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PREPARATION AND STABILITY OF AQUEOUS-BASED ENTERIC POLYMER DISPERSIONS

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Abstract

Aqueous, colloidal dispersions of the enteric polymers, cellulose acetate phthalate (CAP), hydroxypropyl methylcellulose phthalate (HP-55), and polyvinyl acetate phthalate (PVAP) have been developed; and their application in tablet film coating demonstrated. The formation of free phthalic acid as a result of phthalate ester hydrolysis was monitored during storage of the dispersions. Increased free phthalic acid concentrations were found to adversely affect physical stability in dispersions of the cellulose polymers. Storage temperature and pH effects on phthalate ester stability were also considered.

INTRODUCTION

Following a period of approximately 20 years during which application of film coatings from organic solvents dominated the

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pharmaceutical field, aqueous film coating has recently emerged as the preferred method of tablet coating with water-soluble polymers. However, since enteric film-forming polymers are water-insoluble, aqueous coating with enteric polymers has been more difficult. Nevertheless, interest in aqueous enteric coating has prompted the development of numerous enteric coating compositions in which the amount of organic solvent has been reduced or eliminated. Techniques utilized include substitution of water for a portion of the organic solvent [1-3], emulsification of a solution of the polymer in a water-immiscible solvent with water as the external phase [4-6], preparation of aqueous polymer salt solutions [7-13], formation of a polymer hydrosol through neutralization of a polymer salt [14-17], and application of enteric polymer powders either as dusting powders [18] or as aqueous suspensions [19-21]. While seemingly effective in producing enteric properties, these techniques have yet to gain wide acceptance.

Recently, colloidal dispersions of enteric polymers have been produced in which surfactants and small particle size (approximately 1 micron) enhance physical stability and consistency, while promoting film formation. An acrylic polymer product, Eudragit^{R} L 30 D (Rohm Pharma GmbH, Darmstadt, West Germany), is one such colloidal dispersion commercially available for enteric coating. Manufactured by emulsion polymerization, this dispersion or latex is aqueous-based, is

stable to settling, has a high solids content while maintaining low viscosity, and can be applied directly as a tablet coating, with the addition of plastisizers and pigments, to obtain coatings comparable to those from organic solvent solutions [6, 22]. One drawback, however, is concern about the toxicity of trace components from the emulsion polymerization process, a problem this product shares with other acrylic polymer products.

An alternate method of preparing aqueous, polymeric dispersions [23] has been employed to produce a pseudolatex product, Aquacoat^{R} (FMC Corporation, Philadelphia, Pennsylvania), which has been used in both immediate and sustained release coatings [24, 25]. A pseudolatex is a mechanically-produced, colloidal dispersion of a polymeric material which is physically indistinguishable from a true latex. The two systems differ, however, in the types of polymers they contain. Latex systems are limited to polymers produced by emulsion polymerization, while pseudolatices may contain any existing thermoplastic, water-insoluble polymer.

Ortega [26] has successfully developed an enteric polymer pseudolatex suggesting a new avenue for application of pseudolatex dispersions in aqueous enteric coating. However, the formulation contained a toxic component in the surfactant system. Therefore, this study was undertaken to design and produce enteric polymer pseudolatices using components

acceptable for oral use in humans and to measure the physical and chemical stability of these formulations.

MATERIALS

Cellulose acetate phthalate (CAP), polyvinyl acetate phthalate (PVAP), and hydroxypropyl methylcellulose phthalate (HP-55) were the commerically available enteric polymers chosen for study and were supplied by Eastman Chemical Products, Inc., Kingsport, Tennessee; Canada Packers, Ltd., Toronto, Canada, or Colorcon, Inc., West Point, Pennsylvania; and Shin-Etsu Chemical Co., Tokyo, Japan, respectively. Ethylcellulose (Viscosity: 10, Epoxy: Standard) from Dow Chemical Company, Midland, Michigan replaced a portion of the enteric polymer in certain formulations. Surfactants and stabilizers for pseudolatex preparation included Pluronic F68 from BASF Wyandotte Corp., Wyandotte, Michigan; Tween 20, Span 20, Tween 60, and MYRJ 52 from ICI United States, Inc., Wilmington, Delaware; Sodium Lauryl Sulfate, USP; Cetyl Alcohol. USP; Gelvatol 20/30 and 40/10 from Monsanto, Indian Orchard, Massachusetts; and Polyethylene Glycol (PEG) 6000, USP. Hydroxypropyl methylcellulose (Methocel E5) from Dow Chemical Company, Midland, Michigan; Dibutyl Sebacate from Union Camp, Jacksonville, Florida; triethyl citrate (Citroflex 2) from Chas. Pfizer and Company, Inc., New York, New York; and Diethyl Phthalate from Eastman Kodak Company, Rochester, New York were utilized as additives in some formulations. Technical grade solvents were used in the preparation of pseudolatices.

METHODS

To prepare pseudolatices, the film-forming polymer(s), as well as internal plasticizers (dibutyl sebacate, diethyl phthalate, or triethyl citrate) and water-insoluble stabilizers included in certain formulations, were first dissolved in an 80:20 w/w mixture of ethyl acetate and isopropanol. In a separate flask, the selected water-soluble surfactants and/or stabilizers were dissolved in distilled water.

An emulsion was formed at room temperature by dropwise addition of the surfactant solution to the highly agitated organic phase. During this process, phase inversion occurred and was evidenced by a rapid decrease in emulsion viscosity. The stirring rate was then lowered to add the remaining surfactant solution. The resulting emulsion was stirred for an additional 15 minutes, homogenized by a single pass through a hand homogenizer, and sonicated to further reduce particle size. The sonicator was operated using a standard microtip at a setting of 4.5 for 5 minutes per 100 grams in the batch.

The organic solvent and a portion of the water were removed from the dispersion by vacuum distillation using a rotary evaporator. The flask containing the dispersion was submersed in a water bath maintained at 37°C $\pm$ 1°C to provide heat for evaporation.

