

Evaluation of Polymeric Materials I

Screening of Selected Polymers as Film Coating Agents

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A procedure has been developed for the systematic evaluation of mechanical, thermal, and stability properties of polymeric materials through the study of unsupported films. Films of selected vinyl, acrylic, and cellulosic polymers were prepared by the knife edge applicator method and the mercury substrate technique. The mercury substrate technique afforded superior control of film thickness and facilitated film removal. Films that were very permeable to water vapor were rather impermeable to oxygen and vice versa. This relationship is discussed as it relates to a combination of the hydrophilic-lipophilic and pore theories of film structure. The unsupported vinyl films possessed superior mechanical properties of those tested. Moisture absorption by the polymer films was negligible. There was no discernible decomposition according to infrared analysis of the films, due to thermal, photo-oxidation, and/or aging effects.

PHARMACEUTICAL PREPARATIONS are required by law and ethics to contain the ingredients advertised and the potency specified by the manufacturer. The first condition is easily fulfilled, but drug potency often presents a problem. The manufacturer also encounters the difficulty of overcoming unpleasant drug tastes and odors.

The decomposition of most drugs can be classified either as hydrolysis or oxidation. Both of these degradation reactions are catalyzed by atmospheric effects. This has led to the use of dehydrated products sealed in ampuls and protective coatings for solids. Sugar and gelatin were among the first and most popular protective coatings for solids, but had the disadvantage of merely delaying degradation of the product. Pharmaceutical preparations such as sugar coated tablets have a pleasant taste and odor but do not necessarily contain the original potency specified.

This disadvantage of the sugar coating has led to the investigation of other types of protective coatings, such as the film coat. Film coating of tablets on an industrial scale first occurred in 1954 when Abbott Laboratories introduced their "Filmstab." Since then a more general and concentrated interest in this technique has existed.

Film coatings may be defined as thin pliable layers of a physiologically acceptable coating composition. Additives in a film coat may include plasticizers, which make the plastic film former more flexible, and colorants, flavors, and surfactants which facilitate spreading. Modifier materials, such as soluble waxes, are added to affect film solubility or pliability (1-3).

Due to the great increase in the number of

polymeric materials developed in recent years, an examination of these new polymers and their properties for application in pharmaceutical coating is appropriate. An improved method of evaluation is proposed in this work. Films of the polymers were cast and subjected to evaluation for water vapor transmission, oxygen permeability, water absorption, durability, mechanical, and thermal and photo-oxidation effects.

Some of the possible advantages of the experimental method proposed by this study are: (a) the polymers are evaluated for their pharmaceutical coating properties without interference from modifying additives; (b) a more rapid and comprehensive screening of new polymers is provided; and (c) the results can provide a logical basis for the selection of the modifying additives in the coating formulation.

EXPERIMENTAL

Initial Screening Procedure.—Various polymeric materials currently being used in the plastics industry were screened for their film forming characteristics and were classified according to chemical type. A second screening was performed on the basis of oral toxicity and method of drying of the film (air dry, forced dry, or baked), and the following groups of polymers were selected for further study on this basis (4): acrylate, alkyd, cellulose acetate butyrate, cellulose nitrate, chlorinated paraffin, chlorinated rubber, cyclized rubber, hydrocarbon, maleic, oleoresin, polyamide, polyester, silicone, silicone alkyd, polystyrene, styrenated alkyd, vinyl acetate, vinyl alcohol, vinyl butyral, and vinyl chloride acetate.

The following solvent system was selected after analyzing solvent systems suggested by various manufacturers and after studying the Antonides, Fennell, and Peirano investigations (5-7), butyl alcohol, 25%; butyl acetate, 25%; and acetone, 50%. Formulations were prepared containing the particular polymer and the proposed solvent system to yield a 10% solution by weight of the polymer. Clean microscope slides were dipped into the poly-

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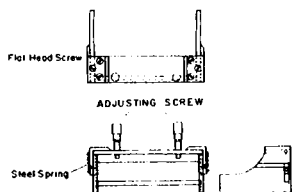


Fig. 1.—Knife edge applicator.

mer solutions to a depth of approximately 3 cm. The coated slides were then observed at 25° for noticeable film formation.

