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HYDROLYSIS OF CELLULOSE ACETATE AND CELLULOSE ACETATE BUTYRATE PSEUDOLATEXES PREPARED BY A SOLVENT EVAPORATION-MICROFLUIDIZATION METHOD

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ABSTRACT

Aqueous colloidal cellulose acetate dispersions have recently been introduced as an alternative to organic polymer solutions for the coating of osmotically active cores with a semipermeable membrane. Cellulose esters are known to hydrolytically degrade in an aqueous environment. This study followed the chemical degradation of pseudolatexes of the cellulose esters, cellulose acetate and cellulose acetate butyrate, over time and as a function of temperature. The pseudolatexes were prepared by a microfluidization-solvent evaporation method. The hydrolysis of the cellulose esters was followed by determining the pH and the amount of the acidic degradation products, acetic and butyric acid, in the aqueous phase of the polymer dispersions with an HPLC assay. The degradation followed a pseudo first-order equation and rate constants and activation energies were calculated. In addition to chemical instability, agglomeration and gelling of the colloidal particles occurred. The pseudolatexes were stable at 4 °C, however, if stored at higher temperatures, the preparation of a redispersible polymer powder is recommended.

INTRODUCTION

Cellulose acetate is the polymer of choice for the preparation of semipermeable membranes in osmotically driven systems (1,2). In the elementary osmotic tablet, a drug-containing osmotic core is coated with a solution of cellulose acetate in an organic solvent or solvent mixture. Because of the potential hazards with organic solvents, water-insoluble polymers are often formulated into aqueous colloidal polymer dispersions (latexes or pseudolatexes) (3,4). A continuous polymeric film is formed around the solid core during coating through the coalescence of the colloidal polymer particles. Various acrylic and cellulosic enteric or non-enteric polymers have been commercially available in the form of colloidal polymer dispersions for several years (5), and recently, a cellulose acetate pseudolatex has become available from a commercial supplier (6).

A key variable in determining the successful use of a particular latex or pseudolatex is the stability of the polymer when in contact with water, since the colloidal polymer particles are dispersed in an aqueous phase. Cellulose esters are prone to hydrolysis; cellulose acetate phthalate, an enteric polymer, had to be formulated into a redispersible powder because of hydrolysis of the polymer (formation of free phthalic acid) (7). With cellulose acetate, several research groups studied the hydrolysis and degradation of reverse osmosis membranes (8-11). The degradation, as measured by changes in the molecular weight or the acetyl content of the membranes, resulted in marked changes in water flux and salt retention.

The objective of this study was to prepare pseudolatexes of the pharmaceutically acceptable cellulose esters, cellulose acetate and cellulose acetate butyrate, by a microfluidization-solvent evaporation method and to follow chemical and physical degradation as a function of storage time and temperature.

MATERIALS AND METHODS

Materials

The following chemicals were used as received: cellulose acetate, CA-398-10; cellulose acetate butyrate, CAB-171-15S (Eastman Kodak Company, Rochester, NY); sodium lauryl sulfate (MCB Manufacturing Chemist, Norwood, OH); methanol; methylene chloride (Mallinckrodt, Inc., Paris, KY).

Methods

Pseudolatex preparation - The pseudolatexes were prepared by a high pressure emulsification - solvent evaporation method. A polymer solution [polymer, 22.5 g, methylene chloride (for cellulose acetate butyrate) or methylene chloride:methanol (9:1 v/v, for cellulose acetate), 200 ml] was pre-emulsified into an aqueous phase

(280 ml) containing sodium lauryl sulfate, 0.5 %w/v, to form an O/W emulsion. This emulsion was then processed with a microfluidizer (standard M-110 laboratory model, Microfluidics Corporation, Newton, MA), a high pressure homogenizing device, to reduce the particle size into colloidal size range (operating pressure = 7000 psi, 5 cycles). The pseudolatexes were stirred for 48 - 72 h at room temperature and ambient pressure to evaporate the solvent and water prior to storage in a glass container. The final solids content of the dispersions was 10 %w/v.

The pseudolatexes (20 ml) were filled into glass vials and stored in an upright position in a refrigerator at 4 °C, at 25 °C and in ovens at 40 and 60 °C. The vials were removed at predetermined time intervals and analysed (n=3).