A typical pseudolatex formula is shown below. Component quantities were increased proportionately for larger batch sizes.

Typical Psedulatex Formula

Ethyl Acetate (organic solvent)	80 g
Isopropanol (organic solvent)	20 g
Cellulose Acetate Phthalate (polymer)	20 g
Pluronic F68 (surfactant)	4 g
Gelvatol 20/30 (polyvinyl alcohol) (stabilizer)	1 g
Distilled Water	100 ml

At selected storage time intervals, pseudolatices were visually inspected for caking of solids on the walls of sample containers or for the presence of sediment. Sediment remaining after shaking by hand was considered non-redispersible while sediment that dispersed into the liquid portion of the sample was termed redispersible.

Pseudolatex pH was determined at room temperature using a glass-calomel combination electrode inserted into the well-shaken sample. Following a 2 to 3 minute equilibration period, the pH of the pseudolatex was recorded.

Free phthalic acid content was measured by a UV spectroscopic method. Following agitation of each sample by hand to assure sample homogeneity, an aliquot of 2.50 g of pseudolatex was weighed in a tared 10 ml beaker, transferred to a 250 ml volumetric flask with distilled water rinses, and diluted to the mark with distilled water. A teflon coated stirring bar was placed in the volumetric flask and the dispersion was stirred for 10 minutes using a magnetic stirrer.

A second dilution was carried out by transfer of 25 ml of dispersion from the 250 ml volumetric flask to a 50 ml

volumetric flask containing 5 ml of 1 N hydrochloric acid. Water was then added to the mark of the 50 ml volumetric flask. Following addition of 2 g of Sodium Chloride, USP to the 50 ml flask, the diluted sample was shaken and allowed to stand overnight.

Membrane filters with 5 micron pore size were used to filter polymer solids from a portion of the diluted sample. Previous boiling in distilled water had removed components from the filters which would absorb UV light at 275 nm if leached out of the filters during filtration. The clear filtrate was measured for absorbance at 275 nm against 0.1 N hydrochloric acid containing 4 g of Sodium Chloride, USP per 100 ml. The percent free phthalic acid relative to phthalate-containing polymer was calculated as follows:

$$\text{Percent free phthalic acid} = \frac{(2)(0.250)(100)(C)}{(2.5)(f)} \qquad \text{(Eq. 1)}$$

where C is the concentration of phthalic acid, in g/l, found in the filtrate; f is the weight fraction of phthalate-containing polymer in the pseudolatex; 0.250 is the volume, in liters, to which 2.5 g of pseudolatex was first diluted, and 2 is the dilution factor for the second dilution.

RESULTS AND DISCUSSION

Formulation Development

Previously, stable CAP pseudolatices, containing 20% polymer by weight, were prepared using sodium lauryl sulfate as

the surfactant and n-decane as a secondary stabilizer [26]. The process involved emulsification of an aqueous solution of the surfactant with a solution of the polymer and n-decane in a mixture of 80:20 ethyl acetate: isopropanol , at a temperature of 63°C ± 2°C, followed by evaporation of the solvent and a fraction of the water under vacuum, to obtain a dispersion of the desired solids content. The resulting product was applied to tablets, rendering them enteric as determined by compendial standards [26].

While trace amounts of ethyl acetate or isopropanol would be safe in a commercial product, presence of the toxic hydrocarbon, n-decane, in the final formulation was not acceptable. Furthermore, reduction of the emulsification temperature was desired to minimize exposure of the enteric polymer to high temperature conditions while in the presence of water. Therefore, alternate surfactant- stabilizer systems containing components acceptable for human consumption were initially studied to identify those which produced physically stable pseudolatices when emulsification took place at room temperature.

The surfactants, Pluronic F68, MYRJ 52, Tween 20, Tween 60, and Span 20, were selected for investigation. Pluronic F68 is reportedly safe for oral use in humans [27, 28] while the Tweens and Span 20 are generally recognized as safe for direct addition to food products. MYRJ 52 is also accepted for direct addition to food products as a defoaming agent [29], and its

TABLE 1

Characteristics of Emulsions Formed from Water and Organic Solvent Solutions of Cellulose Acetate Phthalate Using Various Surfactant Systems.

System	Components	w/w Ratio of Components	w/o Emulsion Formed	Rapid[d] Phase Inversion	Separation of o/w Emulsion
1	Pluronic F68, Cetyl alcohol[a]	2.6:1	yes	yes	48 hr
2	Sodium lauryl sulfate, Cetyl alcohol	1:1.8	no	-	-
3	Tween 20, Cetyl alcohol	1.1:1	yes	no	-
4	Tween 20, Span 20, Cetyl alcohol	1:1:1.8[b]	yes	no	-
5	Tween 20	-	yes	no	-
6	Tween 20, Span 20	3:1[c]	yes	no	-
7	Tween 20, Span 20	1:1[b]	yes	no	-
8	Tween 60	-	yes	no	-
9	MYRJ 52, Cetyl alcohol	8:1	yes	yes	48 hr
10	MYRJ 52, Cetyl alcohol	2:1	yes	yes	30 min

(a) Stabilizing compound.
(b) Effective surfactant HLB 12.6.
(c) Effective surfactant HLB 14.7.
(d) "Yes" represents phase inversion prior to 2:1 w/w ratio of water phase:organic phase being reached.

safety for human consumption has been reported elsewhere [28, 30, 31]. In this preliminary study, cetyl alcohol replaced n-decane as a stabilizer.

