Monolayers of Polyvinylpyrrolidone Copolymers

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Abstract □ The surface properties of graft copolymers of polyvinylpyrrolidone and vinyl acetate were investigated. The vinyl acetate grafts anchor the copolymer to the surface. Compression forces the vinylpyrrolidone residues beneath the surface, imparting considerable flexibility and accounting for the high compressibility and low cohesion observed.

Keyphrases □ Polyvinylpyrrolidone and vinyl acetate copolymers—surface properties of monolayers □ Copolymers, graft—surface properties of polyvinylpyrrolidone and vinyl acetate monolayers □ Surface properties—polyvinylpyrrolidone and vinyl acetate copolymer monolayers

Surface activity is an important attribute of many polymers used in the pharmaceutical industry. Such properties as surface rheology, adhesive strength, and orientation at an interface may be determining factors in certain applications. These properties are conveniently studied by spreading polymers as monolayers at the surface. Using this technique, Jarvis (1) was able to relate the antifoaming activity of some silicones with their low surface viscosity. Glazer (2) investigated the effect of polymer structure on adhesion of some ethoxylin resins. Monolayer experiments suggested that some polymers stabilize emulsions by forming an interfacial barrier to coalescence (3). In addition, monolayer studies provided insight into the molecular properties of polymers used as pharmaceutical coatings (4–7). The behavior of monolayers of some cellulose derivatives was correlated with the ability of these materials to function as enteric coatings (6). The effect of pH on monolayers of cellulose acetate phthalate was investigated (7).

Most surface work on polymers of pharmaceutical interest has dealt with linear molecules. However, for certain applications, graft and block copolymers offer advantages. Homopolymers, which are not usually compatible, may be combined in the same molecule in such a manner that, for the most part, the properties of each component are retained. This type of polymer often finds application as a dispersing agent or surfactant or as a film former. In this communication, experiments on monolayers of graft copolymers of polyvinylpyrrolidone and vinyl acetate are described.

EXPERIMENTAL

Copolymers of polyvinylpyrrolidone and vinyl acetate[1] were purified by precipitation from solution in isopropanol, using *n*-hexane as the nonsolvent. The polymer mass was washed repeatedly with *n*-hexane and then dried *in vacuo* at 50° to constant weight. The relative content of vinylpyrrolidone was determined by nitrogen analysis. The composition of the purified materials is summarized in Table I.

Water was deionized and distilled from an all-glass still. Organic liquids (reagent grade) were found to be free of surface-active impurities (8). Inorganic materials (reagent grade) were not further purified. The trough of the surface balance was made of Teflon. Surface pressure was determined by the Wilhelmy plate method, using a roughened platinum plate. The temperature of the subphase was maintained at 25 ± 0.1° by a Lauda K-2 thermostat, except as otherwise indicated. Water was used as the subphase. The copolymers were spread from solution in isopropanol–benzene, using an Agla micrometer syringe.

[1] Polyvinylpyrrolidone/vinyl acetate copolymers, GAF Corp.

Table I—Composition of Copolymers

Copolymer Designation	Total Monomers, % w/w	Vinylpyrrolidone Content, % w/w	Vinylpyrrolidone Content, % Vinylpyrrolidone Residues
335	<0.01	29.2	24.2
535	<0.01	48.6	42.3
735	<0.01	61.2	55.0

RESULTS AND DISCUSSION

Monolayer Stability—Force–area isotherms for the polyvinylpyrrolidone copolymers studied are given in Fig. 1. At large values of surface area (over about 2 m.²/mg.), compression results in a relatively small increase in surface pressure. Copolymer segments are dilute in the surface, and reduction of available surface area forces water molecules into the subphase. As the surface area is further reduced, copolymer segments are brought into contact with one another, and compression causes the surface pressure to rise more steeply. In the region of close contact, the π–A isotherms are linear. All three curves exhibit a sharp rise in surface pressure at an area of about 0.2 m.²/mg. Monolayer collapse occurs at a surface area below 0.04 m.²/mg. This area is quite small in comparison to the collapse area of most polymer monolayers previously studied.

The copolymers under investigation consist of a "backbone" of polyvinylpyrrolidone onto which vinyl acetate monomers are grafted. Each molecule can be thought of as comprising several polyvinyl acetate strands bound to a single long unit of polyvinylpyrrolidone. It was shown that polyvinyl acetate may be spread as a monolayer on water (9, 10). However, it was found that polyvinylpyrrolidone does not form a stable monolayer, apparently because of the attraction of the vinylpyrrolidone residues for the subphase

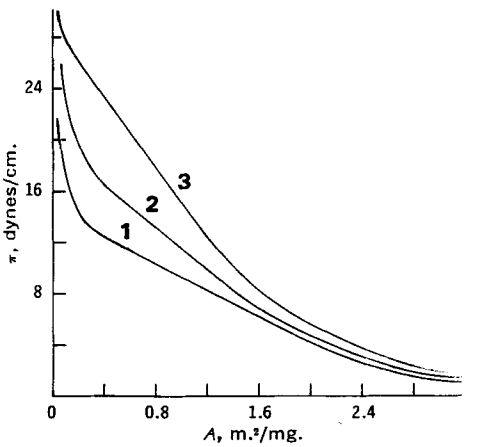

Figure 1—π–A *curves for polyvinylpyrrolidone copolymers. Key: 1, 735; 2, 535; and 3, 335.*

