Monomolecular Film Properties of Protective and Enteric Film Formers I.   Effect of Polymer Side Chain on Surface Pressure-Area Isotherms

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Polymeric film formers of pharmaceutical interest have been investigated using surface monolayer techniques.   Surface pressure-area curves were obtained and evaluated for monomolecular films of several half-esters of poly (methyl vinyl ether/maleic anhydride) at the air-water interface.   The ester side chain was found to contribute significantly to the surface properties of the polymer.

FILM COATINGS are widely used on pharmaceutical dosage forms as protectives and as diffusion barriers to control drug release.   A number of studies has been reported on the physical-chemical properties of free polymeric films (1–7).   Although free films represent a useful model for evaluating the gross properties of applied films, they provide limited information of molecular interactions which in fact dictate the properties of the film.

An interesting approach to the study of polymeric films is the use of techniques devised for investigation of insoluble monomolecular films at the air-water surface.   Monomolecular films or monolayers have been used as models for a number of biologic and physical-chemical processes.   Goddard and Schulman (8) studied the penetration of cholesetrol films by surface-active agents and were able to relate their data to the ability of these surfactants to hemolyze red blood cells.   More recently Schaubman and Felmeister (9) discussed the biologic significance of the penetration of monolayers of lecithin by chlorpromazine, and Torosion and Lemberger (10) considered the physical-chemical interactions between lecithin and lipids in mixed monolayers.

Crisp (11) studied a number of synthetic polymers on a surface balance and concluded that many polymers are spread completely at the air-water surface, a condition which must be met if the experimental results are to be properly interpreted (11–13).   It would appear that the polymer molecule must have a degree of hydrophilic character but possess very limited solubility to form a stable monolayer (13).   The applicability of monolayer techniques for studying polymeric material has been confirmed by a number of other workers (14–20).   The polymer is applied to the aqueous surface or substrate in the usual fashion by dissolving it in a suitable solvent which can spread over the surface and subsequently evaporate or dissolve.

However, the area per chemical segment or monomeric unit, rather than the area per molecule, is the preferred parameter to characterize the system since the force-area curves of polymers have been shown to be independent of the degree of polymerization (11, 14).

Monolayers of film-forming polymers may provide a useful model for the investigation of polymer structure and orientation, as well as the effect of pH and additives, on the properties of the polymer.   The present report concerns the determination and evaluation of surface pressure-area curves for several half-esters of poly (methyl vinyl ether/maleic anhydride).   These polymers have been evaluated previously as sustained-action coatings and appear to have potential for controlling drug release (5, 21).   The structure of these polymers may be represented by

$$\left[-CH_2-\underset{\underset{HO}{\overset{\overset{OCH_3}{|}}{|}}{C}H-\underset{\overset{O=C}{|}}{C}H-\underset{\overset{C=O}{|}}{C}H-\right]_n$$
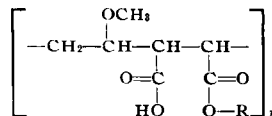
where R is the hydrocarbon side chain.

EXPERIMENTAL

Preparation of Polymer Derivatives—The various half-esters used in this study were prepared from the same lot of poly (methyl vinyl ether/maleic anhydride)[1] (designated as PVM/MA) by slurrying the polymer in the appropriate organic alcohol (previously purified by repeated passage through an alumina-silica gel column), adding 0.1% HCl, and allowing the mixture to reflux at its boiling point for a specified period of time, as indicated in Table I.   The resulting half-esters were purified by precipitation from ethyl ether or n-hexane and repeated washings with these solvents, and subsequently dried at 30° in vacuo to constant weight.   The degree of esterification was confirmed by titrating free acid groups with NaOH.   All acid value determinations agreed within 6% of the theoretical values.

TABLE I—PREPARATION OF POLY (METHYL VINYL ETHER/MALEIC ANHYDRIDE) HALF-ESTERS

Derivative	Segment Formula Weight	Reflux Time, hr.
Ethyl	202	4
n-Propyl	216	6
n-Butyl	230	7.25
n-Pentyl	244	8
n-Hexyl	258	9

Determination of Surface Pressure-Area (π-A) Curves—The surface balance employed was made of Teflon and has been described in a previous report (22).   Water was triple distilled in a glass still from an alkaline permanganate solution.