Emulsions were prepared following the procedure described in the Methods section and using CAP as the enteric polymer. If phase inversion did not occur, additional water, up to 2 parts of water for each part of solvent, was incorporated into the mixture. The results are shown in Table 1. The linear molecular

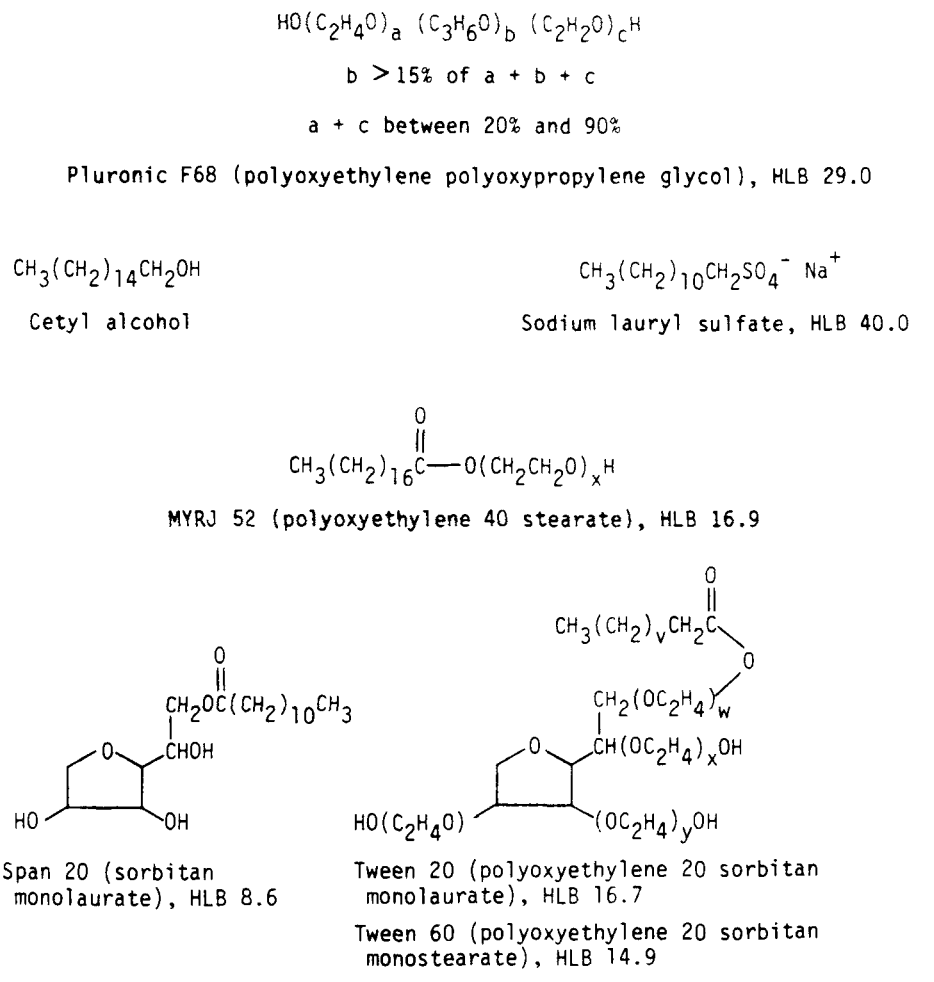

FIGURE 1
Structures and HLB values of selected surfactants and the structure of cetyl alcohol.

structures of the components in surfactant systems 1, 9, and 10,(see Figure 1) were thought to contribute to rapid phase inversion, since the remaining non-ionic surfactant systems each contained at least one structurally bulky, sorbitan-based surfactant. Once phase inversion occurred, surfactant system HLB (hydrophilic-lipophilic

balance) appeared to influence pseudolatex emulsion stability (Table 1). Conventional o/w emulsions generally require surfactant system HLB values between 8 and 16 [32]. However, surfactants producing stable enteric polymer pseudolatex emulsions (sodium lauryl sulfate in Ortega's formulation [26] and Pluronic F68 in the current experiment) had higher HLB values. MYRJ 52, with intermediate HLB, was not sufficiently hydrophilic for long stabilization of pseudolatex o/w emulsions. This resulted in the inability to prepare physically stable pseudolatices using MYRJ 52. Thus, the surfactant, Pluronic F68, was selected for further study.

In the emulsion formed by Pluronic F68 and cetyl alcohol, cetyl alcohol was introduced as a stabilizer via dissolution in the organic solvent phase. While acknowledging the feasibility of this approach, Vanderhoff et al. [23] instead chose to disperse cetyl alcohol in the aqueous phase at a temperature above its melting point, indicating that cetyl alcohol might not be the optimal stabilizing agent when employed at room temperature through dissolution in the solvent phase. For this reason, PEG 6,000 and polyvinyl alcohol (Gelvatol 20/30) were tested as alternate stabilizers in pseudolatex formulations. Both compounds are safe for human consumption. Furthermore, like Pluronic F68, these linear compounds contain hydroxyl groups throughout their structures which can interact with chemical groups on the enteric polymer. Other compounds specified as stabilizers by Vanderhoff et al. [23] were avoided

due to lack of safety for human consumption and the presence of a highly non-polar, terminal hydrocarbyl group which would have poor affinity for an enteric polymer such as CAP, with intermediate polarity [33].

Table 2 lists enteric polymer pseudolatex formulations prepared successfully with Pluronic F68 alone and in combination with PEG 6000 or Gelvatol 20/30. Ethylcellulose, an FDA food-approved polymer, replaced a portion of the enteric polymer in some formulations to maintain a constant polymer content. The Pluronic F68/Gelvatol 20/30 surfactant system worked well in a number of formulations containing either of the cellulosic enteric polymers. Although not as versatile, the Pluronic F68/PEG 6000 surfactant system was effective in pseudolatices containing CAP and ethylcellulose in equal parts. PVAP behaved differently than the cellulosic enteric polymers, forming stable pseudolatices with Pluronic F68 as the lone surfactant.

To demonstrate the feasibility of applying the currently developed pseudolatices to tablets to impart enteric properties, a fresnly prepared pseudolatex (Formula C3 in Table 2), plasticized with diethyl phthalate at a 30% level based on pseudolatex solids, was applied to tablets in an air-suspension coating apparatus. The tablets thus coated were subjected to the USP Enteric Test and found to pass with disintegration times of 11-14 minutes in simulated intestinal fluid, without enzyme,

TABLE 2

Compositions of Pseudolatices Prepared with Pluronic F68 Alone and in Combination with Gelvatol 20/30 or Polyethylene Glycol 6000.

