

## Evaluative Procedures for Film-Forming Materials Used in Pharmaceutical Applications

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The current interest in films for use in many pharmaceutical applications has motivated a study in which meaningful testing procedures have been developed or adapted for evaluating such films. The testing procedures studied were found to be rapid, efficient, reproducible, and valid for the evaluation of the pertinent properties of several different series of film-forming materials. The studies were conducted on the free films which were cast from these materials. Data gathered on solubility, moisture absorption, water vapor transmission rates, and the effects of temperature, humidity, and light on the free films indicate that the testing methods may be used to predict the effects of these variables on the performance of the films when they are utilized in a dosage form.

THE POTENTIAL utilization of films as specialized coatings on medications, as vehicles for medicaments, or as packaging agents has prompted several studies within recent years which evaluated various film-forming materials for these applications.

A study of polyvinylpyrrolidone (1) as a film former established a simple and rapid method for coating tablets. Similar studies were made using polyethylene glycol (2), hydroxyethylcellulose and sodium carboxymethylcellulose (3), and zein (4) as the coating materials. Several patents have been issued on film-coating materials such as silicones (5), sodium carboxymethylcellulose (6), and cellulose acetate phthalate (7). Other investigations have utilized films as moisture-protective barriers on such medicaments as ascorbic acid (8) and sodium *p*-aminosalicylate (9). Films of various compositions have been studied as enteric coatings (10) and as vehicles for medicaments (11).

All of the reported studies indicated that when films were investigated for use as specialized coatings on dosage forms, the film-forming agents were evaluated after being applied to the dosage form. This procedure often gives rise to variables which are not introduced by the film itself and may lead to erroneous or misleading results which may serve to deter an investigator from further study. In addition, many important properties of the film itself are evaluated only

with difficulty after it was been applied to a dosage form. The addition of special modifiers to the film or the combination of two or more film-forming materials in one formula often results in altering the properties of the film. It is therefore desirable to assess the effect of such modifications before applying the film to a dosage form. In this manner, the properties of the free film could be evaluated without being influenced by the nature of the dosage form or the coating technique.

It was the purpose of this study to utilize free films as a means of establishing rapid screening procedures which would evaluate the critical properties of films *per se*. The objectives were (a) the selection of simple methods for accurately producing uniform test films, and (b) the adaptation of methods for rapidly evaluating these films.

### EXPERIMENTAL

The five major film characteristics which were selected as being most critical in pharmaceutical applications are: (a) solubility, (b) moisture absorption, (c) water vapor transmission, (d) reaction to temperature, and (e) reaction to light. Other characteristics which were not included in this study are adhesiveness, tensile strength, hardness, and oxygen transmission. These might be of importance in special cases.

#### Apparatus

**For Film Casting.**—The Gardner Ultra Applicator<sup>1</sup> was selected over other types of film-forming devices since it offered the advantages of simplicity of adjustment and operation in the casting of films. The Ultra Applicator (Fig. 1) is composed of two parts, a block and a blade. The stainless steel rails attached to the block are tapered at a gradient of 10 mils per 2-inch length. A thumb screw holding the blade to the underside of the block permits the

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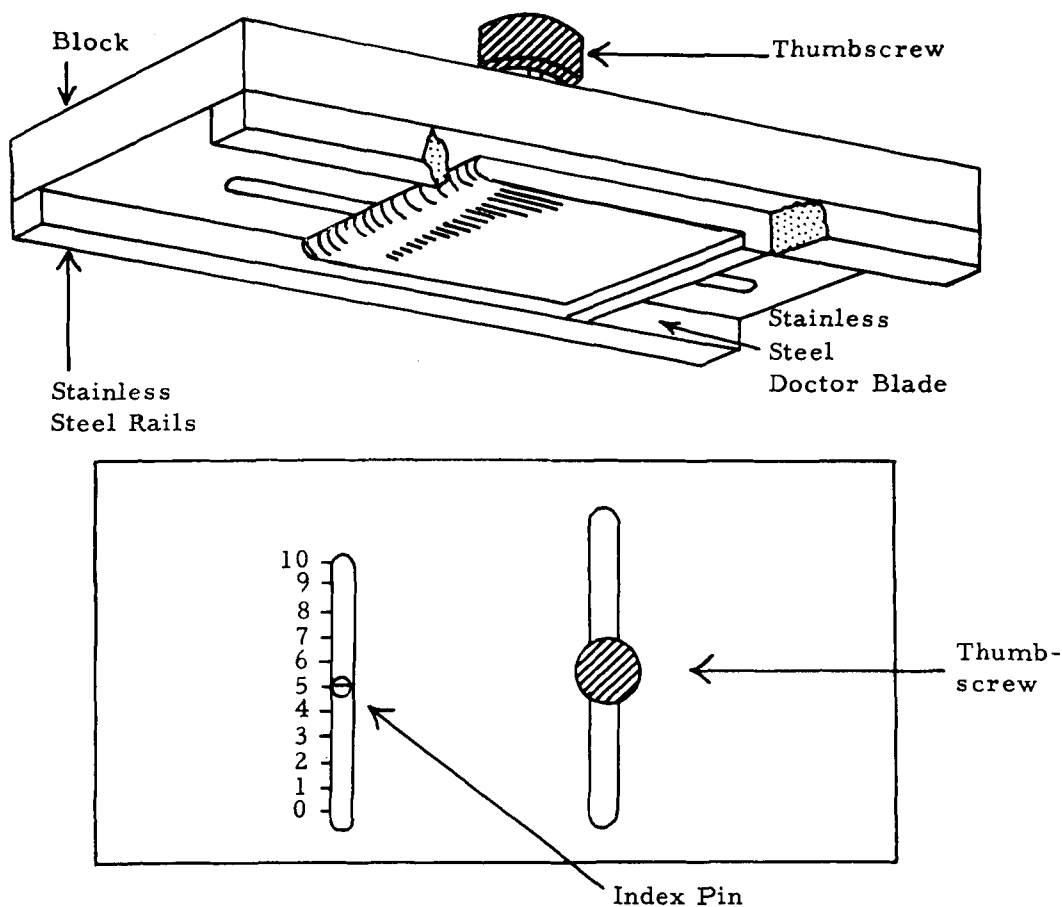


