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Stability of cellulose acetophthalate latex

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Abstract

The stability of cellulose acetophthalate latex (Aquateric^{TM}) was studied with differential scanning calorimetry, spectrophotometry, and scanning and transmission electron microscopy. We investigated the effects of pH, temperature and shaking on physicochemical properties of the latex particles. Stability of the polymer was most strongly affected by pH; hence, we conclude that the stability of this latex reaches a maximum at acid pH values, whereas stability is lost at neutral and alkaline pH. © 1998 Elsevier Science B.V.

Keywords: Differential scanning calorimetry; Latex; Stability

1. Introduction

Due to properties that make them suitable for both internal and external use, latexes are being increasingly used in pharmaceutical preparations [1,2], including tablets, injectables, ophthalmic and topical products [3–5]. Much work has focused on the development of colloidal systems for therapeutic uses, and such systems are providing physicians with new, improved medicaments. Colloidal systems have proven their usefulness in drug release, and have been employed as excipients and vehicles; this research has led to the concept of drug vectors [6].

An important feature of any colloidal system, including those involving latex particles, is the large exposed surface area between particles in the dispersion phase and the dispersion medium. We used spectrophotometry, differential scanning calorimetry (DSC), and scanning and transmission electron microscopy (SEM, TEM) to investigate and validate the stability of cellulose acetophthalate (CAP) latex (Aquateric^{TM}) [7] under different experimental conditions (pH, shaking, concentration and temperature). The results were interpreted in terms of the suitability of this polymer as a vehicle for drug delivery.

2. Experimental

Aquateric^{TM}, the polymer investigated here, is a registered trademark of FMC (USA), and was supplied by Foret SA, Spain [8]. The product is manufactured from CAP latex, and is supplied as a dry, white powder that is insoluble in water. The product consists of 69.7% cellulose acetate phthalate; during synthesis,

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20% Pluronic F-68 (cationic surfactant), Myvacet 9-40 (monoglyceride compound), Tween-60 (polyoxyethylene sorbitan monostearate) and an antifoaming agent (dimethylpolysiloxane) are added [7].

Differential scanning calorimetric analysis of the samples was performed with a Mettler FP85 DSC (Zürich, Switzerland) at a heating rate of 5 °C min^{-1} in a temperature range of 30 to 230°C. Sample weight was between 5 and 6 mg. Analyses with DSC were first done with the Aquateric$^{\text{TM}}$ latex alone. To check for the effect of temperature on latex stability, samples were desiccated at 40 and 60°C. Whenever the pH was a variable, hydrochloric acid and sodium hydroxide solutions were added to latex sample to adjust the pH to between 2 and 11. The samples were then desiccated at room temperature before running the DSC experiments.

The effect of shaking on the latex excipient was tested by treating samples for different periods in a Branson 5200E4 ultrasonic bath set at 450 W ultrasound power.

Particle size and shape in the dispersion were determined by SEM (Hitachi S-510, Japan) [9] and TEM (Zeiss EM 902, Oberkochen, Germany). Samples for SEM examination were metallized with gold. To determine particle size, the maximum horizontal diameter was measured (Feret×diameter) in several photographic fields to sample a representative number of particles (at least 600), as recommended by Allen [10]. These observations were primarily intended to provide complementary morphological information.

3. Results and discussion

3.1. Differential scanning calorimetry

Fig. 1(a) shows the thermograms for CAP latex. Two well-defined events were seen: an endothermal peak at 80°C and an exothermal peak at 180°C. This behavior was further studied in CAP, the major components of the latex (Fig. 1(b)). No prominent transitions were observed; instead, there was a broad endothermal process with a maximum change at ≈105°C, and an exothermal process at about 165°C. The calorimetric changes in the product were thus due to the latex rather than the CAP.

The influence of temperature was studied in samples that were heated to 40° and 60°C for 24, 48 and 72 h. After heating to 40°C (Fig. 2), the endothermal and exothermal transitions remained unchanged. However, the first endothermal event remained present throughout the study period, whereas the exothermal area became smaller as the duration of storage increased. Heating to 60°C had similar effect, although the changes were greater than those observed at 40°C.

To measure the effects of ultrasound, samples were shaken for 4 h at 450 W. This caused a slight shift of the exothermal and endothermal transitions toward lower temperatures (Fig. 3). However, the area of the exothermal curve was smaller than in untreated samples. Ultrasonic energy thus apparently destroyed some of the Aquateric$^{\text{TM}}$ particles, reducing the area under the curve of both peaks.