	Composition (%)						
Formula	CAP	HP-55	PVAP	Ethyl-Cellulose	Pluronic F68	PEG 6000	Gelvatol 20/30
C1	20				4.5		0.5
C2	20				4.25		0.75
C3	20				4		1
C4	20				3.5		1.5
C5	20				4.8		1.2
C6	10			10	4		1
C7	10			10	3	4	
H1[a]		20			5		
H2		20			4		1
H3		15		5	4		1
P1			20		5		

[a]Granular pseudolatex, physically stable for less than 1 week.

after being subjected to simulated gastric fluid, without enzyme, for one hour.

Pseudolatex Stability

Demonstrated chemical and physical stability of the enteric polymer pseudolatices would be necessary for their practical use in industrial scale coating. Since CAP is prone to phthalate hydrolysis, compendial limits have been set for free phthalic acid in CAP powder [34]. Consequently, the rate of free phthalic acid formation with time was determined for various pseudolatices. Concurrently, pseudolatex pH and physical appearance were monitored.

Stability data from various CAP pseudolatex batches (based on Formula C3 in Table 2) are summarized in Table 3. Rates of free phthalic acid formation over time appeared linear and are described using a least squares slope and intercept. The pH data in the table is given as a range for each pseudolatex batch, while Figure 2 presents individual pH readings at various times for batches C3-A through C3-G. The lines in the figure illustrate that unbuffered pseudolatices decreased in pH over time, when stored at 25°C, but maintained a nearly constant pH, when stored at 3°C. Also, the pH adjusted batches (pH 1.5) showed nearly constant pH during storage at either 3 or 25°C.

The right-most columns in Table 3 list the times at which changes in psedudolatex physical stability were observed. A redispersable sediment, comprising approximately one-third of the sample, was generally seen first. A portion of this sediment was presumably deposited on the walls of the sample bottle where it appeared as a dried, white film. Eventually, polymer particles in the sediment coalesced to form a single mass, at which time total separation of the pseudolatex was noted.

A relationship appeared to exist between the rate of free phthalic acid formation and both pseudolatex pH and physical appearance. This relationship identified phthalate hydrolysis as the primary cause of stability problems in CAP pseudolatices. The pH in unbuffered CAP pseudolatices was controlled primarily

TABLE 3

Physical and Chemical Stability Data from Cellulose Acetate Phthalate Pseudolatices (Formula C3).

Batch[a]	Storage Temperature(°C)	Range of pH[c]	Free Phthalic Acid[d] Initial (%)	Free Phthalic Acid[d] Formation Rate (%/day)	Physical Stability[e] Time First Appeared (Months) W	RS	S
C3-A	25	2.35-2.00	2.20	0.0317	DNA	3	5
C3-B	25	2.57-2.20	2.49	0.0316	4	2	5
	3	2.58-2.48	2.51	0.0016	8	DNA	12
C3-C	25	2.48-2.17	2.59	0.0336	4	2	5
	3	2.55-2.43	2.80	0.0006	8	DNA	12
C3-D	25	2.27-2.17	2.32	0.0375	3	3	5
	3	2.60-2.49	2.57	0.0014	7	DNA	12
C3-E	25	2.56-2.41	2.22	0.0306	2	3	7
	3	2.63-2.50	2.24	0.0025	7	DNA	8
C3-F[b]	25	1.71-1.43	2.23	0.0257	3	3	7
	3	1.69-1.43	2.48	0.0018	4	6	12
C3-G[b]	25	1.55-1.41	2.23	0.0225	2	1	6
	3	1.60-1.55	2.27	0.0022	5	9	9

[a] Based on Formula C3 in Table 2.
[b] 1.0 N hydrochloric acid added for pH adjustment.
[c] The higher pH is given first to denote pH decrease, with time, observed at 25°C for Batches C3-A through C3-E. The remaining samples showed no trend in pH. pH readings were obtained initially and periodically through the time period specified in the S column, except for missing initial pH readings for Batches C3-A and C3-D and missing pH readings after 4 months at 25°C for Batches C3-E and C3-G.
[d] Obtained from least squares line for percent free phthalic acid *vs.* time data.
[e] W - Deposits of dried solid found on walls of sample bottle.
RS - Redispersible sediment found in pseudolatex.
S - Total separation of pseudolatex.
DNA - Did not appear.

by the first equilibrium constant for phthalic acid (pKa_1 = 2.97) and the quantity of phthalic acid present in the aqueous phase of the pseudolatex. (Any effects on pH due to the ionization of acetic acid or CAP were negligible, since the pKa values of these acids are 4.73 and approximately 4.5, respectively). As the dissociation equilibrium equation illustrates, increases in free phthalic acid concentration led to

$$K_a = \frac{[H^+]\,[\text{phthalate ion}^-]}{[\text{phthalic acid}]} \qquad \text{(Eq. 2)}$$

proportional increases in ionization of the acid. As ionization proceeded, hydrogen ions were released, decreasing pseudolatex pH. The relatively constant pH of unbuffered pseudolatices stored at 3°C supported this explanation, since in these samples, little free phthalic acid was formed during storage.

Due to pH adjustment with hydrochloric acid, Batches C3-F and C3-G in Table 3 did not show the described pH effects. However, a comparison of Batches C3-A through C3-E with Batches C3-F and C3-G illustrates the relationship between free phthalic acid formation and physical stability.

