

Monomolecular Film Properties of Some Cellulose Esters

JOEL L. ZATZ and BEVERLY KNOWLES

Abstract □ Cellulose acetate butyrate, cellulose acetate stearate, and cellulose acetate phthalate have been studied as monolayers at the air-water interface. Monolayers of the first two were virtually unaffected by changes in subphase pH, whereas the last one, cellulose acetate phthalate, exhibited large differences under the same conditions. Certain monolayer properties of the cellulose esters have been used to interpret the behavior of these polymers as free films and enteric coatings.

Keyphrases □ Cellulose esters—monomolecular film properties □ Film properties, monomolecular—cellulose acetate butyrate, cellulose acetate stearate, cellulose acetate phthalate □ Polymer monolayers—as model for enteric, film coatings

An approach that has provided information on the properties of film-forming polymers is the study of these materials as monolayers at the air-water interface (1). Such studies give insight into the molecular structure of polymers (1, 2) and may be used to investigate interaction of polymers with other substances, such as plasticizers (3).

Among the polymers used as coatings for pharmaceutical dosage forms, the cellulose esters represent an important group. These materials have previously been studied as free films and as coatings applied to tablets. Antonides and DeKay (4) evaluated various cellulose derivatives for possible use as enteric coatings. Patel *et al.* (5) studied water vapor transmission through free films of cellulose esters as a function of temperature and film thickness. Lachman and Drubulis (6) reported the influence of plasticizers on water vapor transmission through free films of cellulose acetate phthalate.

This study is concerned with the monomolecular film properties of three esters of cellulose, cellulose acetate phthalate (CAP), cellulose acetate butyrate (CAB), and cellulose acetate stearate (CAS). By adjusting the pH of the subphase to values of either 3 or 6.5 before spreading the polymer film, it was possible to assess the effect of a large change in environmental pH on the properties of each polymer studied.

EXPERIMENTAL

Materials and Apparatus—The cellulose derivatives were purchased¹ and purified further to remove residual monomers and other possible contaminants. CAP (32% phthalyl) 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. As a result of this procedure, the free phthalic acid content of the polymer was reduced from an initial value of 1.3% w/w to a negligible level. Similarly, CAB (17% butyryl) was precipitated from solution in ethyl acetate by *n*-hexane. The precipitate was washed with *n*-hexane and dried *in vacuo* at 50° to constant weight. CAS was sus-

ended in *n*-hexane, repeatedly washed with that solvent, and dried *in vacuo* at 50°. Water was deionized and then distilled in an all-glass still. The organic liquids employed were of reagent grade and were found to be free of surface-active contaminants (7). The inorganic materials employed were of reagent grade and were not further purified. The Teflon surface balance has already been described (8). Surface pressure was determined by the Wilhelmy plate method.

Procedure—The pH of the subphase was adjusted using HCl to obtain a pH of 3 or a buffer system containing K₂HPO₄ and KH₂PO₄ to obtain a pH of 6.5. The ionic strength of each solution used as subphase was adjusted to 0.1 M using KCl. The polymer under investigation was dissolved in a suitable solvent, and the solution was applied to the surface by means of an Agla micrometer syringe. CAB was dissolved in methylene chloride, CAS in benzene, and CAP in an isopropanol-benzene mixture, 1:1. Preliminary experiments showed that essentially the same results were obtained using other spreading solvents (isopropanol-methylene chloride for CAP and methylene chloride-benzene for CAB). After spreading the polymer, 10 or 15 min. was allowed for equilibration. Then the area available to polymer molecules was slowly decreased (at a rate of about 0.02 m.²/mg./min.); surface pressure was determined as a function of available surface area. All studies were carried out at room temperature (25 ± 0.7°).

RESULTS

Plots of surface pressure as a function of available surface area (π -A curves) for the cellulose esters studied are presented in Figs. 1-3. Each plot is based on at least three independent experiments. The reproducibility was such that at a given surface area, the surface pressure found in each experiment was within 0.6 dyne/cm. of the average value plotted in Figs. 1-3.

The π -A curves for CAB are shown in Fig. 1. The results with a subphase pH of 3.2 were nearly identical with those at a pH of 6.5. Monolayers of CAB collapsed to form a stringy, tenacious coagulum.