The latex in Aquateric$^{\text{TM}}$ protects substances that are altered in acid media, but has no such effect in alkaline media, where it can allow the substances to be released. This property makes Aquateric$^{\text{TM}}$ a valuable component of coatings which are resistant to gastric juices in some tablets formulations [11]. Subsequent studies tested the protective properties of this latex, containing active principles sensitive to pH. As a preliminary step, we tested the stability of this excipient under a wide range of pH values (2–11). Figs. 4 and 5 show that both, the endothermal and exothermal transitions appear in acid pH solutions, but are more pronounced than at the pH of the latex itself [4,5]. However, at pH 7, the endothermal transition was shifted to high temperatures (i.e. about 90°C), and the exothermal transition was replaced by a plateau. At pH 11, the changes were greater still: the endothermal transition appeared at 110°C, and the exothermal transition disappeared entirely. Further tests of samples at pH of 5, 6 and 7 showed that the exothermal transition began to disappear at pH 6. Our results, thus, showed that stability of the latex was most strongly affected by pH: whereas acid media had no effect on stability, the physicochemical properties of Aquateric$^{\text{TM}}$ began to change at pH values approaching neutrality.

3.2. Particle shape and size

Since the results of DSC pointed to pH as the factor that most strongly influenced the stability of the latex

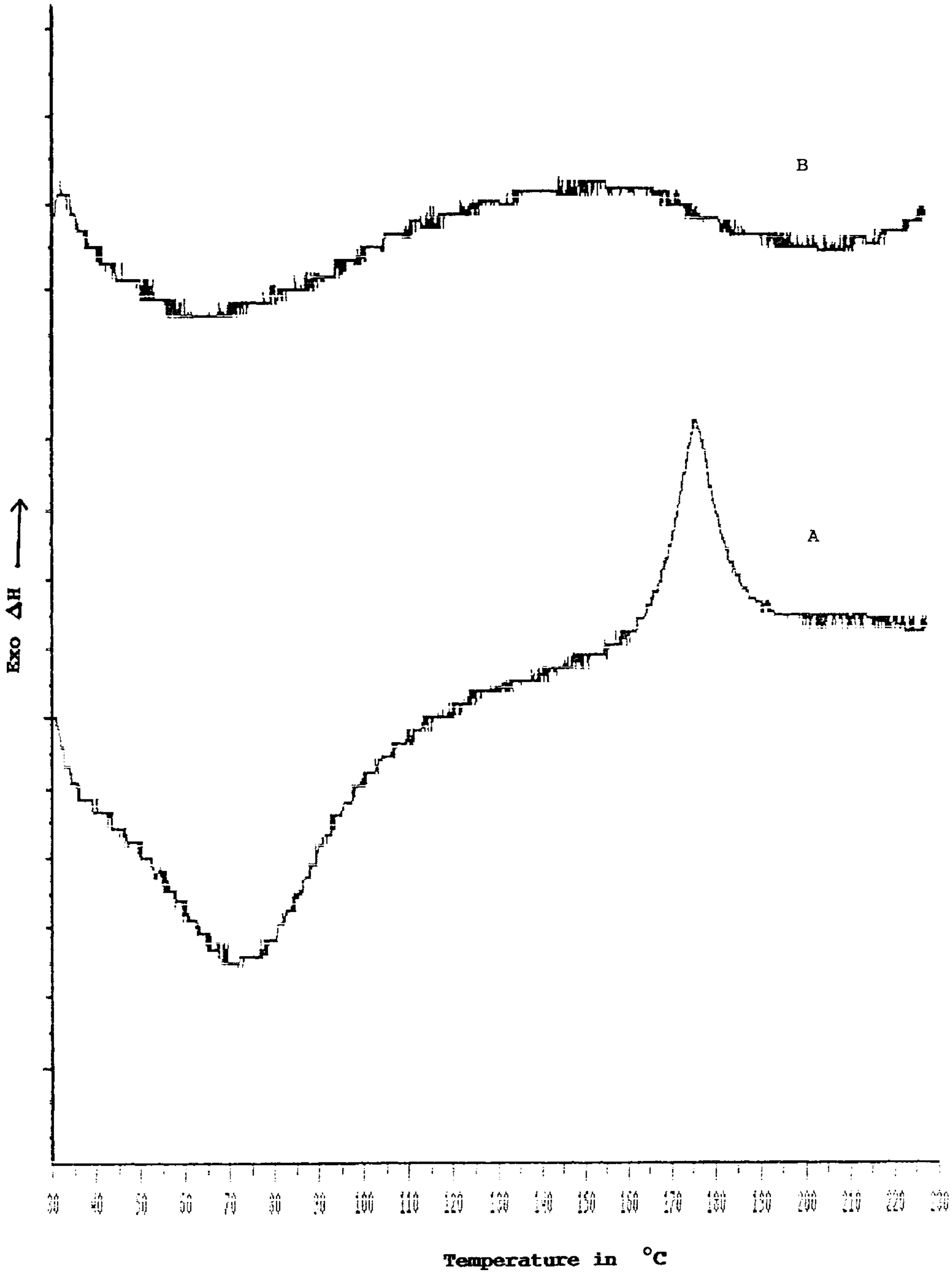

Fig. 1. DSC thermograms of (A) Aquateric^{TM} latex. (B) cellulose acetophthalate.