Colloidal dispersions are known for their physical instability in the presence of electrolytes. The colloidal particle surface charges which prevent interparticulate contact are diminished by interaction with ions of opposite charge, ultimately producing sedimentation and/or coagulation of the

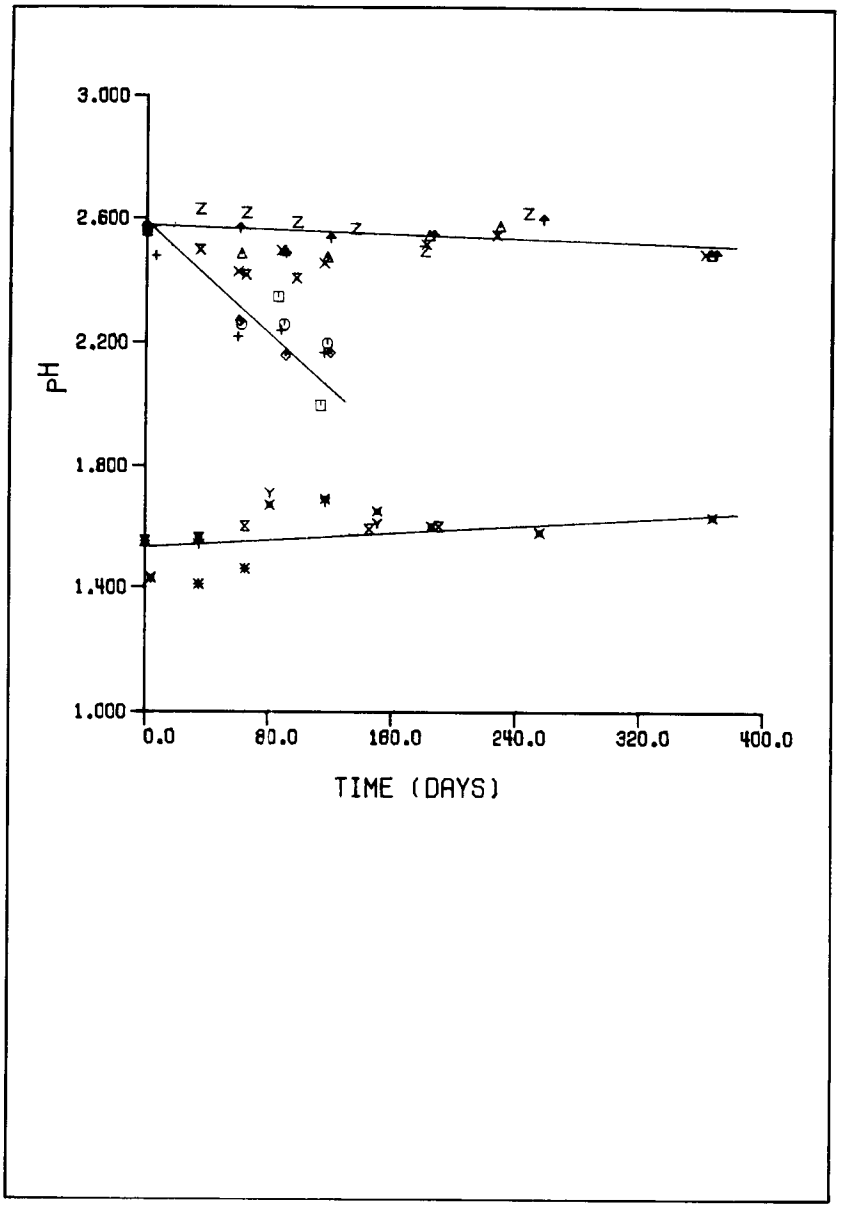

FIGURE 2
pH data from the cellulose acetate phthalate pseudolatices in Table 3. Key: (□)C3-A, 25°C; (o) C3-B, 25°C; (Δ) C3-B, 3°C; (+) C3-C, 25°C; (x) C3-C, 3°C; (◇) C3-D, 25°C; (↑) C3-D, 3°C; (⧖) C3-E, 25°C; (z) C3-E, 3°C; (y) C3-F, 25°C; (⧓) C3-F, 3°C; (*) C3-G, 25°C; and (⧗) C3-G, 3°C. The three lines reflect the pH trends of unbuffered CAP pseudolatex samples stored at 3°C (top line) and 25°C (middle line) and pH adjusted samples stored at either 3 or 25°C (bottom line).

colloid. By adding hydrochloric acid for pH adjustment in Batches C3-F and C3-G, pseudolatex ionic strength was increased, thereby providing ions for interaction with the charged colloidal particle surfaces. As a result, sedimentation and solids formation appeared earlier in the pH adjusted samples than in the unbuffered pseudolatex samples. In unbuffered samples, pseudolatex physical stability was not affected until phthalate ester hydrolysis produced sufficient ionic strength to promote colloid destabilization and sedimentation.

The temperature effect on free phthalic acid formation rates in CAP pseudolatices stored at 3, 25, 40, and 50°C is shown in Figure 3 in the form of an Arrhenius plot in which the logarithm of the rate of free phthalic acid formation is substituted for the logarithm of the rate constant for the reaction. The calculated activation energy of about 23 kcal was relatively large for ester hydrolysis but was reasonable, due to the steric hindrance provided by the polymer backbone. Furthermore, in preparing the Arrhenius plot, the free phthalic acid formation rate was calculated using pseudolatex solids content rather than CAP concentration in solution, and, consequently, was not adjusted, as the rate constant would be, for differences in the aqueous solubility of CAP at different temperatures. Thus, if CAP solubility increased with temperature, the actual activation energy would be lower than the one calculated.