Film test strips to evaluate the polymers further were prepared with a brass film casting knife which was designed according to specifications suggested by the Hercules Powder Co. (See Fig. 1.) The casting knife permitted rapid preparation of films of fairly uniform thickness. The apparatus consisted basically of a knife edge supported by a frame mounted on two runners. A precise gap could be set between the knife edge and the casting surface by using screw adjustments. A smooth plane such as a chromium surface was suggested as ideal for the casting surface (8). The knife, sliding on the support runners, was drawn over the pool of film solution, leaving a wet film of fairly uniform thickness. The films were air dried.

An alternate method was investigated using Petri dishes and casting the films on a mercury surface (mercury substrate technique). This method produced films with a controlled constant thickness. A known quantity of the 10% polymer solution was diluted with acetone to approximately 25 ml. to facilitate spreading. The film thickness could be varied by varying the volume of the 10% polymer solution used in the 25 ml. dilution.

Mechanical Properties.—The stress-strain relationship of solid materials is comparable to the viscosity property of liquids. The stress-strain relationship is an expression of resistance of a solid to dimensional change.

Tensile stress (σ) is defined as the load per unit area of original cross section at any given moment. It is usually expressed in force per unit area. The maximum tensile stress during the test is called the tensile strength. Gauge length is the initial length of the test specimen, while elongation is the increase in sample length produced by a tensile load and is usually measured at the moment of film rupture. Elongation is expressed in a linear dimension (inches); percentage elongation is the per cent conversion. Strain is the change in length per unit of original length.

With a graph, Lever and Rhys (10) explained the general pattern of the elastic modulus, which can be calculated from the slope of the curve where stress and strain are proportional and is an indication of the stiffness of the test material. (See Fig. 2.) In Fig. 2 the yield point *A* is a measure of the material's strength. It is also a measure of the resistance of the material under test to permanent deformation.

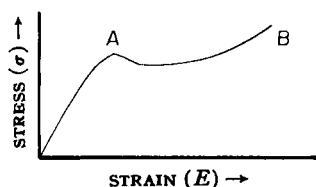


Fig. 2.—Stress-strain relationship.

Elastic deformation then is calculated from the beginning portion of the curve and denotes the ability of a film to return to its original dimensions after being extended. The portion of the curve from *A* to *B* (where the sample breaks) is a measure of plastic deformation. Here the strain is not immediately recoverable. A rough measure of toughness can be found by measuring the area under the curve. This represents the work required to break the test material (10).

Lever and Rhys (10) classify materials as (a) soft, weak—show low modulus of elasticity, yield point, and low elongation at break; (b) hard, brittle—high modulus of elasticity, no well defined yield point, and low strain at break; (c) soft, tough—low modulus of elasticity, low yield point, and high strain at break; (d) hard, strong—high modulus of elasticity, yield point, and moderate stress and strain at break; and (e) hard, tough—high modulus of elasticity, yield point, stress and strain at break. Kinney illustrates some of these physical stress-strain relationships as shown in Fig. 3 (11).

Film samples cast on the mercury pool in a Petri dish were cut to a uniform size of 1 × 5 in. using a razor knife. This size test sample allows a 1-in. width and a 3.5-in. gauge length. Stress-strain curves were determined using an Instron TM strain

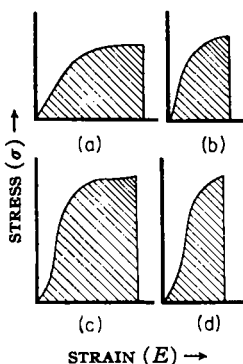


Fig. 3.—Material classification according to stress-strain relationships. Key: (a) soft and hard; (b) weak and brittle; (c) strong and tough; (d) hard and strong.

tester¹ with the CT crosshead, which has a range of 1 to 200 lb. The crosshead speed was 0.2 in. per minute.

"For solids, Hooke's law states that the tension is proportional to the extension or 'stress is proportional to strain,' where stress is the force per unit area (F/A) and strain is the ratio of the extension produced to the original length (l/L). Hence $(F \times L)/(A \times l) = \text{Constant}$ generally denoted by E and is called Elastic Modulus (12)." The elastic modulus (elasticity) was calculated using this formula. Since the Instron strain tester reads in the English system of weights, E was calculated in this system, then converted to the metric system using the conversion factor of 68947.

