Effect of pH on Monolayers of Cellulose Acetate Phthalate

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Abstract ☐ At pH values of 2–4, cellulose acetate phthalate monolayers are uncharged and are arranged in a compact, coherent form. An increase in pH brings about partial ionization and marked changes in monolayer organization. The effects of charge repulsion and increased solvation of charged groups cause marked expansion and decreased stability of cellulose acetate phthalate monolayers. The greatest effect of pH on monolayer properties appears to occur in the vicinity of pH 6.

Keyphrases ☐ Cellulose acetate phthalate monolayers—pH effect ☐ pH effects—cellulose acetate phthalate monolayers ☐ Surface pressure—cellulose acetate phthalate monolayers ☐ Films, cellulose acetate phthalate—compression effect, area

Many properties of interest of polymer coatings depend strongly on the chemical constitution and structural arrangement of the film-forming agent. A better understanding of the molecular properties of polymers would help in interpreting the behavior of pharmaceutical coatings and in predicting the properties of untested formulations. Studies of monolayers of polymers have provided information on polymer structure (1, 2) and interactions (3). The properties of polymer monolayers have been shown to be related to those of free films and enteric coatings (3, 4). Zatz and Knowles (4) examined monolayers of several cellulose esters on subphases of pH 3 and 6.5. The force–area (π–A) isotherms of cellulose acetate butyrate and cellulose acetate stearate were virtually independent of pH. The π–A curves of cellulose acetate phthalate (CAP), on the other hand, were significantly different at the two pH values. In this communication, further experiments on pH effects in CAP monolayers are described.

EXPERIMENTAL

CAP[1] was purified by precipitation from solution in benzene–ethanol (1:1), using n-hexane as the nonsolvent. The polymer mass was washed with n-hexane and dried *in vacuo* at 30° to constant weight. The material thus purified contained 18% by weight of combined acetyl and 32% by weight of combined phthalyl. It was free of monomers and moisture. Water was deionized and then distilled in an all-glass still. Organic liquids were of reagent grade and were found free of surface-active contaminants (5). Inorganic materials employed were of reagent grade and were not further purified. The trough of the surface balance was made of Teflon and was cleaned using live steam. Surface pressure was determined by the Wilhelmy plate method, using a roughened platinum plate.

The pH of the subphase was adjusted to the desired value, using HCl for low pH values (2–5) and a mixture of K_2HPO_4 and KH_2PO_4 for high pH values (5–8). Sufficient KCl was then dissolved in the subphase to bring the ionic strength to 0.1, except as otherwise indicated. The results at pH 5 were independent of whether the subphase contained HCl or the phosphate buffers, indicating that the buffering agents did not interact with the monolayer. CAP, dissolved in isopropanol–benzene (1:1), was applied dropwise to the surface by means of an Agla micrometer syringe. Essentially the
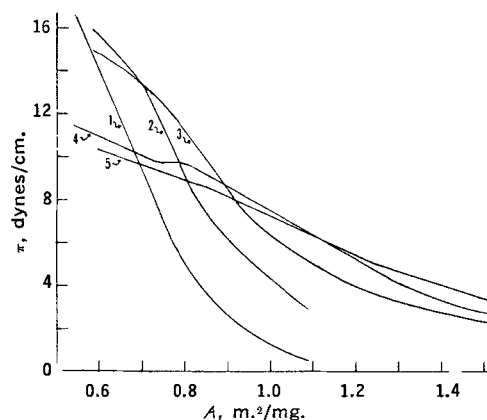
Figure 1—π–A *curves of monolayers of CAP at various subphase pH values:* (1) 2, 3, and 4; (2) 5.1; (3) 5.6; (4) 6.1; and (5) 7.0.

same results were obtained when isopropanol–methylene chloride was employed as the spreading solvent (6). After spreading the polymer, 10 or 15 min. was allowed for equilibration. The rate of compression in all experiments was about 0.02 m.²/mg./min. Compression was continued until surface pressure no longer varied with available surface area. This limiting surface pressure was reproducible within 0.5 dyne and was taken to be the collapse pressure of the monolayer. All studies were carried out at room temperature (25.5 ± 0.7°).