Some difficulty was encountered in spreading CAS at the surface. Droplets of spreading solution formed from the tip of the Agla syringe appeared to lose their clarity after a few seconds because of polymer adsorption and precipitation at the surface of the drop. Certain proteins are known to behave in a similar manner (9). Since all of the polymer was not in solution when applied to the surface, it is possible that the CAS was not completely spread. The π -A results, given in Fig. 2, show a slight variation in surface pressure as a function of pH. However, at a given surface area, the difference in surface pressure is always less than 2 dynes/cm. and

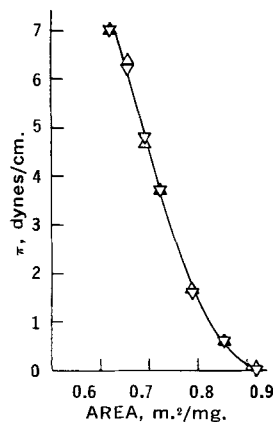


Figure 1—Surface pressure (π)-area (A) isotherms of CAB at two subphase pH values: ∇ , pH = 3.2; and \star , pH = 6.5.

¹ Eastman Organic Chemicals, Rochester, NY 14650

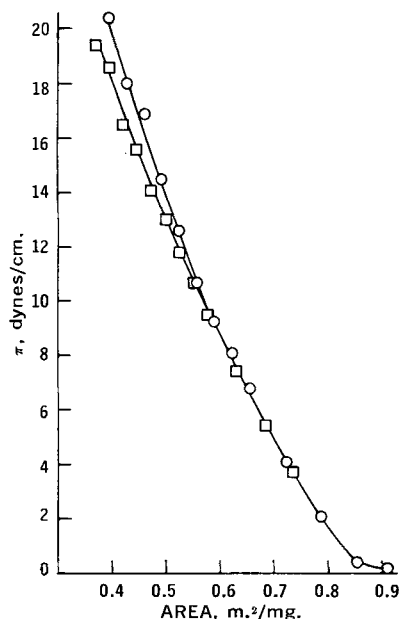


Figure 2—Surface pressure (π)-area (A) isotherms of CAS at two subphase pH values: \square , pH = 3.2; and \circ , pH = 6.5.

is probably the result of experimental error. The two curves in Fig. 2 are quite similar and indicate that no significant change in the properties of CAS occurs when the subphase pH is changed from 3.2 to 6.5.

Quite another result is obtained for CAP monolayers (Fig. 3). At a pH of 3.1, the π -A curve exhibits a condensed region at areas smaller than about 0.8 m²/mg. In the same region, the monolayer on a subphase of pH 6.5 appears to be much more expanded. Monolayer collapse pressure at a pH of 3.1 is 16.6 dynes/cm. The corresponding value for a pH of 6.5 is 11.4 dynes/cm. At a pH of 3.1, the extrapolated area at zero pressure of the film is 0.89 m²/mg., increasing to 1.56 m²/mg. at a subphase of pH of 6.5.

DISCUSSION

Monolayers of CAB and CAS were virtually unaffected when subphase pH was raised from about 3 to 6.5, whereas large changes occurred in the monolayer properties of CAP. These changes may reflect an alteration in conformation at the interface, which CAB and CAS do not undergo. Therefore, it may be inferred that neither CAB nor CAS could function as an effective enteric coating. Because the properties of these polymers are independent of pH, tablet disintegration could occur in: (a) either the stomach or small intestine, or (b) neither the stomach nor small intestine. For both of these polymers, the second alternative was actually found to be the case (4).

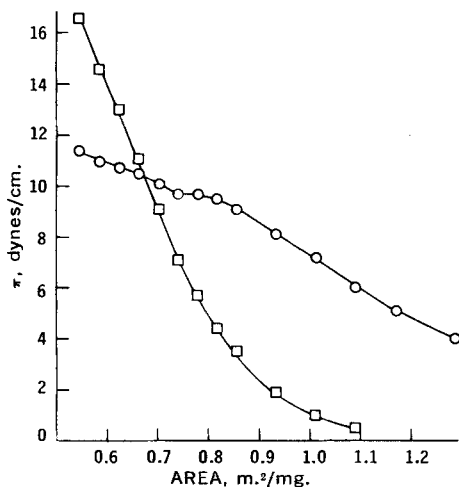


Figure 3—Surface pressure (π)-area (A) isotherms of CAP at two subphase pH values: \square , pH = 3.1; and \circ , pH = 6.5.