Linear expansion of the films was measured by the ASTM test No. D 1042-54. Film strips were cut 1 in. wide and 6 in. long and inscribed as prescribed by the American Society for Testing and Materials. The inscribing distance was 100 mm. Holes were punched in one end of the film strips, and the strips were suspended from cross rods. The marked test samples were then subjected to 93% relative humidity and 40° for 24 hours. A saturated solution of ammonium phosphate was used to produce the

¹ Instron Engineering Corp., Canton, Mass.

relative humidity for the test. After 24 hours, the films were again inscribed and the distance measured. Any change in length was observed and measured with a calibrated microscope at $\times 10$ power. The same test samples were then subjected to 60° for 24 hours and again measured under the microscope.

Film test samples in a thickness range of 5 to 10 mm. were cut using a 1 by 3 in. microscope slide as a template. They were then immersed in artificial gastric and intestinal fluids to determine solubility and/or enteric properties. A sample was placed in a vertical position in each chamber of the U.S.P. tablet disintegrator and completely submerged in artificial gastric fluid at 37° . The U.S.P. disintegration apparatus disks were not used since the film strips tended to adhere to them. The end point was complete solution of the film. After 3 hours, the gastric fluid was removed and replaced with artificial intestinal fluid. To confirm the results, three test samples were run for each polymer.

Thermal Properties.—Test samples were cut and were mounted on sample holder cards. These cards are the same dimensions as the calibration card for the Perkin Elmer model 21 spectrophotometer. The infrared spectrum was initially recorded for each polymer and after a 2-month interval to note any changes produced by temperature and aging.

Stability Properties.—*Water Vapor Permeability.*—A modification of ASTM:E96-53T was developed to measure water vapor transmission. Through the use of ASTM designed cups² and controlled humidities on both sides of the film, the water vapor transmission was determined. The test was conducted with 0% relative humidity inside the cup (maintained by Drierite)³ and 93% relative humidity outside at room temperature. The 93% relative humidity was maintained with a saturated solution of ammonium phosphate in a paper chromatography jar, 10 in. in diameter and 18 in. deep. The cups were weighed initially and then every 2 hours over a 24-hour time period, the water vapor transmission was calculated from the straight line portion of the plot of moisture gain *versus* time. Water vapor transmission is usually expressed as the number of grams of moisture gain per 24 hours per square meter. Preliminary data indicated that weighing the films every 4 hours over a 12-hour period was adequate, and this procedure was subsequently followed. Utsumi (13) has suggested the following water vapor transmission formula: $Q = (WL)/(S)$ where W = Gm. of water/24 hours, L = film thickness in cm., S = surface area in cm.², and Q = weight of water in Gm.cm. thickness/cm.² area 24 hours.

The American Society for Testing Materials suggests the following formula for calculating the water vapor transmission: $WVT = (g \times 24)/(t \times a)$ where g = weight gain or loss, in grams, a = exposed area in square cm., t = time, in hours, during which g was observed, 24 = to convert the actual weighing time, t , to the time basis of 24 hours.

Since Utsumi's formula took the thickness of the film sample into consideration, it was used in this investigation.

Oxygen Permeability.—The method of determining oxygen permeability of the films involved the

complexation of oxygen by pyrogallol acid in an alkaline solution (14). The following reagent was used in this study: pyrogallol acid, 4 Gm.; sodium hydroxide, 10 Gm.; and distilled water *q.s. ad.* 1000 ml. Test tubes were filled to a volume of 35 ml. with the reagent solution and sealed with the films under oxygen free conditions as provided by high purity nitrogen. The quantity of oxygen passing through the films was determined by the Beckman model B spectrophotometer at room temperature. The wavelength of 425 m μ was used as suggested by Williams, *et al.* (14). The presence of oxygen was also noted visually by the change of a nearly colorless solution to varying shades of brown and then to black. The quantity of oxygen present was measured at intervals of 30 minutes until a constant rate of gain was reached. The oxygen permeability was calculated according to the first equation.