RESULTS AND DISCUSSION

The π–A curves for monolayers of CAP as a function of subphase pH are presented in Fig. 1. At subphase pH values of 2–4, the identical π–A curve is obtained, indicating that the film is essentially uncharged over this pH range. The polymer molecules would be expected to have the pyranose rings lying flat at the surface to allow the contact of subphase water molecules with all hydrophilic groups in each ring (7). However, even at low values of surface pressure, the repeating groups are not horizontally oriented. Based on the chemical composition of the polymer, the average formula weight per repeating group was calculated to be 317. Each milligram of polymer contained, therefore, 1.9 × 10¹⁸ repeating groups. From the amount of material spread and the surface area, one may calculate the area occupied by each group. At a surface area of
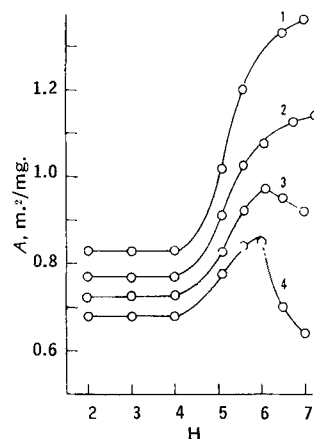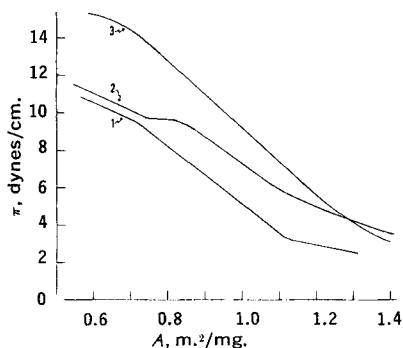

Figure 2—*Surface area of CAP as a function of pH at various values of surface pressure:* (1) 4 dynes/cm.; (2) 6 dynes/cm.; (3) 8 dynes/cm.; and (4) 10 dynes/cm.

Figure 3 — π - A *curves of monolayers of CAP at various subphase ionic strengths with pH = 6.5: (1) 0.03; (2) 0.1; and (3) 1.0.*

Figure 4—*Monolayer collapse pressure and dA/dπ as a function of subphase pH.*

2 dynes/cm., the surface area available to CAP molecules is 0.96 m.^{2}/mg., which is equivalent to 51 Å^2 per pyranose unit. This is very nearly equal to the area occupied by the unsubstituted, horizontally oriented pyranose ring of cellulose (7) and is clearly too small to allow the more bulky repeating groups of CAP to lie flat at the interface. The rings of CAP are, therefore, tilted from the horizontal. In addition, some ester substituents may be folded over or under the main polymer chain. Examination of Dreiding molecular models shows that, in this way, the effective surface area occupied by each pyranose group may be reduced. These considerations, coupled with the relatively high collapse pressure of CAP compared to monolayers of other cellulose esters (4), suggest that uncharged films of this polymer are rather compact and coherent.

An increase in subphase pH (above 4) causes monolayer properties to become pH dependent. In the expanded region (1) (at surface areas greater than about 0.9 m.^{2}/mg.), surface pressure generally increases with a rise in pH. Collapse pressure decreases over the same pH range. In general, the π-A curves tend to become flatter as pH is increased, so that the monolayers appear to be more expanded.

Above a subphase pH of 4, the monolayers are negatively charged due to ionization of the carboxyl group of the phthalate moiety. Repulsion of like charges would be expected to cause an increase in surface pressure according to the relation:

$$\pi = \pi_0 + \pi_r \qquad \text{(Eq. 1)}$$

where π is the observed surface pressure, π_0 is the surface pressure of an unionized film, and π_r is the surface pressure component resulting from charge repulsion (8). This theory predicts that, at a given surface pressure, a charged film will always occupy a larger area than an uncharged one. Figure 2 shows the effect of subphase pH on the surface area available to CAP molecules at various values of surface pressure. Up to a surface pressure of about 6 dynes/cm., the expected relation appears to hold (Curves 1 and 2, Fig. 2). At higher surface pressures (Curves 3 and 4, Fig. 2), it does not, indicating that charge repulsion is not the only factor involved.