Chromatographic conditions - The chromatographic system and conditions were described in a previous paper (12). The sample solutions were obtained after separation of the colloidal polymer particles from the aqueous phase by ultracentrifugation (40,000 rpm, 1 hour, 5 °C, Beckman L5-50). The supernatants containing the free acids were diluted with water, if necessary.

pH measurements - The pH of the supernatant of the stored pseudolatexes was measured after a 2 min equilibration period with an Orion Research pH-meter (model 701A) at room temperature after separating the polymer phase by ultracentrifugation.

Particle size measurement - The average particle size of the pseudolatexes was determined by photon correlation spectroscopy (BI-200SM goniometer, BI-2030 digital correlator, Brookhaven Instruments Corporation, Holtsville, N.Y., Melles Griot 10 mW He-Ne laser).

RESULTS AND DISCUSSION

Although it is desirable to prepare aqueous colloidal polymer dispersions of water-insoluble polymers in order to overcome problems encountered in the coating with organic polymer solutions, problems in chemical and physical stability of the dispersions may dictate the preparation of redispersible polymer powders to be dispersed in the aqueous phase just prior to coating, or even the coating with organic solvents. The degradation of cellulosic esters in an aqueous environment is well-known. Several studies have reported the hydrolysis of cellulose acetate membranes under various pH and temperature conditions (8, 10, 11). The polymer degradation involves the hydrolysis of the ester groups and, possibly, the breakdown of the polymer backbone as was measured with cellulose triacetate by gel-permeation chromatography (9).

With pharmaceutical polymer dispersions, degradation of the polymer during storage may change the permeability of the resulting films or coatings and hence the drug release pattern. In addition, the physical stability of the colloidal polymer dispersion may be negatively affected. In this study, the hydrolysis of colloidal cellulose acetate and cellulose acetate butyrate dispersions was investigated.

The pseudolatexes of the cellulosic esters were prepared by a microfluidization - solvent evaporation method, which was similar to the process used previously to prepare drug-containing nanoparticles (13). The polymers were dissolved in a water-immiscible solvent or solvent mixture and emulsified into an aqueous phase containing sodium lauryl sulfate as surfactant, followed by microfluidization (high pressure homogenization) in order to obtain colloidal polymer particles. Cellulose acetate did not dissolve in methylene chloride and, in order to solubilize the polymer, methanol, which was also a nonsolvent, was added. The pseudolatexes were stabilized with sodium lauryl sulfate, an anionic surfactant. This surfactant has proven its stabilizing effect in a commercially available ethyl cellulose pseudolatex, Aquacoat (14). After solvent evaporation, the pseudolatexes were concentrated to a solids content of 10 %w/v. The size of the resulting polymer particles was in the range of 250-300 μm. The pseudolatexes were then stored in glass vials at different temperatures.

The hydrolysis of cellulose esters, which will remove acetyl and butyryl groups from the polymers, is generally followed by analysis of the remaining functional groups on the polymer. Standard methods of testing for the cellulose esters include assays for the hydroxyl, acetyl, propionyl, and butyryl content (15). A previously developed HPLC method was used to analyse the acidic degradation products, acetic and butyric acid, in the aqueous phase of the respective pseudolatexes (12); these concentrations were then converted to the amount of acetyl or butyryl groups remaining on the polymer backbone (the calculations were based on 1 L of a 10 %w/v pseudolatex). The colloidal polymer particles were separated from the aqueous phase by ultracentrifugation prior to injection of the polymer-free supernatant. The formation of free acetic acid or butyric acid as a result of ester hydrolysis was monitored as a function of temperature and time.