TABLE I.—POLYMERS USED IN THIS STUDY

Chemical Designation	Trade Name and Manufacturer ^a	Film Formation (Free Film)
Acrylate and methacrylate	Lucite 42 (1)	Yes
	Lucite 44 (1)	Yes
	Lucite 46 (1)	Yes
Alkyd	Sytex H-3 (2)	No
Cellulose acetate butyrate	1/2 Second Butyrate (3)	Yes
Chlorinated paraffin	Clorowax 70 (4)	No
Chlorinated rubber	Parlon (5)	No
Coumarone	Nevidene (6)	No
	Neville R16-A (6)	No
	Picco 450-L (7)	No
Oleo-resin modified	Carbasol 6 (8)	No
	Carbasol 30 (8)	No
	Staybrite Ester 10 (5)	No
Phenol modified	Cellolyn 102 (5)	No
	Pentalyn A (5)	No
	Pentalyn 802A (5)	No
Vinyl acetate	Nevillac Hard (6)	No
	F.C.D. 101 (9)	No
	Gelva V-15 (10)	Yes
Vinyl butyral	Gelva C-3, V-10 (10)	Yes
	Vinac E1-52 (11)	No
	Bakelite AYAF (12)	Yes
Vinyl acetate/stearate	Lemac 541-20 (13)	Yes
	Butvar B-90 (10)	Yes
	Flexbond B-142 (11)	No
Vinyl chloride copolymer	Exon 470 (15)	Yes
	Exon 471 (15)	Yes
	Exon 497 (15)	Yes
Polyvinyl ethyl ether	Bakelite EDBM (12)	No
Styrene	Lytron 810 (15)	No
	Lytron 820 (15)	No
Silicone	S.R. 83 (16)	No
	F.C.D. 16 (9)	No
	R. 62 (12)	No
	Neville 118-123 (6)	No
	Bakelite VMCH (12)	No
	Piccoflex 100 (7)	No
	Bakelite VAGH (12)	Yes

^a The manufacturer of the polymer is designated by the number in parenthesis: 1, E. I. du Pont de Nemours & Co.; 2, Jones-Dabney Co.; 3, Eastman Chemical Products, Inc.; 4, Diamond Alkali Co.; 5, Hercules Powder Co.; 6, Neville Chemical Co.; 7, Pennsylvania Industrial Chemical Corp.; 8, C. J. Osborn Co.; 9, France, Campbell, and Darling; 10, Shawing Resins Corp.; 11, Colton Chemical Co.; 12, Union Carbide Corp.; 13, The Borden Chemical Co.; 14, Firestone Plastics Co.; 15, Monsanto Chemical Co.; and 16, Schenectady Resins Div.

² Thwing Albert Instrument Co., Philadelphia, Pa.

³ W. A. Hammond, Drierite Co., Xenia, Ohio.

TABLE II.—EVALUATION OF STRESS-STRAIN RELATIONSHIPS AND LINEAR EXPANSION

Polymer	Stress-Strain Relationships				Linear Expansion		
	Film Thickness $\times 10^{-3}$ cm.	Elasticity $\times 10^4$ dyne/cm. ²	Tensile Strength $\times 10^6$ dyne/cm. ²	% Elongation	Film Thickness $\times 10^{-3}$ cm.	At 40°C. + 93% R.H.	At 60°C.
Lucite 44	2.54	2.484	0.436	68.5	5.59	2.19	5.00
Lucite 46	2.00	4.388	1.630	1.7	5.08	-1.00	3.30
Gelva V-15	1.83	5.614	2.642	4.5	4.57	3.00	...
Gelva C-3, V-10	0.970	4.117	2.429	8.9
Bakelite AYAF	0.710	5.506	1.642	3.7	3.05	2.10	0.60
Lemac 541-20	0.990	3.861	2.455	4.2	4.06	-2.70	...
Butvar B-90	1.65	1.735	5.390	27.1	4.32	0.27	-0.92
Exon 471	2.21	0.705	2.375	3.1	5.59	1.80	-8.00
Exon 497	0.380	7.023	1.587	2.1	5.84	-0.30	-2.90
Bakelite VAGH	0.990	5.984	2.153	2.4

Photo-Oxidation.—The procedure of determining photo-oxidation was the same as that used to measure the effect of temperature upon the polymers. A sample card was prepared as previously described for each polymer and an initial spectrum recorded. The sample cards were then exposed to indirect sunlight passing through a north window. Infrared spectra were again recorded after a 2-month interval had elapsed.