product, our SEM and TEM studies focused on the changes in particles during dispersion caused by different pH values. Fig. 6(A) and Fig. 6(B) are TEM micrographs of desiccated latex particles. In an aqueous dispersion of Aquateric^{TM} at its normal pH (4.5), two different populations of particles were

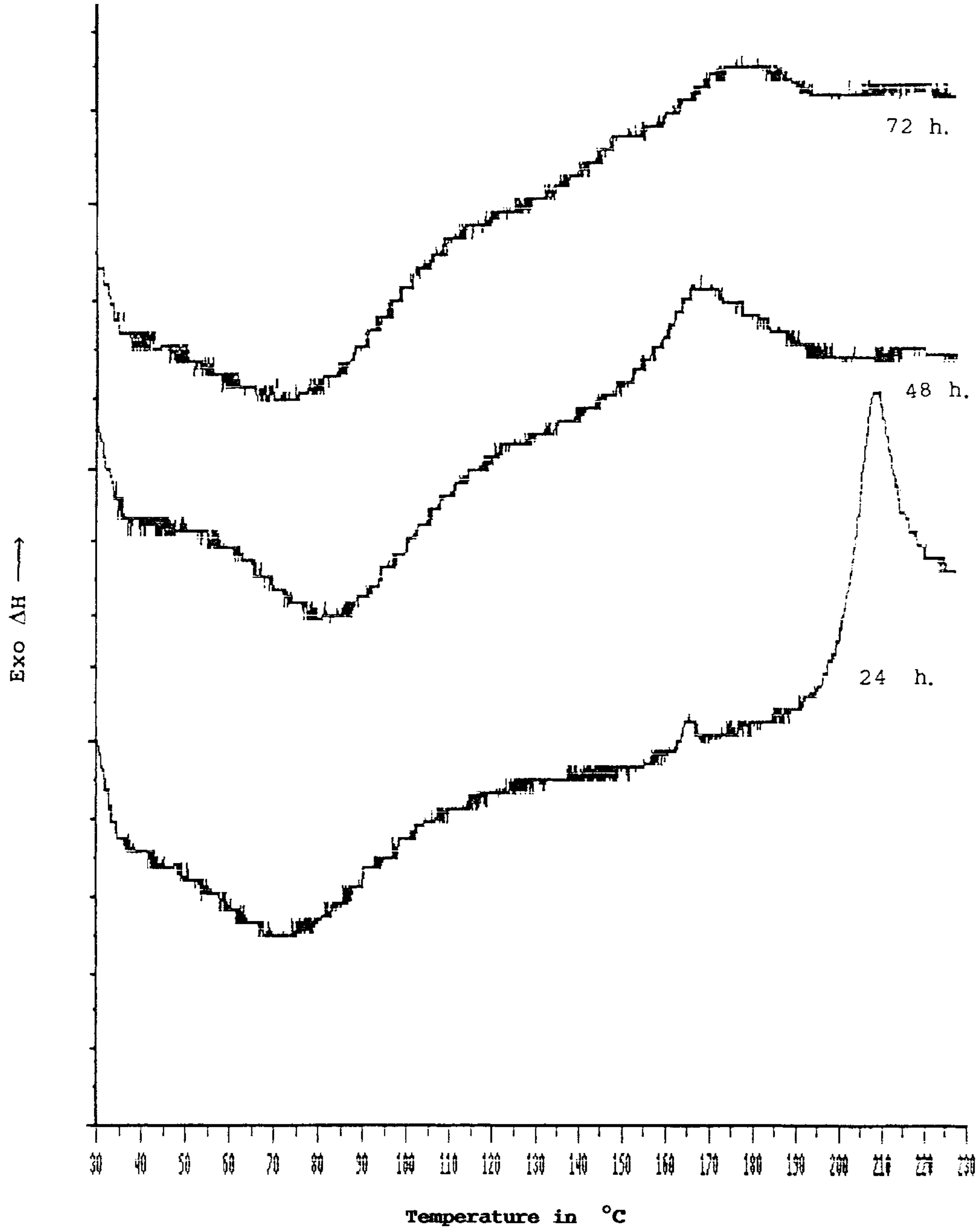

Fig. 2. DSC thermograms of Aquateric^{TM} latex heated at 40°C for 24, 48 and 72 h to 40°C.

seen: those with a mean diameter of 4.0 μm (Fig. 6(A)), and a much smaller number of larger particles, with a mean diameter of ≈25–30 nm (Fig. 6(B)).