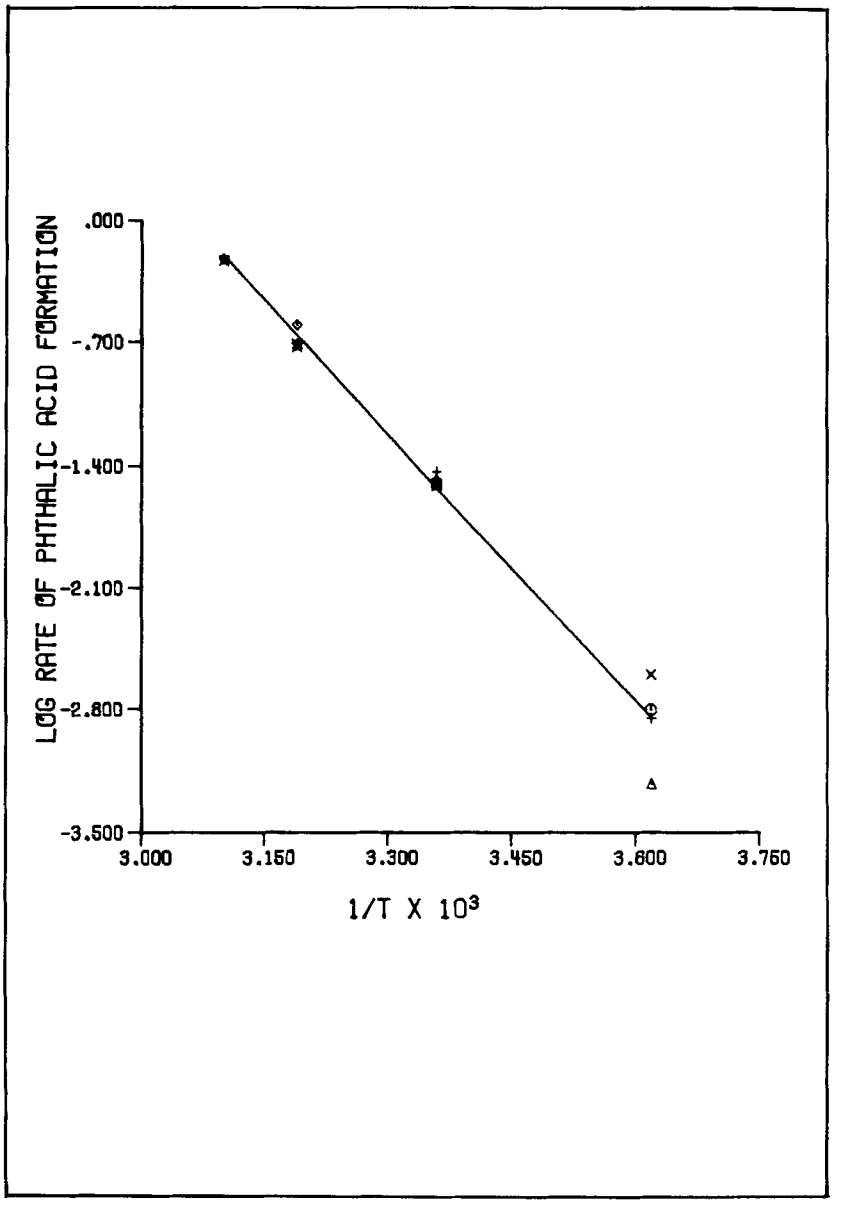

FIGURE 3
Arrhenius plot for cellulose acetate phthalate pseudolatices. Key: (□) C3-A, (o) C3-B, (Δ) C3-C, (+) C3-D, (x) C3-E, (◇) C3-H, (↑) C3-I, and (x̄) C3-J.

Two pseudolatex formulas were utilized to study the effect of pH on phthalate hydrolysis in CAP pseudolatices stored at 25°C. The first formula contained CAP as the only film-forming polymer while the second, termed a mixed polymer pseudolatex, contained equal amounts of CAP and ethylcellulose. CAP pseudolatices had an initial pH of about 2.6, while mixed polymer pseudolatices had a pH of about 3.0. Since this difference in initial pH between the two types of unbuffered pseudolatices would confound the effects of pH and enteric polymer content, the latter effect required study under controlled pH conditions. Therefore, the effects of pH and enteric polymer content were studied concommitantly.

Although the chemical stability of CAP was of primary interest in this experiment, the physical stability of pseudolatex samples was also noted following acid or base addition for pH adjustment. Addition of sodium hydroxide was particularly detrimental to pnysical stability with granular solid particles appearing immediately upon base addition. The incorporation of hydrochloric acid produced a delayed effect, evidenced by an eventual increase in pseudolatex viscosity and the appearance of solids on the walls of the sample container.

Since the adjustment of sample pH above 4.0 and below 1.0 produced highly viscous samples, the pH range selected for study was limited to pH values from 1.0 to 4.0, inclusive. The graph in Figure 4 depicts the pH profile for free phthalic acid