Moisture Absorption.—Test samples were prepared as previously described, placed in relative humidity chambers, and weighed at definite time intervals. The per cent moisture absorbed was calculated on a weight basis, and the time required for maximum absorption was determined. Relative humidity chambers were constructed using large battery jars covered with glass plates. Holes were punched in one end of the film strips, and the strips were suspended from cross rods. The film strips were subjected to 10, 52, and 93% relative humidity using saturated solutions, respectively, of zinc chloride, magnesium nitrate, ammonium phosphate, and were weighed at weekly intervals. The Serdex⁴ relative humidity meter was used to check the relative humidity.

Coating of Tablets.—In order to evaluate each polymer for coating efficiency on a moving tablet bed, film hardness, and effect upon disintegration time, selected film coatings were applied to placebo tablets. The following formula was selected for the placebo tablets: calcium sulfate, 40%; lactose, 40%; starch, 20%, granulating agent: starch paste, 10%; and lubricant: magnesium stearate, 1%.

Tablet disintegration and friability were used to measure durability, ease of handling, and tablet firmness. To check these properties, tablets were coated, and disintegration and friability tests were conducted. The tablets were coated with a 10% solution of the polymer using the solvent system previously mentioned. One per cent sorbitan monooleate,⁵ was added to facilitate spreading on the tablets. A 0.1% concentration of FD&C yellow No. 4 was added to permit visualization of tablet coating. A standard 12-in. coating pan revolving at 36 r.p.m. was used, and the coating solution was laded on the moving tablet bed.

The disintegration tests were conducted according to the manner prescribed by the U.S.P. XVI for uncoated tablets using both artificial gastric and

intestinal fluids. A blank was determined using uncoated tablets.

The friability test was conducted according to the method suggested by Perlman (15). This test utilizes a metal can (5¹/₄ in. in diameter and 8 in. high) containing three 1-in. metal baffles. The tablets were placed in the can, and the can was sealed with plastic electrical tape. The tablets were rotated on a jar mill rolling machine⁶ for 5 minutes at 90 r.p.m.

RESULTS AND DISCUSSION

Experimental work was conducted to evaluate selected polymeric substances for use as pharmaceutical film coating agents. After preliminary screening the polymers listed in Table I were selected for further evaluation.

Further screening using the film casting knife indicated that 13 polymers formed free unplasticized films. A free unplasticized film was defined as an unsupported sheet of film containing no additives such as plasticizers or alloying agents. These results are also shown in Table I.

At the end of the preliminary screening the 13 polymers forming free films (Table I) were selected for further evaluation of properties of interest in pharmaceutical film coating.

Evaluation of Mechanical Properties of Free Films.—Experimental work was conducted to obtain a comparison of the flexibility and toughness of the polymers evaluated. The polymers were evaluated for modulus of elasticity, tensile strength, and per cent elongation; the results are shown in Table II.

Lever and Rhys (10) indicated that tension tests gave reasonably accurate information when employed under definite test conditions. The tests cannot be considered significant when the application conditions differ widely. It appears from this that these properties are best evaluated when one is modifying an original formulation and desires to know the effect of such modifications. Polymers could also be compared if the same test conditions were used.

For use in film coating, the per cent elongation and tensile stress should both be high in relative value. A polymer having these properties would produce a strong and tough film, which is especially desirable in tablet coating. The value of the elastic modulus could be either high or low, depending upon the intended application of the polymer. A higher value denotes a harder film (e.g., tablet coating),

⁴ Serdex, Inc., Boston, Mass.

⁵ Marketed as Arlacel 80 by the Atlas Powder Co., Wilmington, Del.

⁶ Paul Abbe, Little Falls, N. J.

TABLE III.—EFFECT OF SOLVENT UPON STRESS-STRAIN RELATIONSHIPS

Polymer	Age	Film Thickness $\times 10^{-3}$ cm. ²	Elasticity $\times 10^6$ dyne/cm. ²	Tensile Strength $\times 10^6$ dyne/cm. ²	% Elongation
Exon 471	4 mo.	2.21	0.705	2.375	3.1
	2 days	1.55	0.884	0.294	74.5
Butvar B-90	4 mo.	1.65	1.735	5.390	27.1
	2 days	1.47	2.378	...	over 125

while a lower value indicates a soft and more flexible film (e.g., spray bandage).