In samples at pH 2, two clearly different-sized populations were also found, although both were larger than at pH 4.5. The smaller particles had a mean diameter of about 62.0 nm,

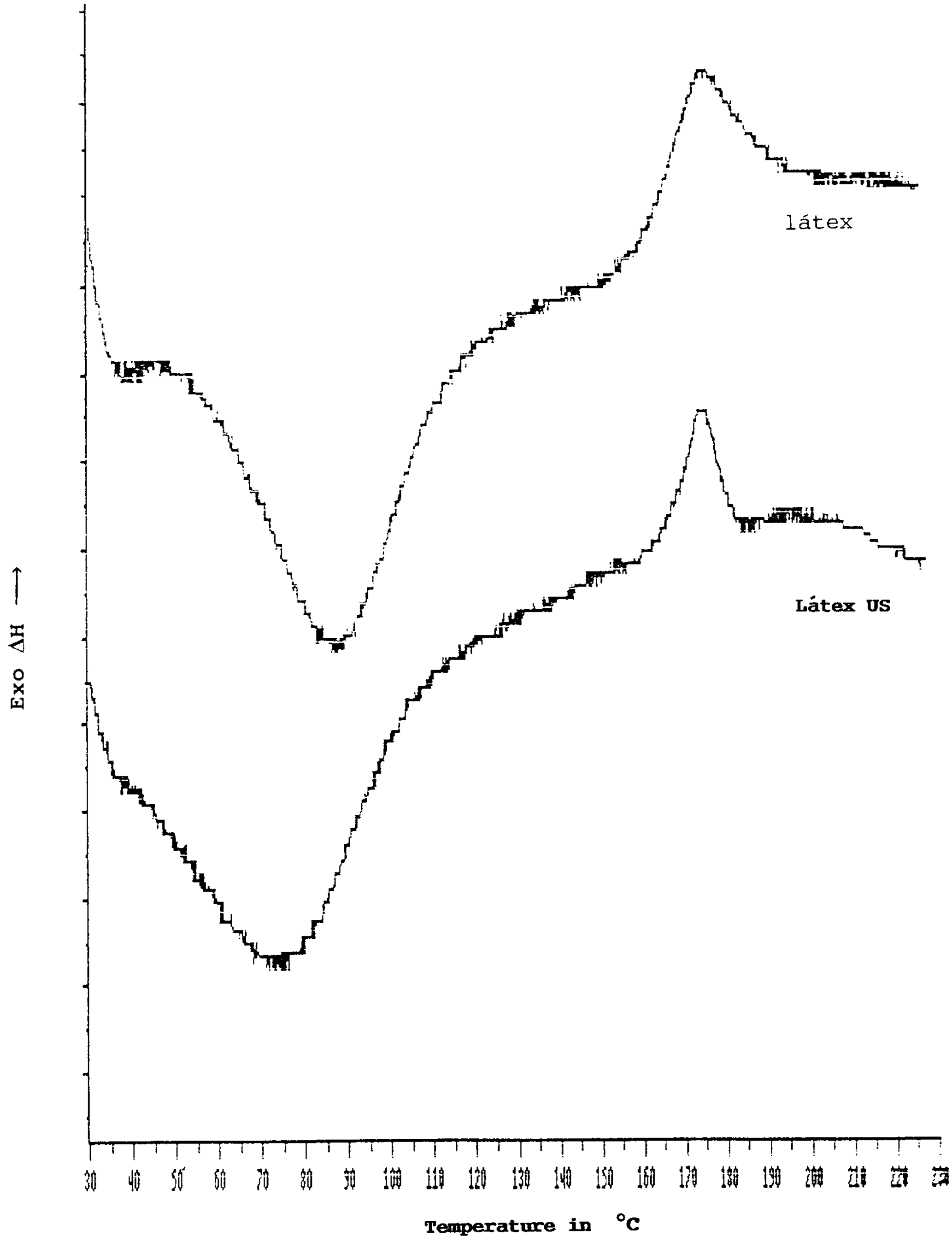

Fig. 3. DSC thermograms of Aquateric^{TM} latex with and without shaking.

and the larger particles measured ≈20 μm. These findings may reflect coalescence, as was seen with the naked eye in dispersions prepared in acid media: at lower pH values slight sedimentation appeared as a result of precipitation of the larger particles.