The saponification of esters in general follows second-order reaction kinetics, dependent on the concentrations of the ester and water. In the systems used here,

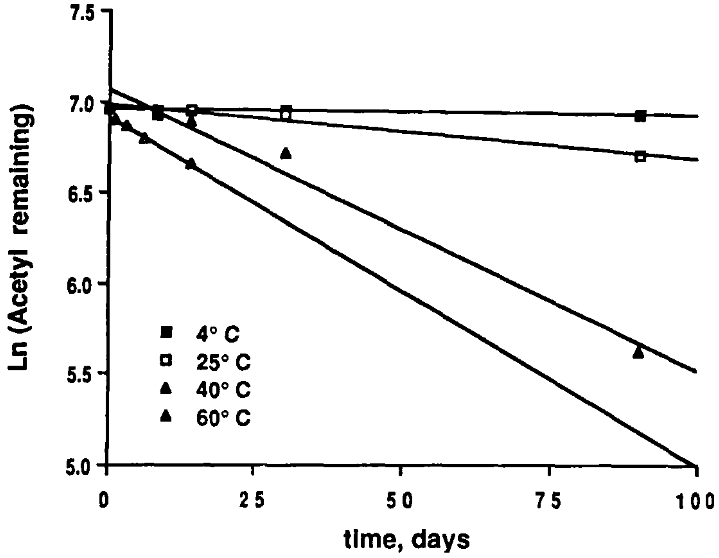

FIGURE 1

Semilog plots for the disappearance of acetyl groups versus time as a function of temperature in a cellulose acetate pseudolatex.

the water activity was essentially constant. The hydrolysis of the cellulose esters under these conditions was treated as a pseudo-first order reaction. The decrease in acetyl content in cellulose acetate pseudolatexes over a 90 days period at different temperatures followed first-order reaction kinetics (Figure 1). The acetyl content did not change significantly during storage in the refrigerator, but decreased at the other temperatures. The rate constants for cellulose acetate and cellulose acetate butyrate pseudolatexes, which were obtained from the slopes of the graph, are shown in Table 1. The energy of activation was determined from the Arrhenius equation by plotting the rate constants versus the inverse of temperature (Figures 2 and 3). The activation energy for cellulose acetate was 16.1 kcal/mole. With cellulose acetate butyrate, the activation energies for the acetyl and butyryl groups were 26. 9 and 31.9 kcal/mole, respectively. The higher activation energies for hydrolysis of the acetyl group, when compared to the cellulose acetate pseudolatex, could probably be explained with the more hydrophobic character of cellulose acetate butyrate (16).

TABLE 1

Effect of Temperature on the Hydrolysis Rate Constant, K, of Cellulose Acetate and Cellulose Acetate Butyrate Pseudolatexes.

	rate constant, k (x10,000, 1/day)		
Temperature, °C	4	25	40
Pseudolatex			
Cellulose Acetate	3.8	29.5	155.0
Cellulose Acetate Butyrate			
- acetyl group	0.1	1.8	32.0
- butyryl group	0.5	0.6	19.3

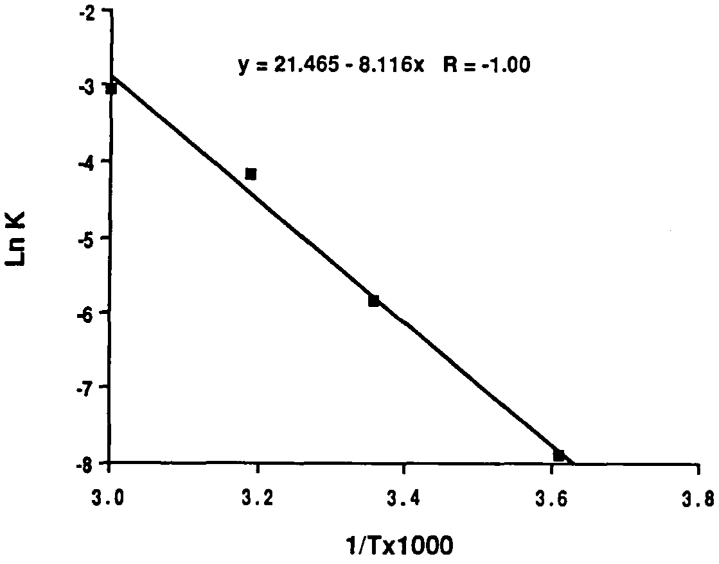

FIGURE 2
Arrhenius plot of cellulose acetate pseudolatexes.

