragit 4110D is anionic polymer prepared from methyl acrylate, MMA, and MAA, while Eudragit RL100 is cationic polymer prepared from ethyl acrylate, MMA, and QMA.

The BA level in all latexes of this group was the same as that in the polyampholyte latex 7. Anionic latexes 16–19 were prepared with the same three monomers (BA, MMA, and MAA) as in the polyampholyte latexes 1–7, but the cationic monomer QMA was omitted. Cationic latexes 20–23 were also prepared with the three monomers (BA, MMA, and QMA) as in the polyampholyte latexes 1–7, but in this set the acid monomer MAA was omitted. The latex 7 was prepared with 2.50 wt % MAA and 2.20 wt % QMA. If the latexes 18 and 22 had the same % solids and they were mixed at the 1 : 1 mass ratio, the monomer composition of the resulting latex mixture (in wt %) would be: BA (47.50)/MMA (48.50)/MAA (2.00)/QMA (2.00). Such a monomer composition is similar to that of the latex 7. For the polyampholyte latex 7 the measured  $T_g$  was 18.6°C, while anionic latexes 16–19 showed  $T_g$  values of ~21°C, and for cationic latexes 20–23 the  $T_g$  values ranged from 13 to 17°C. All anionic latexes in this study showed particle sizes of 140–148 nm, while the sizes of cationic latexes were about 166 nm. Both anionic and cationic latexes had 38–40 wt % solids. Similar to the weak acid/strong base polyampholyte latexes, at strongly acidic pH the mixture of MAA-containing anionic latex and QMA-containing cationic latex exists as low-viscosity dispersion, while an increase in the pH results in polymer coacervation and setting. Several latex coatings were prepared by deposition of anionic and cationic latexes on a glass surface. In one example anionic latex 18 was deposited first, followed by the cationic latex 22. The pendulum hardness (König) of the resulting coating was 64.7, and this high hardness resulted in a brittle coating. In another example the cationic latex 22 was deposited first, followed by the anionic latex 18. The pendulum hardness (König) was 50.4, and this hardness is higher than for any of the weak acid / strong base latexes from this work (see Table II).

### Pharmaceutical Application Tests

Latexes from all classes in this study were evaluated as potential tablet coating materials. In a typical commercial tablet coating process, an aqueous formulation (solution or dispersion) is sprayed over tablets in a tablet coater system with nozzles that require a low viscosity of the sprayed formulation.<sup>46,47</sup> Tablet coating materials on the market today are primarily based on hydroxypropyl methyl cellulose (HPMC), poly(vinyl alcohol) (PVOH), and acrylic polymers (e.g., Eudragits). These polymers have limited solubility in water, and their aqueous solutions can have high viscosity even at low concentration.<sup>30,31</sup> Therefore, current commercial pharmaceutical tablet coating technology requires the removal of >75% water during the manufacturing process. Development of tablet coating technology that minimizes this drying step would significantly reduce required coating time and energy. Table VI shows the viscosities of representative aqueous solutions from polymer types studied in this work, along with viscosities of latexes prepared in the course of this work. All latexes evaluated in this study were aqueous dispersions with high solids levels, and their viscosities

**Table VI.** Solids Levels and Viscosities of Aqueous Solutions and Dispersions

Sample	Solids (wt %)	Viscosity (cP) <sup>a</sup>
HPMC VLV <sup>b</sup>	10	34.0
PVOH EG-05	4	5
Eudragit L100 <sup>c</sup>	3.7	37.4
Weak acid/strong base latex 7	37.1	26.6
Strong acid/weak base latex 14	39.9	29.3
Anionic latex 18	38.6	38.8
Cationic latex 22	39.8	32.2

<sup>a</sup> Measured at 100 rpm with RV1 spindle.

<sup>b</sup> Low- $M_w$  HPMC with very low viscosity (relative to other HPMC materials).

<sup>c</sup> Copolymer of MMA (50.0) and MAA (50.0 wt %).

were similar to those of HPMC and Eudragit solutions with substantially lower solids levels.