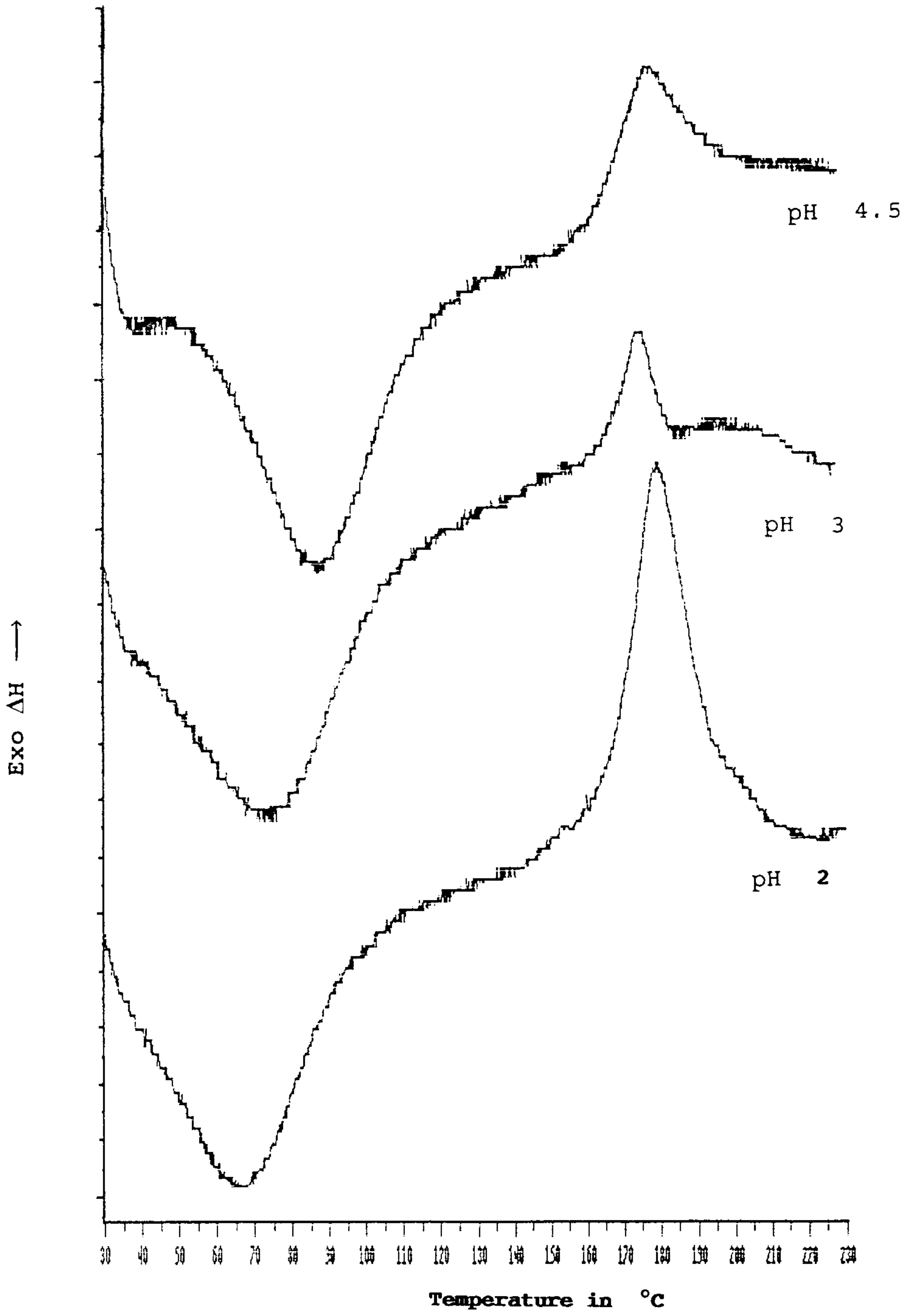

Fig. 4. DSC thermograms of Aquateric™ latex pH 2, 3 and 4.5.