Changes in the adhesion of the monolayer to the subphase must also be considered (2, 9). Charged groups are strongly attracted to the underlying water molecules as a result of ion–dipole forces. Thus, above a pH of 4, as a result of both solvation of charged groups and repulsion of like charges in the film, the polymer structure is rearranged from the compact, coherent form assumed in the unionized state to a more open, extended conformation. The degree of expansion is dependent upon the degree of ionization and, therefore, upon pH. Compression of the charged monolayers causes a fairly rapid increase in surface pressure at large areas because of the contribution of π_r. As the area available to polymer molecules is reduced, solvation of charges may cause the molecules to assume an "accordion" conformation in which ionized groups are immersed in the subphase as completely as possible. The increase in adhesion reduces film stability and causes the charged films to collapse at lower surface pressures.

Support for this mechanism comes from experiments in which the ionic strength of the subphase was varied. The π-A isotherm of uncharged monolayers of CAP (subphase pH = 3) was independent of ionic strength when the latter was varied over a range of 0.001–1.0. On the other hand, changes in salt concentration had a decided influence on the properties of monolayers of CAP at pH values above 4. The π-A results at a pH of 6.5, under conditions of varying ionic strength, are presented in Fig. 3. As the salt concentration is
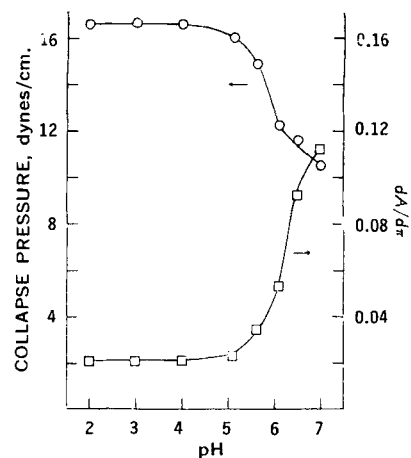
raised, the thickness of the electrical double layer around charges on the monolayer is reduced, thus weakening the effects of charge repulsion. Salting out effects are probably also involved, so that solvation and attraction of the polymer for the subphase are reduced. Therefore, increasing ionic strength should cause the charged CAP monolayer to become more condensed and to collapse at a higher surface pressure. These tendencies are observed in Fig. 4.

Inspection of Fig. 1 reveals that changes in monolayer properties are not a smooth function of pH. Instead, there appears to be a fairly narrow range of pH over which substantial changes in collapse pressure and slope occur. Figure 4 shows that the sharpest decrease in collapse pressure takes place at a pH of about 5.8. In the same figure, the reciprocal of the slope of the condensed portion of each curve, $dA/d\pi$, is plotted *versus* pH; $dA/d\pi$ is related to the compressibility of the film, which is a measure of its compressional elasticity. The sharpest increase in $dA/d\pi$ occurs at a pH of about 6.2 (Fig. 4). Plots of the area occupied in CAP molecules as a function of pH, at surface pressures at which the monolayers are condensed (Curves 3 and 4, Fig. 2), exhibit breaks around pH 6.0. The greatest effect of pH on monolayers of CAP appears, therefore, to occur in the vicinity of pH 6.

The results of this investigation suggest that complete dissolution of coating material may not be necessary for a drug to be released from a dosage form coated with CAP. In the highly acid environment of the stomach, CAP is unionized and probably quite coherent. In the duodenum, where the pH is approximately 6, ionization of accessible phthalate groups will occur, probably causing expansion and allowing penetration of water and ions. Although the coating may not be completely dissolved, sufficient penetration of water molecules through the coating may bring about disintegration or leaching.

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