Table II shows that most of the elastic moduli were 10^9 dyne/cm.² with 2 to 10% elongation. It appeared from the data presented that nearly all of the polymers would have application as film coating agents. Lucite 44 has a low tensile strength when compared to the other polymers and might be unsuitable. The data in Table II resulted from samples that had been aged approximately 4 months. Table III indicates that residual solvent can have an effect upon the mechanical properties of a polymer and indicates that these tests should be conducted on aged films.

The tensile strength for Butvar B-90 is unavailable because the film did not break under the test conditions. The extension limit of the testing procedure was exceeded. This also accounts for the approximate value for the per cent elongation. As was expected, the film samples became more flexible but less tough due to the residual solvent being present (16). This could account for the fact that commercial film coated pharmaceuticals often chip and crack easily upon aging, while freshly coated

samples may have been chip resistant and resilient in the laboratory.

When the results from Tables II and III were compared to those of Utsumi (13), it was found that his synthesized polymers exhibited a somewhat greater elastic modulus (the higher the elastic modulus, the stiffer the film). Some of the difference may be attributed to the different methods used as well as the different polymers employed.

The linear expansion of the film test samples was in the order of $\pm 3\%$ as shown in Table II. Lucite 46, Exon 497, and Lemac 541-20 probably would be unsuitable for film coating where both high temperature (40°) and high relative humidity (93%) are involved. Any shrinkage in a film would be likely to cause a film coating on a pharmaceutical product to fissure and become unacceptable. It is interesting to note that the linear dimensions of Butvar B90 and Exon 471 test samples increased slightly upon exposure to high relative humidities, but decreased when subsequently exposed to high temperature (60°). The only difficulty in evaluating polymers using this method is that some samples are not able to be measured accurately due to

TABLE IV.—PERMEABILITY OF FREE FILMS TO WATER AND OXYGEN
(Gm.cm./cm.² 24 HOURS)

Polymer	Sample Thickness $\times 10^{-3}$ cm.	Water Permeability $\times 10^{-6}$	Average $\times 10^{-6}$	Sample Thickness $\times 10^{-3}$ cm.	Oxygen Permeability $\times 10^{-4}$	Average $\times 10^{-4}$
Exon 497	0.432	1.11	1.29	3.10	1.33	1.33
	0.406	1.48				
Exon 470	0.950	1.95	1.77	0.915	4.25	4.61
	0.910	1.85				
Butvar B-90	0.900	1.51	2.18	1.80	23.8	21.4
	0.432	2.32				
Lucite 44	0.381	2.05	4.47	2.70	14.9	16.0
	0.457	4.91				
Bakelite VAGH	0.482	4.04	7.91	2.30	17.2	16.0
	0.127	8.18				
Lucite 46	0.102	7.64	6.16	0.970	5.70	6.06
	1.75	6.01				
Lemac 541-20	1.96	6.31	8.10	1.96	15.6	14.8
	0.356	8.40				
Lucite 42	0.331	8.60	8.39	0.990	7.52	8.00
	1.02	7.90				
Gelva V-15	1.47	7.89	10.1	1.27	9.85	9.85
	1.44	8.96				
Bakelite AYAF	1.55	8.32	8.94	0.740	5.80	5.80
	1.02	10.9				
Exon 471	0.810	10.4	14.3	2.30	1.60	1.16
	0.483	8.90				
Gelva C-3, V-10	0.787	9.63	17.4	2.20	8.09	8.78
	0.711	8.25				
1/2 Second Butyrate	2.34	13.8	68.4	0.330	2.27	2.03
	2.03	14.8				
	2.59	16.7		0.380	1.79	
	0.991	19.2				
	2.54	16.3				
	1.57	74.0				
	1.27	56.8				
	1.52	74.4				

curling and/or melting of the film at the higher temperature (60°). Bakelite AYAF and Exon 471 exhibited the least dimensional distortion at an elevated temperature or at an elevated temperature and humidity. It would appear that these polymers would be suitable as pharmaceutical coating agents.