Fig. 1.—Gardner Ultra Applicator.

positioning of the blade along the gradient so that films of any desired wet film thickness may be drawn on a suitable surface. The critical dimensions of the applicator itself are held within 0.0001 inch tolerance which assures optimum accuracy of draw downs over its entire length. Models of the Ultra Applicator are available for producing wet films ranging from 0 to 20 mils in thickness, and from 0.75 to 6 inches in width.

When used, the blade position is adjusted for the desired wet film thickness and the block is placed over a small pool of the solution of the film former on a smooth surface. The entire applicator is then drawn downward over the pool to spread it evenly over the surface. The resulting wet films are then dried and removed for evaluation.

The surface onto which the films are cast also affects the production of uniform films. Highly polished chromium plated stainless steel plates, measuring 8 by 13 inches, were selected for this purpose since it has been shown that film-forming materials drawn over such a surface encounter less resistance in flowing over it than over ordinary steel surfaces (12).

**For Film Evaluation.**—The dry film thickness was measured by means of an Ames dial comparator, model 2w.<sup>2</sup> This dial comparator was fitted with an

indicator capable of accurately recording 0.0001 inch thicknesses. Contact point area and contact pressure was designed to meet A.S.T.M. standards for thickness measurement of plastic film or similar materials. Contact pressure was controlled by use of a 19-oz. dead weight.

Water vapor transmission (W.V.T.) rates of free films were established by using the water vapor permeability cup, No. 305-7, Carson type, cast wax seal.<sup>3</sup> This type of vapor permeability cup meets the specifications of the A.S.T.M. test No. E96-53T, and is available with wax casting template and weighing cover.

#### Materials

In order to evaluate films which are indicative of a wide range of pharmaceutical applications, this investigation was conducted with the following film forming agents which represent four major groups of films based on solubility. The agents which were used were: (a) ethylcellulose, representing water-insoluble films; (b) methylcellulose, representing water-soluble films; (c) zein, representing varying solubility depending on pH; and (d) polyvinylpyrrolidone and ethylcellulose combination, representing slowly soluble films.

<sup>2</sup> B.C. Ames Co., Waltham 54, Mass.

<sup>3</sup> Thwing Albert Instrument Co., Philadelphia 44, Pa.

The combination of polyvinylpyrrolidone and ethylcellulose was chosen because it offered the possibility of evaluating a film which was composed of water-soluble and water-insoluble components, both of which are soluble in a common solvent such as ethanol, and could thus be cast as a single film.

Preliminary work was done to establish the optimum conditions for film casting and drying. Various solvent systems, concentrations of film forming materials, wet film thicknesses, and drying times and temperatures were tried for each of the materials studied.

### Procedure

Once a particular formulation was found to be suitable, a bulk solution of sufficient volume was prepared from which all film samples could be produced for evaluation. The following solutions were used in this investigation:

Solution A	
Ethylcellulose, 50 cps.	10% w/v
Alcohol U.S.P.	20% v/v
Toluene	70% v/v

Films of various thicknesses were produced by drying the wet films at 94° for 8 minutes.

Solution B	
Methylcellulose, 400 cps.	5% w/v
Purified water	95% v/v

Films were prepared at a drying temperature of 80° at drying times of 8 to 14 minutes.