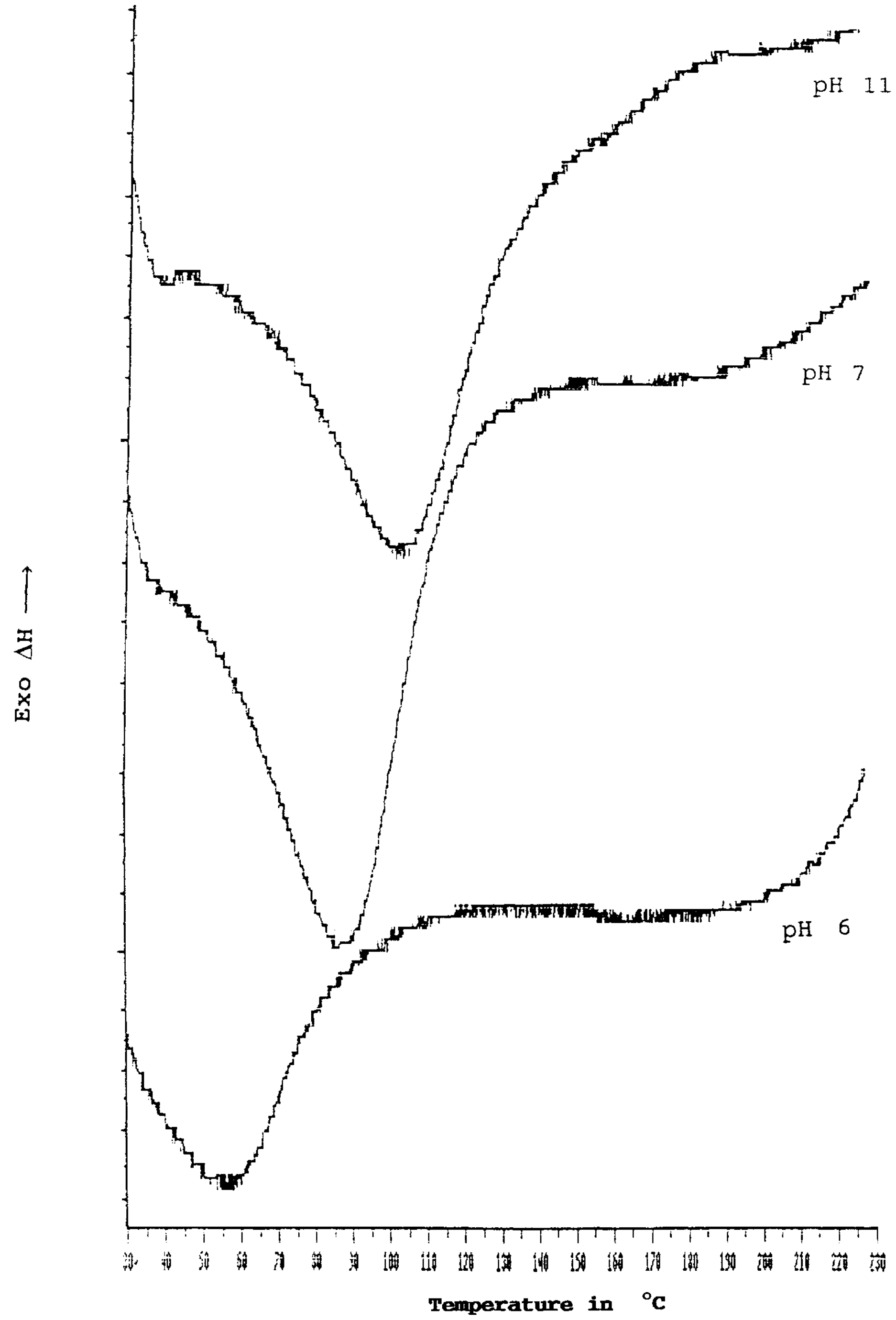

Fig. 5. Same as Fig. 4 at pH 6, 7 and 11.

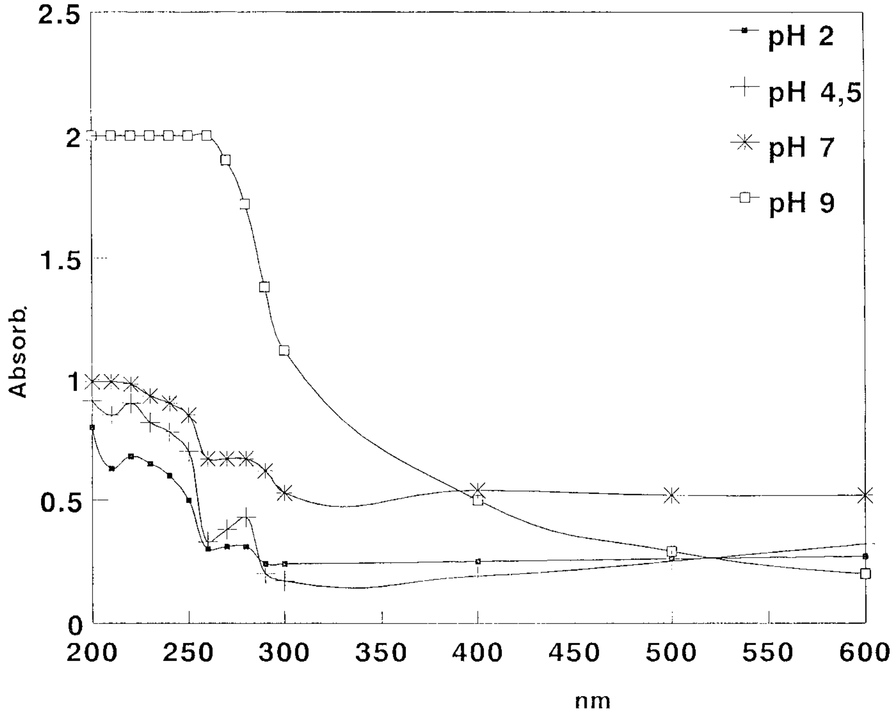

Fig. 6. Spectra of Aquateric^{TM} latex at different pH 2, 4, 5, 7, 9.