Film test strips were cut as previously described and placed in artificial gastric and intestinal fluids to determine solubility and/or enteric properties. All of the polymers were insoluble in both artificial gastric and intestinal fluids, except Bakelite AYAF and Gelva C-3, V-10 which exhibited possible enteric properties. From this it would appear that those polymers which are insoluble would not be suitable for film coatings unless modified with other agents. However, it is possible that all coated products do not disintegrate by dissolution of the coating, but some release the medicament according to the water permeability of the coating. Experimental data that support this hypothesis will be shown in a later section.

Evaluation of Thermal Properties of Free Films.—Test samples of the polymers were prepared as previously described and evaluated for their temperature stability at 25, 40, and 60° for a period of 2 months. Visual examination of the films disclosed no physical changes during that period of time. Infrared spectra were also recorded for each of the polymers initially and after storage. Comparison of the spectra disclosed no differences and/or formation of new peaks. It was concluded that there was no decomposition of the films.

Evaluation of Stability Properties of Free Films.—*Water Vapor Transmission and Oxygen Permeability.*—The water vapor transmission and oxygen permeability of the polymers have been determined by the procedure outlined in the *Experimental* section. The magnitude was in the order of 10^{-3} to 10^{-6} Gm.cm./cm.² 24 hours as shown in Table IV.

The values for water permeability all fall within a range which indicates that they would be suitable film coating agents (13) according to the value for shellac of 8.813×10^{-4} Gm.cm./cm.² 24 hours, which has been suggested as a control for maximum permissible water vapor transmission.

One might assume that these films would be as effective against oxygen as they are against water vapor transmission, although no experimental work was found in the literature to indicate what range of oxygen permeability was satisfactory for the prevention of auto-oxidation of film coated drugs. Future work along these lines will be undertaken.

It appears from Table IV that there was an inverse relationship between the water vapor transmission and oxygen permeability. The noticeable exceptions were the values for Exon 497 and 470 which were low in both cases and Gelva C-3, V-10 which was high. The following hypothesis is offered to explain this relationship. The water vapor permeability of a free film has been shown to be dependent upon the number of polar groups that the polymer contains (17).

Polymers that contain hydrophilic groups attract the water molecule and cause it to penetrate more readily than those with lyophilic groups. The "Pore Theory" could be applicable to the method of oxygen permeability. Since the oxygen molecule is smaller than the water molecule, it can penetrate molecular holes in the film which are

too small to permit passage of the water molecule. Films which are lipophilic and contain very small molecular holes would have a small rate of both water and oxygen permeability, such as Exon 497 and 470. This would be a desirable property of a film coating agent. Conversely, a hydrophilic film with large pores would be highly permeable to both water and oxygen.

Moisture Absorption.—Experimental work was conducted to evaluate the effect of relative humidity upon the film properties of the polymers. The film samples were weighed at 2, 4, 8, and 12-week intervals, and the average weight change was determined for each sample. The polymers were neither affected by changes in relative humidity, nor did they absorb moisture during the test period. The standard deviations of the weight changes were also determined. The statistical *t*-test values for the mean differences were determined at the 99% confidence level according to the procedure outlined by Davies, *et al.* (18).

No statistically significant increases in moisture absorption were determined for film samples exposed to any of the three relative humidities. Exon 471 when exposed to 10% relative humidity exhibited a 1.5% average increase in weight over the 12-week period. This was the greatest increase in moisture content of any of the polymers studied at the three relative humidities.

Some of the polymers decreased in average weight over the test period. This can occur due to the gradual evaporation of any remaining residual solvent. The greatest decrease was .81% average weight loss by Gelva V-15 when exposed to 93% relative humidity. There were no visual differences in the samples. This magnitude of moisture absorption correlates with the results obtained by Goodman (8) for ethyl cellulose, representative of a typical water insoluble polymer.

Evaluation as Tablet Coating.—Coating solutions were prepared as previously described. Initially, some preliminary work was conducted using a small wire basket, and the tablets were dipped into the coating solution. This method in its cursory evaluation was unsatisfactory. No dusting powder was used so that the tablets could be evaluated for the apparent effectiveness of the polymer coating alone. Tackiness was present with some of the coatings and was appreciable in the films of Butvar B-90.