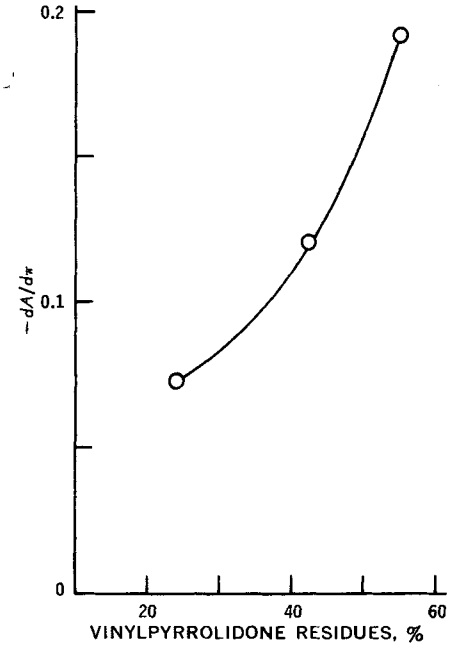

Figure 2—*Effect of vinylpyrrolidone content on monolayer compressibility.*

(11). Because of their polyvinylpyrrolidone content, the copolymers are somewhat water soluble. (One gram of the 735 copolymer, which has the highest polyvinylpyrrolidone content, dissolves in about 100 ml. of water.) This information, coupled with the extremely small area at collapse, promotes the suspicion that either spreading of the monolayer is not complete or that some material is lost from the surface during an experiment (9, 12). However, experimental evidence demonstrates that spreading is indeed complete and that dissolution of copolymer from the surface into subphase does not occur:

1. The π–A curves obtained when the copolymers were spread from isopropanol–benzene solution were identical to those in which methylene chloride was the spreading solvent. Also, in some experiments, the concentration of copolymer in the surface was increased by spreading additional material rather than by compression. Both techniques yielded the same result. The copolymers were, therefore, completely spread (9, 12).

2. If the monolayers were compressed, expanded, and then recompressed, the initial π–A curve was reproduced. Surface pressure readings were independent of the rate of compression and of the period of time allowed to elapse after spreading before compression was begun. In addition, surface pressure readings were found to be

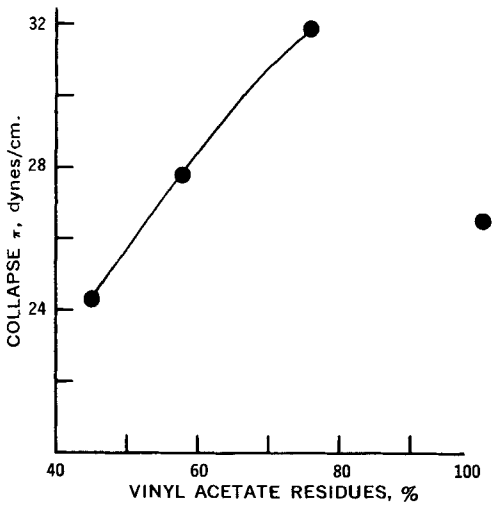

Figure 3—*Influence of vinyl acetate content on monolayer collapse pressure.*

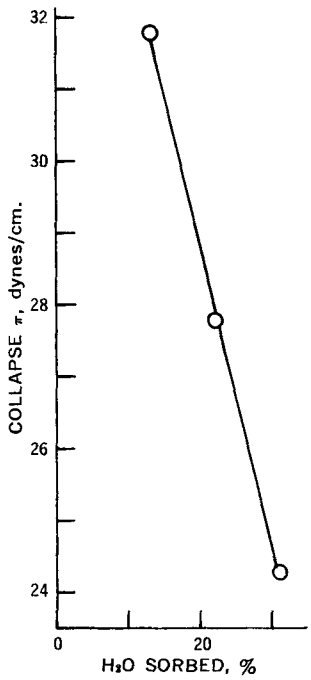

Figure 4—*Relationship between monolayer collapse pressure and moisture sorption (at 80% relative humidity) in free films of polyvinylpyrrolidone copolymers.*

stable when the monolayers were allowed to stand under compression at constant area for up to 30 min. These results indicate that dissolution of copolymer from the surface did not occur during an experiment.

Cohesion at the Interface—Gaines (13) defined a polymer monolayer as a system in which each residue of the macromolecule is adsorbed at the interface. When the residues are closely packed, compression causes changes in orientation which allow the segments to be accommodated at the interface. In this state, cohesion between hydrocarbon portions of polymers is often apparent (4) and many substances form two-dimensional gels (9).