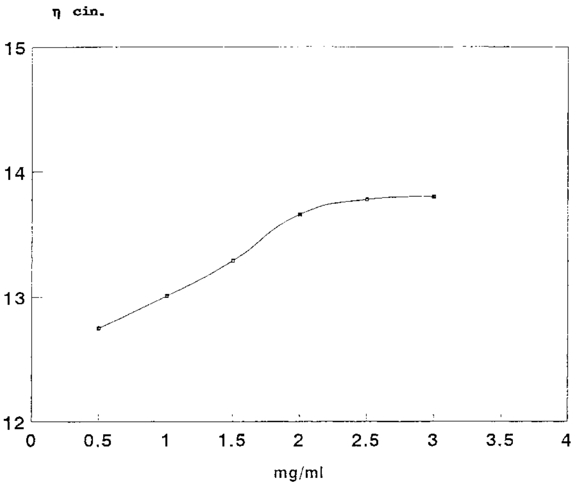

Fig. 7. Effect of concentration Aquateric^{TM} latex on viscosity.

At pH 8, only small particles (mean diameter 100–125 nm) were seen (Fig. 7). The larger particles found at acid pH values were absent. Observation of alkaline preparations with the naked eye also showed a different behavior from acid preparations: the dispersion was uniformly opaque, and no sediment was formed. The alkaline pH was probably responsible for these alterations in the behavior of the dispersion.

Scanning electron micrographs of preparations at natural and acid pH showed that their behavior was similar under both conditions (Fig. 8). Particles of many different sizes were seen, and coalescence was confirmed: particles clumped together to form larger triangular, hexagonal, or rosary-bead-like aggregates. In all such cases the particles were hollow,

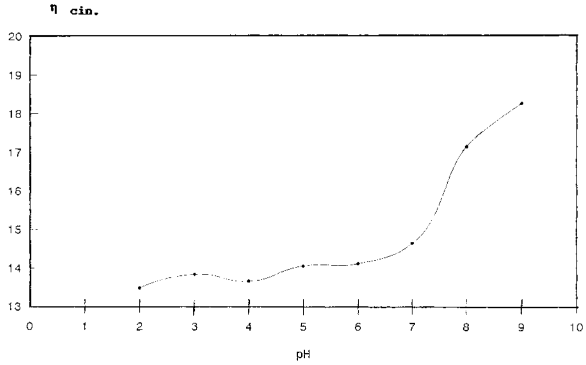

Fig. 8. Effect of pH on viscosity Aquateric^{TM} latex.