Several polyampholyte latexes from this study were selected for further screening using pharmaceutically relevant application tests. From the class of weak acid/strong base polyampholytes, latexes 2, 4, and 5 were selected as representative candidates that could enable evaluation of the effect of latex composition and  $T_g$  on film properties. In addition, strong acid/weak base latex 14 was included in this testing. Films prepared with these latexes were studied for their mechanical properties (characterized by the puncture test), optical properties (clarity, haze, and light transmission) and water permeability (Table VII). Reference films were prepared with commercial polymers HPMC and PVOH, and the results of their testing are also included. All four latex films from this study showed an excellent combination of optical properties (high clarity, very low haze, and high light transmission), comparable to optical properties of the HPMC-based film (evaluated as a reference). They also showed very low water vapor permeability (six to seven times lower than that of the HPMC film), indicating excellent water vapor barrier properties. Water vapor permeability is typically indicative of oxygen permeability,<sup>48</sup> suggesting that tablet coatings prepared with amphoteric acrylate latexes would serve as excellent oxygen barriers. This is a critical requirement for long-term protection of pharmaceutical actives from oxidative degradation.

Tablet coatings were prepared from a limited subset of the latexes developed here in a preliminary demonstration of the feasibility of using these types of latexes in tablet coating applications. In the preparation of tablet coatings, representative materials from different latex classes were evaluated. The results from Table VII suggest that among the tested weak acid/strong base latexes the composition and  $T_g$  of latexes did not have a major effect on their film properties. Therefore, only one latex from this class was used in the preparation of a tablet coating. Our DOE study suggested that the latex 7 had the most desirable balance of properties, and this latex was selected for testing. The latex 7, strong acid/weak base latex 14, and a combination of the cationic latex 22 and the anionic latex 18 were sprayed over placebo tablets. Red Carmine pigment was added to the

**Table VII.** Mechanical, Optical, and Permeation Properties of Polymer Films

	Puncture force <sup>a</sup> (g mm <sup>-1</sup> )/5000	Clarity (%)	Haze (%)	Light trans. <sup>b</sup>	Water perm. <sup>c</sup>
HPMC E6	25	74.7	0.64	94.9	8.75
Opadry I HPMC <sup>d</sup>	23.0	85 ± 5	0.9	95.2	11.4
PVOH OKS <sup>e</sup>	20	85.0	0.19	95.1	2.14
Opadry II PVOH <sup>f</sup>	8.0	0	96.8	88.6	5.00
Weak acid/strong base latex 2	2.1	91 ± 1	7.6 ± 1.0	93.4	2.04
Weak acid/strong base latex 4	4.1	95.4 ± 0.8	7.4 ± 1.1	93.4	1.27
Weak acid/strong base latex 5	8.8	86 ± 2	5 ± 2	93.5	1.22
Strong acid/weak base latex 14	4.4	79 ± 3	0.4 ± 0.3	94.2	1.40

<sup>a</sup> Normalized puncture force = [(film rupture strength (g))/(thickness of a film (mm) × 5000)].

<sup>b</sup> Light transmission (%).

<sup>c</sup> Water permeability (g Pa s<sup>-1</sup> m<sup>-1</sup>) × 10<sup>7</sup>.

<sup>d</sup> Colorcon–Opadry I HPMC = HPMC / PEG 400 (91.0/9.0).

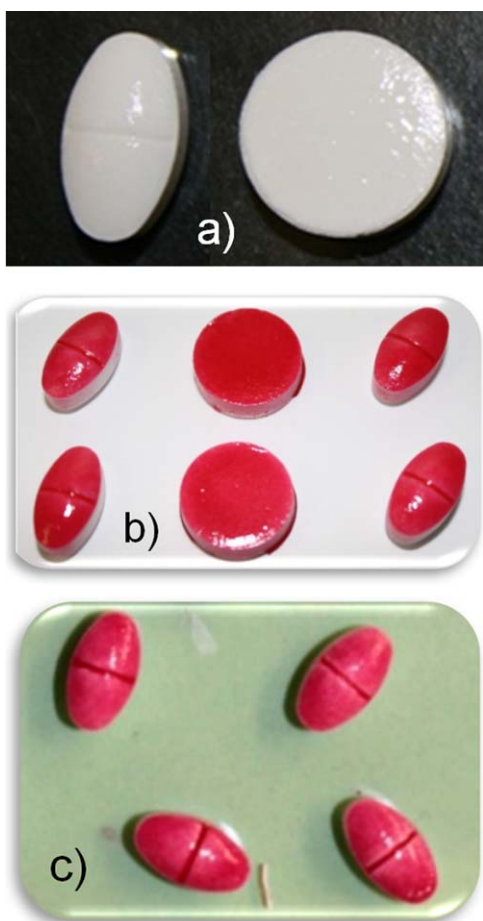
<sup>e</sup> Nippon–Goshenol OKS.