Qualitative surface viscosity measurements (14) revealed that gel formation at the surface did not occur with any of the polyvinylpyrrolidone copolymers. The monolayers remained fluid up to collapse. Other experiments were performed in which the temperature of the subphase was changed to 15 and 35°, respectively. The temperature dependence of surface pressure was found to be negligible for all of the copolymers. The enthalpy of spreading was, therefore, very close to zero (15). This finding argues against the existence of significant interactions between neighboring copolymer segments and is consistent with the rheological data. Another consideration is the small surface areas to which the copolymer monolayers may be compressed, thus making inclusion of all copolymer residues in the surface impossible. It appears that these monolayers do not conform to Gaines' definition.

Surface Structure of Polyvinylpyrrolidone Copolymers—When a large area is available to the copolymer molecules, it is likely that both the vinylpyrrolidone and vinyl acetate residues occupy the interface. As the area available to the molecules in the surface is reduced, some of the polymer segments leave the surface. It is possible that partial collapse occurs, resulting in the formation of an "overfilm" (9). However, it appears more probable that the attraction of water molecules for the vinylpyrrolidone segments causes them to penetrate into the subphase. This arrangement imparts considerable flexibility to compression to the copolymers and makes them more highly compressible than if all of the segments were constrained to remain at the surface.

In Fig. 2, $-dA/d\pi$, a measure of monolayer compressibility (16), is plotted as a function of vinylpyrrolidone content. The increase in compressibility as a function of the percentage of vinylpyrrolidone residues is consistent with the notion that compression results in their submersion into the subphase. The ability of the copolymers to respond to compression by forcing a portion of the molecule into an adjacent bulk phase explains how the monolayers can be compressed to very small areas prior to collapse and accounts for the fact that the monolayers are fluid and exhibit little cohesion. The polyvinyl acetate grafts serve to anchor the copolymers to the surface and are largely responsible for stability of the monolayers.

Figure 3 shows the relationship between collapse pressure and vinyl acetate content. The collapse pressure of pure polyvinyl acetate (10) is included for comparison. Increasing the vinyl acetate content results in higher collapse pressure. It is apparent that some interaction occurs between vinylpyrrolidone and vinyl acetate residues, since the collapse pressure of the 335 copolymer is higher than that of pure polyvinyl acetate.

Relation between Monolayers and Free Films—Previous work showed that certain properties of monolayers may be related to those of free films (5, 6). Collapse pressure in a group of related polymers is a measure of "hydrophobicity." A similar relation was found with the materials studied here. As shown in Fig. 4, moisture sorption in free films is inversely proportional to monolayer collapse pressure.

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Influence of Drug Particle Size after Intramuscular Dosage of Phenobarbital to Dogs

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Abstract □ Phenobarbital suspensions containing drug particles of different size ranges were separately administered, intramuscularly, to beagle dogs. The particle size of the dose affected the blood drug level curves. A comparison of the areas under the curves with the respective particle sizes indicated that particle size influenced the biological availability of phenobarbital. Data obtained suggest that by controlling the drug particle size, one may be able to regulate the duration of action of phenobarbital.

Keyphrases □ Particle size, drugs—effect on intramuscular administration of phenobarbital, beagle dogs □ Phenobarbital, intramuscular administration—effect of particle size on blood levels and bioavailability, beagle dogs □ Blood levels, dogs—effect of phenobarbital particle size after intramuscular administration □ Bioavailability—effect of phenobarbital particle size, intramuscular administration, beagle dogs

Within the last 15 years, it has become increasingly apparent that the biological availability of drugs can be altered considerably by their dosage forms and their physical properties. Particle-size influences on drug availability constitute an important part of pharmaceutical technology (1). Most reported studies to ascertain the influence of drug particle size were conducted with oral dosage forms, and only a few of these studies treated its effect in parenteral forms (2). Drugs in the GI tract are subjected to varying degrees of agitation and fluid composition; however, at intramuscular injection sites the agitation intensity is very low and the fluid composition should remain relatively constant. The intramuscular route may, therefore, be more useful in studying the influence of drug particle size. Reported herein are preliminary studies to determine the effects of drug particle size by intramuscular injection.

EXPERIMENTAL

Phenobarbital USP and sodium phenobarbital USP were utilized in these studies. The purities of the two drugs, based on dry weight, were determined by USP methods to be approximately 100% for the phenobarbital crystals and 92% for the sodium phenobarbital granules.

Twenty-five healthy, male, beagle dogs of approximately the same age and weighing between 10 and 15 kg. were the test subjects. From this group, three sets of eight were selected and alternated so that the same animal was not used for two successive experiments. The dogs were fasted for 18 hr. prior to use, but free intake of water was allowed. Intravenous injections were given in the cephalic vein of one foreleg, while the intramuscular injections were given in the gluteus medius; blood samples were drawn from the cephalic vein of the foreleg not used for the intravenous injection.

The particles to be studied were prepared by precipitating free phenobarbital from aqueous solutions of sodium phenobarbital with a 0.5 *N* hydrochloric acid solution. This procedure was done in an alcohol–dry ice bath at −10° under varying degrees of agitation and precipitation rates. A gross analysis of the crystals was made using a microscope, and the particle-size distribution was determined with a Coulter counter[1] (Fig. 1).

[1] Model B, Coulter Electronics Industrial Division, Chicago, IL 60614