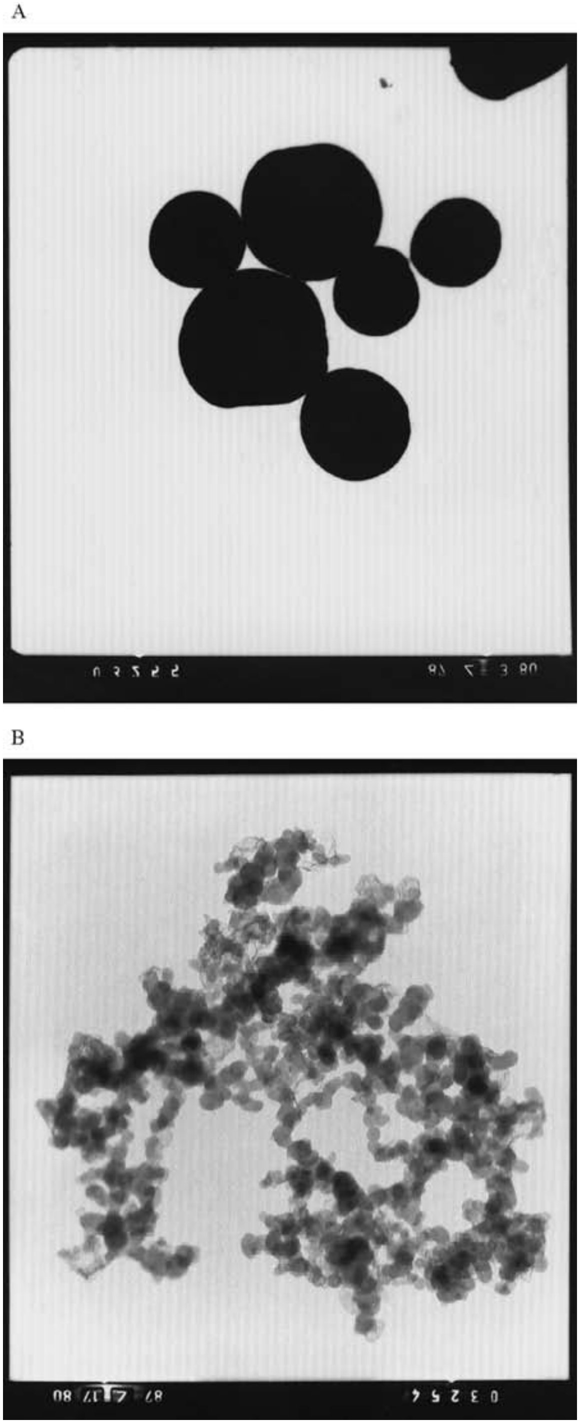

Fig. 9. (A) and (B). Photomicrographs of Aquateric$^{\text{TM}}$ latex obtained by TEM at pH 3 and 4.5.

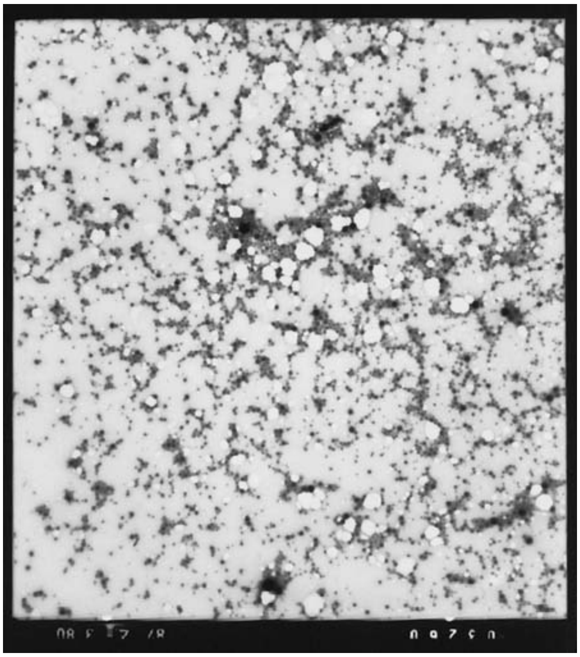

Fig. 10. Same as Fig. 9 at pH 8.

had a rough surface, and a spongy-appearing interior. Some particles appeared damaged or broken in two or more fragments. This may have been caused by the method of preparation used to obtain the latex.

As suggested by the physical appearance of the dispersions, the microscopic findings at alkaline pH were different from those in neutral or acid media. The particles were severely damaged (Figs. 9–12), and

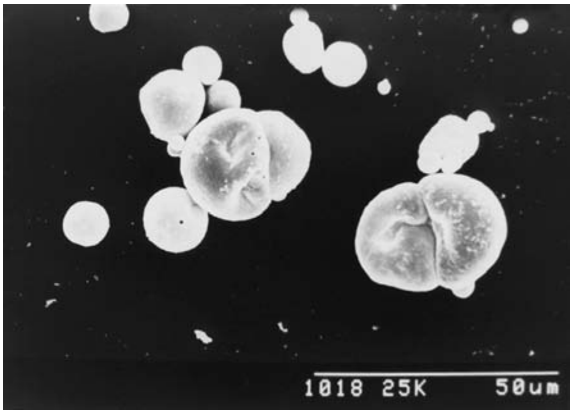

Fig. 11. Photomicrograph of Aquateric$^{\text{TM}}$ latex obtained by SEM at pH 3 and 4.5.

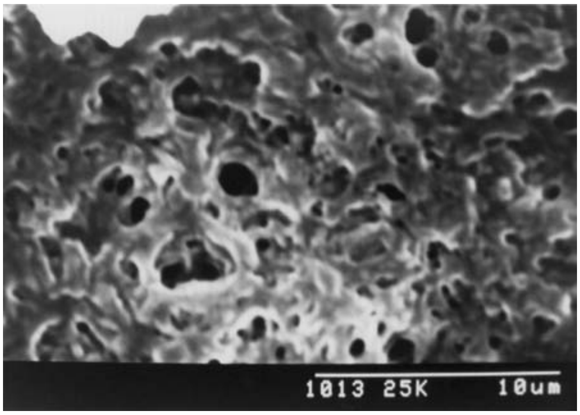

Fig. 12. Same as Fig. 11 at pH 8.

formed a more or less homogeneous mesh intermingled with fragments of particles.

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