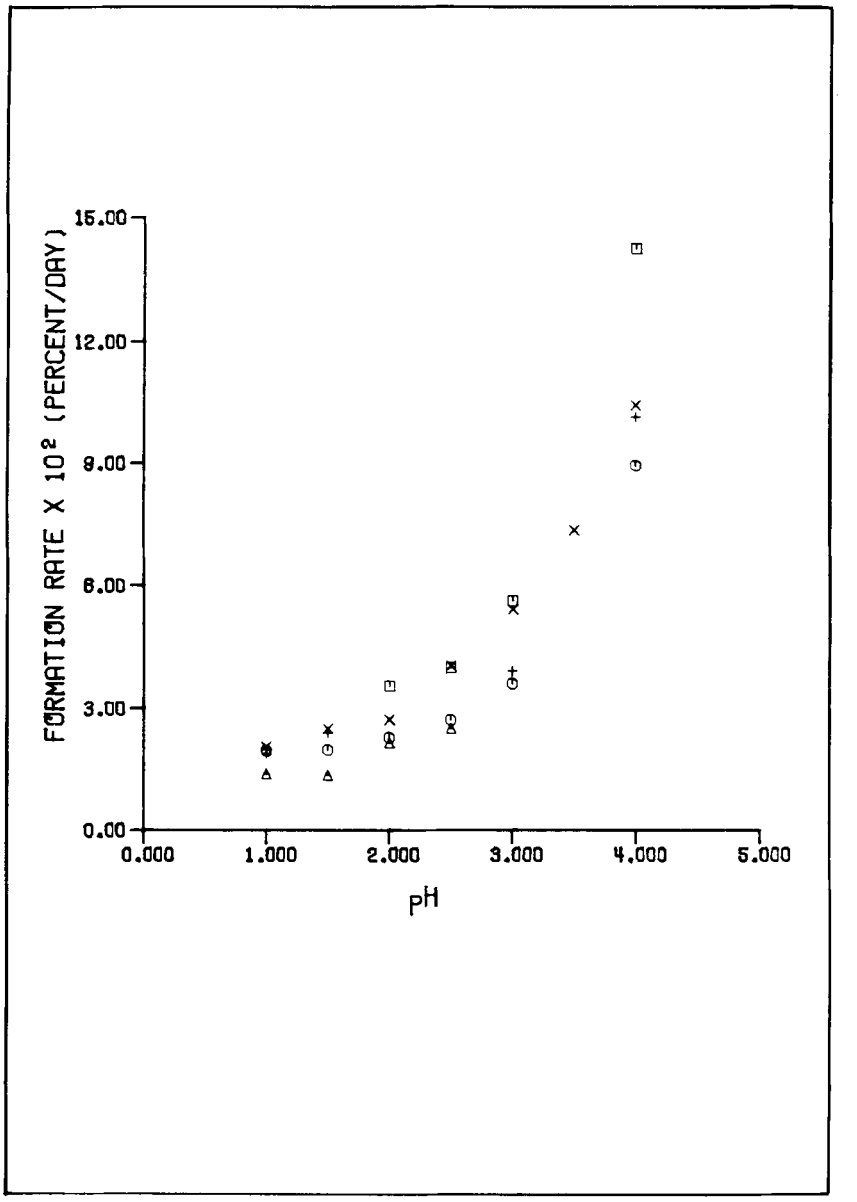

FIGURE 4
pH profile of the rate of phthalic acid formation on cellulose acetate phthalate pseudolatices and in ethylcellulose:cellulose acetate phthalate pseudolatices. Key: (+) C3-E, (□) C3-K, (Δ) C3-L, (o) C8-A, and (x) C8-B.

TABLE 4

Physical and Chemical Stability Data from Mixed Polymer Pseudolatices.

Batch[a]	Storage Temperature(°C)	Range of pH[c]	Free Phthalic Acid[d] Initial (%)	Free Phthalic Acid[d] Formation Rate (% day)	Physical Stability[e] Time First Appeared (Months) W	RS	S
C6-C	25	2.71-2.45	3.74	0.0386	5	8	9
	3	2.90-2.70	3.62	0.0012	DNA	DNA	12
C6-D[b]	25	1.62-1.50	2.37	0.0278	5	3	9
	3	1.63-1.50	2.59	0.0013	4	12	12

(a) Based on Formula C6 in Table 2.
(b) 1.0 N hydrochloric acid added for pH adjustment.
(c) The higher pH is given first to denote pH decrease, with time, observed at 25°C for Batch C6-C. The remaining samples showed no trend in pH. pH readings were obtained initially and periodically through the time period specified in the S column.
(d) Obtained from least squares line for percent free phthalic acid vs. time data.
(e) See footnote (e) in Table 3.

formation. Some improvement in polymer chemical stability was shown through a reduction in pseudolatex pH. Long-term stability data from CAP pseudolatices (Table 3) as well as mixed polymer pseudolatices (Table 4) confirmed that the rate of free phthalic acid formation was decreased at 25°C by lowering sample pH. However, as suspected, the addition of acid to the pseudolatices led to more rapid appearance of solid material on the container wall and redispersable sediment in the pseudolatex, particularly in the refrigerated samples.

Besides pH adjustments, other formulation changes were made to study their effects on CAP chemical and physical stability. These changes included varying the ratio of surfactant system components, increasing the quantity of surfactants, adding hydroxypropyl methylcellulose to the finished pseudolatex as a protective colloid, and adding the plasticizers, dibutyl sebacate, diethyl phthalate, and triethyl citrate, to the organic solvent solution of CAP during pseudolatex preparation. The data obtained from these studies is summarized in Table 5.

A comparison of the stability data in Table 5 with that from Batches C3-A through C3-G in Table 3 indicates that neither the changes made in the surfactant system nor the components (protective colloid, plasticizers) added to the basic pseudolatex formula, with the exception of diethyl phthalate, had any discernable effect on CAP chemical stability or pseudolatex physical stability. Only an increase in the amount of surfactant in the formula (Batch C7-A), led to any improvement in pseudolatex stability. However, in this product, physical stability alone was enhanced to a limited degree while the chemical stability of the polymer was unchanged. Furthermore, the water solubility of the surfactant system components precluded large increases in their quantities, since these increases might affect enteric properties. Thus, the formulations tested provided no improvement in the chemical stability

TABLE 5

Physical and Chemical Stability Data from Cellulose Acetate Phthalate Pseudolatices (Formulas C1, C2, C4, C5, and C10 - C13).

Batch[a]	Storage Temperature(°C)	Range of pH[e]	Free Phthalic Acid[f] Initial (%)	Free Phthalic Acid[f] Formation Rate (%/day)	Physical Stability[g] Time First Appeared (Months) W	RS	S
C1-A	25	2.40-2.19	2.56	0.0306	3	4	7
	3	2.57-2.32	2.46	0.0019	6	DNA	12
C2-A	25	2.46-2.18	2.43	0.0301	3	3	7
	3	2.60-2.46	2.41	0.0017	6	DNA	12
C4-A	25	2.56-2.29	2.71	0.0298	3	3	7
	3	2.72-2.50	2.74	0.0007	12	DNA	12
C5-A	25	2.60-2.26	2.53	0.0299	4	5	8
	3	2.70-2.60	2.62	0.0009	6	DNA	12
C10-A[b]	25	2.72-2.41	2.22	0.0273	4	4	8
	3	2.72-2.49	2.31	0.0024	5	1	9
C10-B[b][c]	25	1.61-1.43	2.14	0.0255	2	1	6
	3	1.61-1.43	2.32	0.0022	4	1	9
C11-A[b]	25	2.48-2.26[e]	2.42	0.0211	3	3	5
	3	2.63-2.47	2.37	0.0008	3	DNA	12
C12-A[b]	25	2.41-2.25[e]	2.53	0.0283	3	4	5
	3	2.61-2.50	2.56	0.0012	3	DNA	12
C13-A[b][d]	25	-	-	-	-	-	-
	3	-	-	-	-	-	-