The half-esters were dissolved in a mixture of isopropanol and hexane and spread on the aqueous subphase by means of an Agla micrometer syringe. Preliminary experiments indicated that the addition of 10^{-3} M HCl to the subphase was sufficient to suppress ionization of the free carboxyl groups of the polymer derivatives. Surface pressure was determined at room temperature ($24.0° \pm 0.5°$) as a function of area using the Wilhelmy plate method (23, 24).

RESULTS AND DISCUSSION

The surface pressure-area (π-A) isotherms determined with each half-ester are shown in Fig. 1. Each curve represents the average of three determinations. Data points have been eliminated to attain clarity. When the films were spread with other spreading solvents, e.g., ethanol–chloroform–hexane, 1:1:3, or at different initial surface areas, curves identical to those in Fig. 1 were obtained indicating complete spreading (13).

The π-A isotherm obtained with the hexyl half-ester of PVM/MA is presented in Fig. 2 to depict the various regions of the curve which may be defined. In the expanded region (α) the molecules are relatively far apart and do not interact. Compression (i.e., decreasing the surface area occupied by the film) produces a "squeezing out" of water molecules and the segments approach each other. This phenomenon is reflected by the transition region (β) in the π-A curve. In the condensed region (γ) the segments are in close contact. In this region of the curve, a small change in area results in a comparatively large change in surface pressure. The marked increase in π in the condensed region probably reflects changes in orientation or configuration of the polymer. Crisp (11) has suggested that, in the condensed region, there is a gradual expulsion of hydrophobic groups from the surface into an "overfilm" above the monolayer. The polymer molecule, however, remains anchored to the surface probably because of hydrogen bonding between hydrophilic groups and the water molecules.
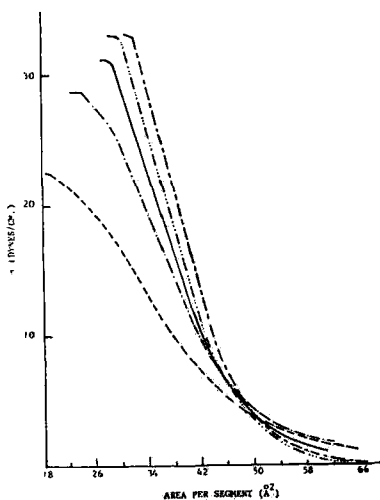
As compression is continued, a point is reached where the film can no longer be accommodated as a monomolecular layer and the film collapses to form a three-dimensional bulk phase. The surface pressure at which this phenomenon occurs is termed the collapse pressure (Point A in Fig. 2). The collapse pressure is a function of both cohesional forces between polymer segments and adhesional forces between the polar groups of the polymer and the subphase (15).

Point B in Fig. 2 represents the limiting area per molecular segment at zero surface pressure. It is obtained, as indicated, by extrapolating the condensed region of the curve to the abscissa. At the limiting area the film is in a hypothetical state in which it is condensed under no external pressure.

Examination of the π-A isotherms in Fig. 1 indicates a number of interesting relationships. For example, the collapse pressure is found to increase with increasing chain length of the ester. This suggests that cohesional forces, due to van der Waals' interactions between the ester chains, contribute significantly to the physical-chemical properties of the polymer.

Previous workers (16, 17) have reported that ester groups of polymers are oriented in the cis-configuration at the air-water surface. Hence, the ester chain protrudes through the surface toward the gas phase. It is likely that the side chains of the PVM/MA half-esters are oriented in a similar fashion since the limiting area for all five derivatives is 48–50 Å.^{2}/segment. This observation implies identical configuration in the limiting case and thereby, the lack of contribution of the ester side chain to the limiting area. If the ester chain were oriented in the plane of the surface, then a direct relation between limiting area and the length of the ester chain would be apparent.