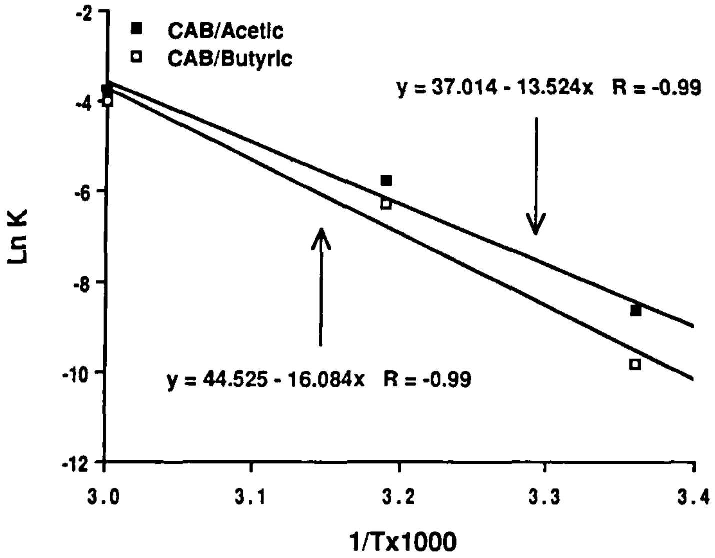

FIGURE 3

Arrhenius plot of cellulose acetate butyrate pseudolatexes.

The pH of the colloidal cellulose acetate dispersions decreased during storage as a result of the formation of free acetic acid in the aqueous phase (Figure 4). The pH dropped more rapidly at higher temperatures, this being consistent with the increased formation of acetic acid. The pH dropped from an original value of 4.5 to pH 3.4 at 4 °C, pH 3.0 at 25°C, 2.3 at 40 °C and pH 2.0 at 60 °C after 90 days storage. The reduction in pH upon storage at different temperatures was also seen with the colloidal cellulose acetate butyrate dispersion (Figure 5). The pH of the freshly prepared cellulose acetate butyrate pseudolatexes was lower when compared to the pH of the cellulose acetate pseudolatexes, pH 4.5 vs pH 6.3, respectively. This was indicative of the presence of higher amounts of free acids in the cellulose acetate powder when compared to the cellulose acetate butyrate powder prior to making the pseudolatexes. A washing of the polymer prior to the preparation of the colloidal dispersions may therefore be a feasible approach to remove any free acid present.

Increased free acetic and butyric acid concentrations were also found to adversely affect the physical stability of the cellulose ester dispersions. Except for

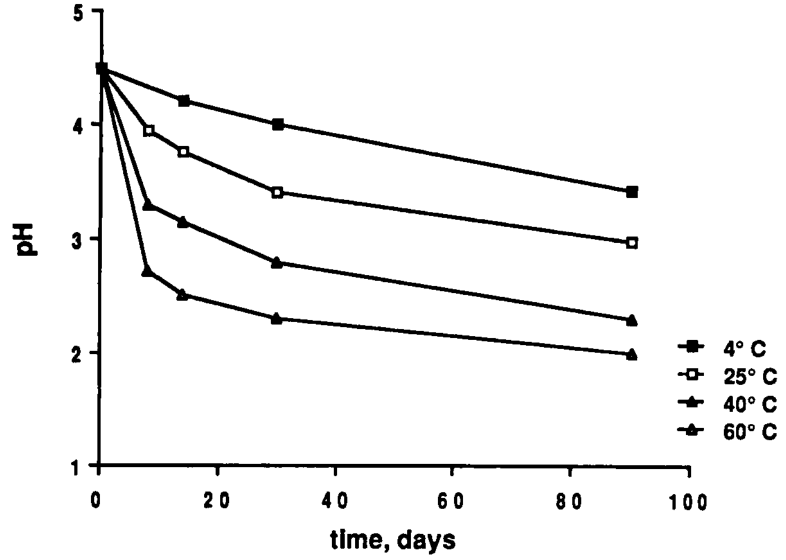

FIGURE 4

pH of cellulose acetate pseudolatexes as a function of temperature and time.