(a) Based on formulas from Table 2.
(b) Formulas same as Formula C3 in Table 2 except that C10, C11, C12, and C13 also contained 0.5% hydroxypropyl methylcellulose, 5% triethyl citrate, 5% dibutyl sebacate, and 5% diethyl phthalate, respectively.
(c) 1.0 N hydrochloric acid added for pH adjustment.
(d) Pseudolatex settled in one day.
(e) The higher pH is given first to denote pH decrease, with time, observed at 25°C for Batches C1-A, C2-A, C5-A, C7-A, C10-A, C11-A, and C12-A. The remaining samples showed no trend in pH. pH readings were obtained initially and periodically through the time period specified in the S column, except for missing initial pH readings for Batches C11-A and C12-A and missing pH readings after 6 months at 25°C for Batch C10-A and after 4 months at 25°C for Batch C10-B.
(f) Obtained from least squares line for percent free phthalic acid vs. time data.
(g) See footnote (e) in Table 3.

of the polymer or the physical stability of the pseudolatex relative to CAP pseudolatex Formula C3, given in Table 2.

The instability of CAP relative to HPMCP, when in powder form [35], prompted a comparison of pseudolatices containing the other carboxylic acid enteric polymers. The stability data for HPMCP (HP-55) and PVAP (two sources) pseudolatices are given in Table 6 and may be compared with the data for CAP pseudolatices found in Table 3. HPMCP (HP-55) exhibited the best chemical stability even though pseudolatex pH was somewhat higher than that found in CAP pseudolatices. In fact, the HPMCP (HP-55) pseudolatex stored at 3°C showed no apparent change in free phthalic acid for over one year. The improved chemical stability was presumably due to steric hindrance of the hydrolysis reaction by the hydroxypropyl groups substituted on the polymer. This effect has previously been used to explain the superior chemical stability of HPMCP over CAP when these polymers were stored under high temperature and high humidity conditions in their powder forms [35].

PVAP was found to have intermediate chemical stability, with polymer from one source having a free phthalic acid formation rate about 50% greater than the polymer from the second source. As with CAP, pH adjustment to lower pH in PVAP pseudolatices improved chemical stability at 25°C. Also, since the free phthalic acid formation rates of the two PVAP polymers remained at approximately the same ratio in the pH adjusted system as in

TABLE 6

Physical and Chemical Stability Data from Hydroxypropyl Methylcellulose Phthalate and Polyvinyl Acetate Phthalate Pseudolatices.

Batch[a]	Storage Temperature(°C)	Range of pH[e]	Free Phthalic Acid[g] Initial (%)	Free Phthalic Acid[g] Formation Rate (%/day)	Physical Stability[h] Time First Appeared (Months) W	RS	S
H2-A	25	3.23-2.39	1.51	0.0113	3	7	11
	3	2.97-2.80(f)	1.44	0.0003	3	DNA	12
P1-A[b]	25	3.50-3.05	1.86	0.0169	NA	NA	12
	3	3.59-3.44	1.76	0.0014	NA	NA	12
P1-B[b]	25	3.45-3.02	1.83	0.0234	NA	NA	6
	3	3.52-3.37	1.92	0.0023	NA	NA	6
P1-C[b][c]	25	1.60-1.40	1.81	0.0074	NA	NA	12
P1-D[b][c]	25	1.68-1.47	1.82	0.0098	NA	NA	6
P1-E[d]	25	3.08-2.68	1.17	0.0124	NA	NA	6
	3	3.20-2.83	1.13	0.0014	NA	NA	6
P1-F[d]	25	3.12-2.65	1.22	0.0128	NA	NA	6
	3	3.20-2.97	1.20	0.0012	NA	NA	6
P1-G[c][d]	25	1.60-1.44	1.10	0.0064	NA	NA	6
P1-H[c][d]	25	1.75-1.52	1.27	0.0037	NA	NA	6

(a) Based on formulas from Table 2.
(b) Polymer source: Canada Packers, Ltd.
(c) 1.0 N hydrochloric acid added for pH adjustment. Pseudolatex not stable when refrigerated.
(d) Polymer source: Colorcon, Inc.
(e) The higher pH is given first to denote pH decrease, with time, observed at 25°C for Batches H2-A, P1-A, P1-B, P1-E, and P1-F. The remaining samples showed no trend in pH. pH readings were obtained initially and periodically through the time period specified in the S column.
(f) Initial pH 3.23, then equilibrated between pH values given.
(g) Obtained from least squares line for percent free phthalic acid vs. time data.
(h) See footnote (e) in Table 3. NA - Not applicable.

the unbuffered system, it appeared that the difference in chemical stability between the polymer materials from the two different sources was not attributable to the difference in pseudolatex pH found in the unbuffered products.

Physical stability differences were also seen among the polymers, primarily in the manner in which physical instability was manifested. HPMCP (HP-55) pseudolatex behaved similarly to CAP pseudolatex, showing somehwat better physical stability due to its superior chemical stability. However, separation of phases in PVAP pseudolatices occurred much differently. PVAP pseudolatices underwent slow formation of a sticky cake which began within the first month of storage and continued over time with no noticeable change in pseudolatex consistancy. Following 6 months storage, a 3-5 mm cake had accumulated which appeared white at the surface that was in contact with the pseudolatex, and was clear to yellowish below that surface. Furthermore, pH-adjusted PVAP pseudolatices were unable to withstand low temperature storage and congealed to form a single mass of polymer within the first month of storage.

Conclusion

Pseudolatices have been shown to be effective in the aqueous-based application of enteric film coatings. Exposure of the enteric polymer to water in these systems, however, leads to hydrolysis of phthalate ester bonds and the formation of free phthalic acid. This study, has examined the chemical and

physical stability of various enteric polymer pseudolatex formulations to identify factors affecting pseudolatex stability.

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