The interactions between polymers and plasticizers, as well as the relationships between polymer chain length, plasticizer, and water vapor transmission are presently under investigation in an effort to elucidate the molecular considerations which control the properties of polymeric films. Finally, the results obtained using monomolecular
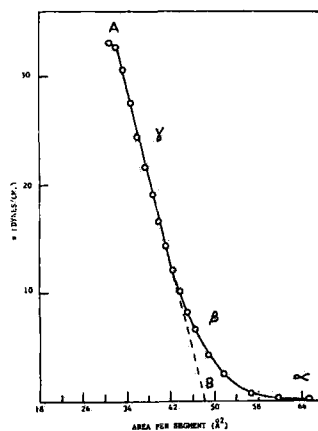
Fig. 1—Surface pressure-area (π-A) isotherms for various half-esters of PVM/MA. Key: — · —, n-hexyl; — · · —, n-pentyl; ———, n-butyl; - - -, n-propyl; - - -, ethyl.

Fig. 2—Surface pressure-area (π-A) isotherm for the n-hexyl half-ester of PVM/MA. The plot denotes the expanded (α), transition (β), and condensed (γ) regions of the film upon compression, as well as the collapse of the film (A) and the theoretic limiting area (B).

films will be compared with literature data on free films in order to evaluate the utility of the model.

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🔑 *Keyphrases*

Monomolecular films—polymeric film formers

Surface pressure-area isotherms—determination

Compression—film effect

Lipids from the Seeds of *Abrus precatorius*

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The lipids obtained from *Abrus precatorius* were separated into a saponifiable and unsaponifiable fraction. Analysis of the saponifiable fraction by gas-liquid chromatography (GLC) showed the presence of a series of C-8 to C-24 saturated and C-16 to C-24 unsaturated acids. Column chromatography of the unsaponifiable material yielded a hydrocarbon, alcohol–methyl sterol, and sterol fraction. GLC showed that the hydrocarbon fraction contained squalene, a homologous series of C-16 to C-35 normal, iso and/or anteiso, and possibly multibranched compounds. The alcohol–methyl sterol fraction contained a series of C-14 to C-28 normal alcohols in addition to β-amyrin and cycloartenol. Stigmasterol, β-sitosterol, and campesterol were the major sterol constituents identified by GLC.

A *brus precatorius* (also called Jequirity, Gunja, Kunch, and Rati) is a perennial twiner belonging to the family *Leguminosae* that grows throughout India and other tropical countries (1). It contains some of the most lethal plant poisons in the tropics. Many children have been attracted to its color and have accidentally swallowed the seed. Jequirity beans are frequently used as eyes in dolls, toys, necklace beads, and clothing ornaments. Some of the preparations from this plant induced severe cytotoxicity in concentrations of less than 0.01 mcg./ml. of solid material. Extracts of *Abrus precatorius* initially suppressed the growth of cancer cells and prolonged the survival of laboratory animals (2).

The biological effects of extracts of the seed have stimulated the need for further information concerning the identity of the compounds contained in *Abrus precatorius*.

EXPERIMENTAL

Source and Preparation of Material—Ripe seeds of *Abrus precatorius* were obtained from Herbst Brothers, Seedsmen, Inc., Brewster, N. Y. Approximately 65 g. of seeds dispersed in powdered dry ice were ground to a powder in a Wiley mill.

Extraction of Seeds—The powdered seeds were extracted successively with two 200-ml. portions of *n*-hexane, ethyl ether,[1] and distilled water at room temperature, and finally with two 500-ml. portions of 95% ethyl alcohol in a Soxhlet for 6 hr. Evaporation of 250 ml. of the hexane and ether fractions yielded, respectively, 372 and 177 mg. of yellow oils.

Saponifiable and Unsaponifiable Fractions—The saponifiable and unsaponifiable fractions were extracted (3). The alkaline soaps obtained were acidified with 1 + 1 HCl, extracted three times with petroleum ether, and then converted to the methyl esters (4).

Gas-Liquid Chromatography of Methyl Esters[2]—The mixture of methyl esters was subjected to GLC, using a Wilkins Aerograph model 1520 instrument fitted with a flame-ionization detector. The 2.7 m. × 0.6 cm. i.d. (9 ft. × 1/4 in.) aluminum column was packed with 20% polydiethylene glycol

[1] The ether and hexane extracted residues did not inhibit the growth of diploid cells (Hayflick strain, Wistar 138; obtained from Baltimore Biological Laboratories, Cockeysville, Md.).
[2] Stationary phases, packings, and standards were obtained from Applied Science Laboratories, State College, Pa.