TABLE V.—PHYSICAL PROPERTIES OF FILM COATED TABLETS

Polymer	Friability Coat Loss	Disintegration Rate	
		Artificial Gastric Fluid	Artificial Intestinal Fluid
Uncoated tablets	...	30-45 Sec.	40 Sec.
Gelva C-3, V-10	0.07%	480	150
1/2 Second Butyrate	0.37	70	60
Bakelite VAGH	0.56	180	60
Exon 471	0.78	120	90
Exon 470	1.13	135	180
Lucite 44	1.20	420	300
Gelva V-15	1.42	240	270
Lucite 42	1.43	300	240
Exon 497	1.46	225	90
Lemac 541-20	2.23	210	300
Lucite 46	2.47	180	180
Butvar B-90 (5%)	6.67	90	540
Bakelite AYAF	12.85	210	240
Butvar B-90 (10%)	20.20

It was necessary to dilute the solution of Butvar B-90 to a 5% concentration to facilitate tablet coating. To evaluate the durability, ease of handling, and coating friability, disintegration and coating friability tests were conducted as described in the *Experimental* section. The results are shown in Table V.

The disintegration tests were conducted using a different sample of tablets for each of the artificial fluids since the tablets quickly disintegrated. It is believed that the film coated tablets disintegrated by means of water vapor transmission through the film with the transmitted water, reacting with the starch that was present in the tablets.

A 10% coating solution of Butvar B-90 and Bakelite AYAF produced a coating that was rather friable. All of the other tablets lost only a small percentage of their coating.

Correlation of Screening Procedure with a Formulated Product.—A coating formulation was developed from information obtained by the above screening procedure. The mercury substrate technique was employed using various concentrations of diethyl phthalate and sorbitan monooleate⁶ from 8 to 30% of each by weight of the polymer. Exon 470 was selected as the film former. Visual examination of the cast films indicated that the following formula was superior to any of the others for use with Exon 470: Exon 470, 5%; diethyl phthalate, 20% by weight of the polymer; Arlacel 80, 2%; FD&C red No. 3, 0.05%; isopropyl alcohol, 25%; butyl acetate, 40%; and acetone, *q.s. ad.*, 100%.

The coating formulation was applied to placebo tablets in a 12-in. coating pan using a Binks airless spray system.⁷ A nozzle tip with a 40° dispersion and a 0.009-in. opening was used, and the solution was applied under a pressure of 30 p.s.i. The following formula was selected for the placebo tablets: calcium sulfate, 90%; starch, 10%; granulating agent: methylcellulose 1500, 3% solution; and lubricant: talc, 3%.

The disintegration and friability tests were conducted according to the procedure outlined in the *Experimental* section. The placebo tablets disintegrated in approximately 55 minutes in either artificial gastric or intestinal fluid, while the coated tablets disintegrated in approximately 2 hours and 15 minutes and 2 hours and 50 minutes, in the respective fluids. There was 1.98% coat loss. The tablets had a smooth glossy appearance and retained their original design and shape.

SUMMARY AND CONCLUSIONS

1. This investigation has led to the development of a screening procedure to evaluate unsupported polymeric films for their mechanical, thermal, and stability properties.
2. The results can provide a logical basis for the selection of the modifying additives in the coating formulation.

3. Unsupported film test samples of each polymer were prepared by two different methods—knife edge applicator and mercury substrate technique. The mercury substrate technique was superior because control of film thickness and film removal was easier.

4. The 13 polymers remaining after the primary screening were evaluated according to the physical and mechanical properties of: elastic modulus, tensile strength, linear expansion, and solution rate. The following polymers appeared to be superior of the 13 tested: (a) 1/2 Second Butyrate, (b) Bakelite AYAF, (c) Lucite 44, (d) Gelva V-15, and (e) Exon 470.

5. There was no discernible decomposition of any of the 13 polymers due to thermal, photo-oxidation, and/or aging effects according to infrared analysis.

6. Evidence that an inverse relationship may exist between the water permeability and oxygen permeability of the free films could be explained by a combination of the hydrophilic-lipophilic and pore theories.

7. Moisture absorption by the polymers was negligible.

8. Nearly all of the films appeared to be applicable as film coating agents based upon friability and disintegration studies. Butvar B-90 and Bakelite AYAF produced a highly friable coating and would not be suitable.

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⁷ Binks Manufacturing Co., Chicago, Ill.