<sup>f</sup> Colorcon–Opadry II PVOH = PVOH/PEG3000/lecithin/talc (57.2/17.1/1.7/24.5).

polyampholyte latex 14, as well as to the anionic latex 18 to enable visualization of the coating. Figure 6 shows images of the resulting coated tablets. All tablet coatings were glossy and

showed uniform distribution of the red pigment, as well as strong adhesion to the tablet. Figure 6(C) shows that replacement of single polyampholyte latex with a mixture of anionic and cationic latexes results in similar tablet coating characteristics. While the concept of combining anionic and cationic latexes for tablet coatings has several advantages (described above), the commercial tablet coating process would require either a two step process [used for tablets in Figure 6(C)] or a simultaneous application of both latexes using two sets of nozzles.

The pH-tunable dissolution of films and coatings prepared with polyampholyte latexes was also studied. The weak acid/strong base latex 7 was sprayed over placebo tablets using a tablet coater system to give uniform coating over the entire tablet surface. Two coated tablets were placed in small vials and to one of them was added buffer pH 2.0, while into another vial was added buffer pH 6.0. Both vials were placed on a shaker. After 1 h at ambient temperature the coated tablet that was exposed to the pH 2.0 buffer started to disintegrate (indicated by hazy liquid phase and sediment on the bottom of the vial), while for the coated tablet in the pH 6.0 buffer the liquid phase remained clear. In a reference experiment, uncoated placebo tablets were exposed to buffers pH 2.0 and 6.0, and in both cases tablet disintegration started immediately. Therefore, the tablet coating prepared with the weak acid/strong base latex 7 is resistant to neutral aqueous solutions, but at gastric pH it quickly disintegrates and this could allow release of the active ingredient from the tablet. Such coating would be useful for immediate release applications. In another experiment, the strong acid/weak base amphoteric latex 14 was sprayed over placebo tablets. One coated tablet was placed in a vial, pH 1.2 buffer was added, and the vial was placed on a shaker. After 1 h at ambient temperature this coating did not show any signs of disintegration, confirming resistance of this latex to highly acidic pH. Such acid-resistant coatings would potentially be useful for delayed release (enteric) pharmaceutical applications, although no direct comparisons were made for the purposes of this preliminary study.



**Figure 6.** Images of tablets coated with coacervation latexes: (a) tablets coated with weak acid / strong base latex 7; (b) tablets coated with strong acid/weak base latex 14; (c) tablets coated first with the cationic latex 22, and then with the anionic latex 18. [Color figure can be viewed in the online issue, which is available at [wileyonlinelibrary.com](http://wileyonlinelibrary.com).]

## CONCLUSIONS

Three types of coacervation latexes were studied: weak acid/strong base latexes, strong acid/weak base latexes, and combinations of anionic latexes and cationic latexes. These latexes can each exist within a certain pH range as aqueous dispersions with high solids levels, and their viscosities were similar to those of HPMC and Eudragit based coating solutions that had substantially lower solids levels. Upon a pH shift to the vicinity of their isoelectric point they undergo ionic coacervation to quickly form a film, and their setting efficiency as a function of pH and polymer composition was studied. For weak acid/strong base latexes, a design-of-experiment methodology was applied to identify a desirable latex composition with good film forming properties (strong setting efficiency, as well as good hardness and nil tackiness of its film). A strong acid/weak base latex with the similar properties was also identified. Films of these latexes showed an excellent combination of optical properties: high clarity, very low haze, and high light transmission. They also showed very low water vapor permeability, about 15% of that of an HPMC film. Tablet coatings prepared with these latexes showed a pH-tunable formation and dissolution, and this is expected to enable delivery of active pharmaceutical ingredients in different stages of the digestion process (gastric release vs. intestinal release).

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