Table I—Some Properties of Unionized Cellulose Esters

Polymer	Collapse Pressure, dynes/cm.	Extrapolated Area at Zero Pressure, m ² /mg.
CAB	7.0	0.82
CAS	19.4	0.74
CAP	16.6	0.89

The change in monolayer properties of CAP with pH is due to the presence of the ionizable carboxyl group in the phthalate moiety, which is presumably uncharged at a pH of 3.1 but negatively charged at a pH of 6.5. The satisfactory performance of CAP as an enteric coating has been ascribed to its insolubility in the strongly acid stomach fluids, where the polymer is uncharged, and its corresponding solubility in the weakly acid small intestine, in which the polymer is charged (10).

A very important property of polymer coatings is permeability to moisture. Moisture permeates polymer films by simple diffusion and by an additional mechanism involving clustering of water molecules about polar centers (11). In a series of related polymers, the most hydrophobic will generally exhibit the lowest moisture permeability.

It is instructive to compare the collapse pressures of the unionized cellulose esters as given in Table I. Collapse pressure, a measure of monolayer stability, is dependent on the balance between adhesion and cohesive forces in the film (12). In a series of compounds, those that exhibit strong intermolecular interactions will have higher collapse pressures. The most important contribution to monolayer stability appears to arise from van der Waals' interactions between hydrophobic groups. Thus, for a group of monolayers of similar constitution, monolayer collapse pressure may be taken as a qualitative measure of "hydrophobicity." Such a relationship has been demonstrated for the half-esters of poly-(methyl vinyl ether/maleic anhydride) (3). Based on collapse pressure values, one may conclude that CAS is more hydrophobic than CAB and that films of CAS should be less permeable to moisture than films of CAB. This predicted order is in agreement with experimental results (5). CAP differs from the other cellulose derivatives studied because it contains an additional polar group, the carboxyl group. Its presence would be expected to increase the interaction of CAP with the subphase and to influence the monolayer collapse pressure. For this reason the collapse pressure of monolayers of CAP should, strictly speaking, not be compared with those of CAB and CAS to predict relative moisture permeability of films. Nevertheless, values for both collapse pressure (Table I) and moisture resistance (5) increase in the order CAB, CAP, CAS.

By using polymer monolayers as a model for enteric and film coatings, a great deal of basic information may be obtained within a relatively short time. This new approach may be utilized in the evaluation of new polymers and of polymer mixtures as potential coating materials, and it will hopefully result in the introduction of novel formulations with superior properties.

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Received November 28, 1969, from the *Department of Pharmacy, College of Pharmacy, Rutgers University, Newark, NJ 07104*
Accepted for publication March 9, 1970.

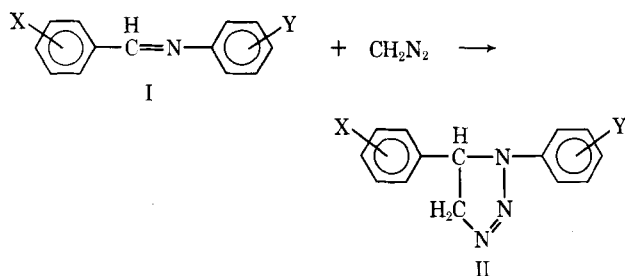
Triazolines VI: Evaluation of 1,5-Diaryl- Δ^2 -1,2,3-triazolines and Arylidene Anilines for Herbicidal Activity

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Abstract □ A large number of 1,5-diaryl- Δ^2 -1,2,3-triazolines and arylidene anilines (from which the triazolines are derived) have been examined for the first time for herbicidal activity. Although the majority of the compounds as a class showed no activity, those bearing 3 or 4 halogen substituents evinced slight activity in post-emergence tests.