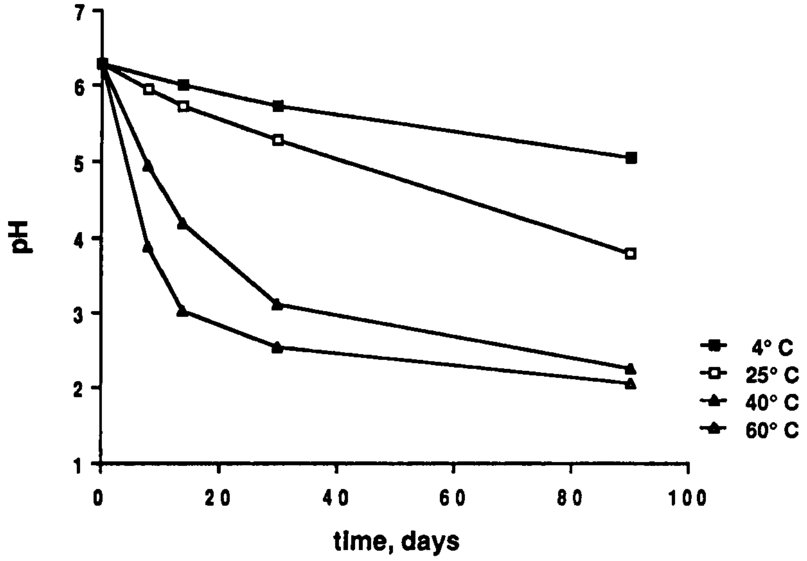

FIGURE 5

pH of cellulose acetate pseudolatexes as a function of temperature and time.

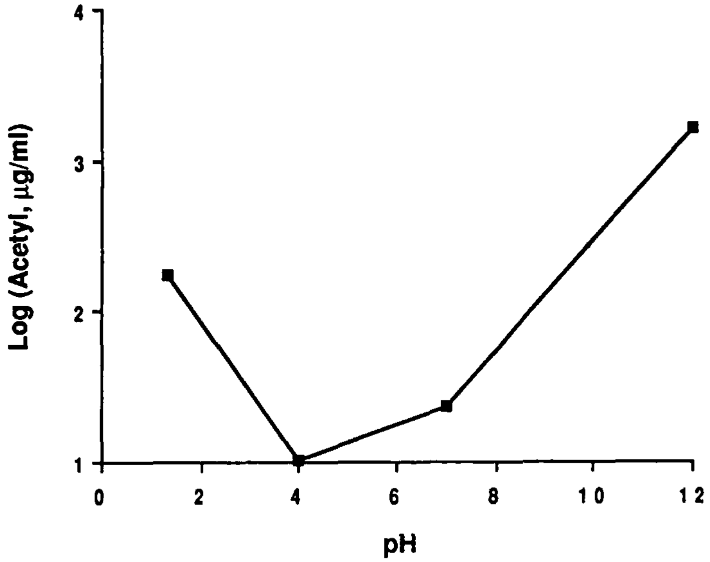

FIGURE 6

Effect of pH on the formation of free acetic acid in cellulose acetate pseudolatexes.

the pseudolatex stored at 4 °C, all cellulose acetate dispersions gelled over time. For example, cellulose acetate pseudolatexes stored at 25 °C for 9 months formed an almost clear, viscous gel. The cellulose acetate butyrate dispersions did not gel but flocculated over time. In addition to the degradation observed with the polymer, the decrease in pH also decreased the ionization of sodium lauryl sulfate (pka = 1.9), the anionic surfactant used to stabilize the pseudolatexes, thus impairing its stabilizing effect of electrostatic repulsion of the colloidal particles and possibly contributing to the agglomeration and physical instability.

The hydrolysis of cellulose acetate membranes has been studied as a function of pH (8). Minimum hydrolysis was observed at a pH around 4.5. Similar results were obtained after buffering the cellulose acetate pseudolatex to various pH values (pH 1 to 12) and measuring the formation of free acetic acid. The pseudolatex was most stable between pH 4 and 7 (Figure 6). The cellulose acetate pseudolatexes could therefore be stabilized by adjusting the pH of the aqueous phase. However, the buffer substances used would also be present in the dried polymer film after coating. The presence of the inorganic materials could negatively affect important film characteristics such as mechanical properties and permeability. Since it is also not feasible to store polymeric dispersions below room temperature, the preparation of a redispersible polymer powder is recommended. The colloidal cellulose ester dispersions could be converted into a powder through spray- or freeze-drying techniques. The resulting powder could then be redispersed in an aqueous phase just prior to the coating experiment.

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