Keyphrases □ 1,5-Diaryl- Δ^2 -1,2,3-triazolines—herbicidal activity □ Arylidene anilines—herbicidal activity □ Herbicidal activity—1,5-diaryl- Δ^2 -1,2,3-triazolines, arylidene anilines

Studies in the author's laboratories on solvation effects and the role of protic-dipolar aprotic solvents in 1,3-cycloaddition reactions (1-5) have helped pave the way to the proper understanding and application of solvation energy to assist bimolecular cycloaddition reactions. Thus, the accelerating effect of water on the 1,3-cycloaddition of diazomethane to Schiff bases (arylidene anilines) (I) has led to a versatile general method for the synthesis of the rarely encountered Δ^2 -1,2,3-triazolines (II) (3, 6) (Scheme I). By carrying out



the addition reaction in aqueous dioxane solutions, a variety of previously unknown 1,5-diaryl-1,2,3-triazolines have been obtained in good yields. Earlier methods of syntheses (7, 8) have either failed to give a triazoline adduct or have yielded only insignificant amounts of the products. As a result, there is no reference in the literature to any studies on the biological properties of this group of heterocyclic compounds. The cycloaddition reaction in aqueous dioxane solutions has now made a large number of 1,2,3-triazolines readily available in sufficient quantities to permit, for the first time, a detailed screening of these compounds for biological activity. In this paper, a brief report on the results of screening for herbicidal activity is presented.

About 30 1,5-diaryl-1,2,3-triazolines (II) bearing one or two substituent groups on the C-phenyl and/or the N-phenyl and the respective arylidene anilines (I), from which the triazolines are derived, were screened for preemergence, postemergence, and defoliant activities. Although the majority of the 1,2,3-triazolines and arylidene anilines showed no activity, compounds bearing 3 or 4 halogen substituents evinced slight activity. The latter compounds caused visible chlorosis, contact and formative effects, and necrosis in the broad-leaf species in postemergence applications; the cereals, however, were unaffected. Both cereals and broadleaf species also were not affected in preemergence or defoliant tests.

EXPERIMENTAL

The 1,5-diaryl-1,2,3-triazolines and arylidene anilines containing such substituents as the nitro, chloro, bromo, methyl, methoxy, or carbalkoxy groups on the C-phenyl and/or the N-phenyl ring, in the *o*-, *m*-, or *p*-positions (with the exception of the carbalkoxy groups, which were present only in the *p*-position of the N-phenyl ring) were previously prepared in the author's laboratory (1-6). The *p*-aminobenzoic esters necessary for the preparation of the arylidene *p*-aminobenzoates were synthesized, in a convenient one-step reaction, by refluxing the *p*-aminobenzoic acid with excess alcohol in the presence of commercial boron trifluoride ethyl ether as the catalyst (9).

The test compounds were dissolved in acetone containing 0.5% polysorbate 20¹ and sprayed vertically onto potted seedlings aged 7 days from planting at the time of treatment. The spray volume used was 12 ml. directed evenly over 3 sq. ft. of area, and the spray rates were such that applications equivalent to 0.1 and 1 lb./acre were obtained. Each rate was applied to 12 pots simultaneously (two pots of each of the six species used). Observations were then made from four plants of each broadleaf species (two plants per pot) and 20 plants of each cereal species (10 plants per pot) at intervals of 1-2, 5, and 10-14 days for individual visual effects, the latter comprised of abscission, chlorosis, contact and formative effects, curvature, galling, killing, necrosis, abnormal pigmentation, quilling, adventitious root formation, and stunting.

Compounds bearing one or two halogen atoms, either alone or in conjunction with another group, showed little activity. Those bearing 3 or 4 halogen atoms, either alone or otherwise, produced visual effects, the tetrahalogen compounds being more powerful. Among those tested, 1-(3,4-dichlorophenyl)-5-(2,4-dichlorophenyl)-1,2,3-triazoline and 2,4-dichlorobenzylidene-3-chloroaniline appeared to be the most active and produced a greater variety of visual effects in a greater variety of crops than any of the other compounds.

¹ Tween 20, Atlas Chemical Industries, Wilmington, Del.