Solution C	
Zein	21.60% w/v
Oleic acid	15.90% v/v
Alcohol U.S.P.	56.25% v/v
Purified water	6.25% v/v

Films were produced from this solution after drying the wet films for 6 to 10 minutes at 51°.

Solution D	
Ethylcellulose, 50 cps.	10.2% w/v
Polyvinylpyrrolidone	3.2% w/v
Citroflex a-4	3.5% v/v
Alcohol U.S.P.	83.1% v/v

Films were developed and dried for 4 minutes at 44°.

Oleic acid in solution C, and Citroflex a-4 in solution D were added as plasticizers to eliminate brittleness of films as they dried.

### Testing of Films

**Solubility of Films.**—Film samples were cut to uniform size by using a 1 × 3 inch glass microscope slide as a cutting template. A scalpel was used to cut strips of films of these dimensions and these strips were evaluated initially and again at stated intervals after being exposed to test conditions.

A sufficient number of strips of each different film of various thicknesses was stored in 4-ounce, wide-mouth glass containers with plastic screw caps and maintained at room temperature, 40°, and 60°. Samples of each were withdrawn at 1, 2, 4, 8, and 12-week intervals and were checked for any changes in solubility. In all cases, solubility tests were conducted in both artificial gastric and artificial intestinal fluids. The U.S.P. formulations for these solutions were employed.

The strips of film were immersed completely in 100 ml. of test fluid which was maintained at 37°. The test fluid was constantly kept in motion by means of a magnetic stirrer and the rate of movement was adjusted so as to create and maintain a small vortex. The solubility of the films in the testing solutions was rated visually; the end point being a complete solution of the film. Reproducibility of results was obtained within a very small range of time measured in seconds in several determinations of different samples of the same film. A similar evaluation procedure was used by Jarrell in a study involving the solubility of carboxymethylcellulose films (13).

**Moisture Absorption by the Films.**—A standardized method for determining water absorption by plastics has been approved by the A.S.T.M. and has been designated as A.S.T.M. test No. D570-59T. This test is designed for all shapes of plastics, including sheets, rods, and disks. A modification of this method was used for the testing of films in this study as follows: Films were prepared and cut into 1 × 3 inch strips. The strips were then conditioned by placing them in an oven at the temperatures and for the drying times which had been used originally in drying the wet films. This step was carried out to insure uniformity of the films within each group before testing. The conditioned sample strips were then suspended by means of fine wire in relative humidity chambers. The wire was made to pierce each strip in such a manner as to permit free access of the moist air to all surfaces of the films. Three chambers were set up to produce relative humidities of 10, 52, and 93%, respectively. The relative humidity in the chamber was controlled by the use of different saturated solutions containing excess solute. The conditioned film specimens were accurately weighed, placed in the relative humidity chambers, and then removed and weighed again at the end of 1, 2, 4, 8 and 12-week intervals. Increase or decrease in weight, changes in physical appearance or in solubility were then observed. Per cent moisture absorption was calculated by means of the following formula

$$\frac{\text{weight of exposed film} - \text{weight of conditioned film}}{\text{weight of conditioned film}} \times 100$$

The percentages calculated by means of this formula were plotted against time to establish the point of maximum absorption for each specimen film.

Moisture absorption data on films must include consideration of the following factors before the results may become applicable: (a) dimensions of the specimen, (b) conditioning time and temperature, (c) exposure procedure used, (d) time intervals of exposure and sampling, (e) percentage increase in weight, (f) observations as to changes in physical appearance of film specimens, and (g) effects on solubility.

**Water Vapor Transmission.**—The method employed to measure W.V.T. was a modification of the A.S.T.M. test No. E96-53T. Procedure E of this test for materials in sheet form was adapted for measurements of W.V.T. at an elevated temperature, with a low humidity on one side of the film and a high humidity on the other side.

The Carson type water vapor permeability dish was employed as the testing apparatus. These aluminum dishes are made with specially designed

flared edges upon which disks of film specimens may be placed and sealed in place with a wax seal. Drierite desiccant, No. 8 mesh, was placed within the dish to a height of within 3 mm. of the film sample being tested. In order to insure perfect sealing of the film disk to the edges of the dish and thus prevent leakage of water vapor around the film, a specially designed template was employed to define the test area and to help in forming the wax seal. The template was carefully placed over the film specimen, which was resting on the edges of the dish, and molten wax was poured into the space between the beveled edge of the template and the outer edge of the dish. When the wax solidified, the template was removed by gently twisting it until it came free. A mixture of 60% microcrystalline wax and 40% paraffin was found to be adequate for sealing the edge of the film to the edge of the dish.

Four specimens of each film were prepared in this manner. The entire assembly was accurately weighed and then placed in a constant humidity chamber at  $37.8 \pm 1.5^\circ$  and 91% R.H.  $\pm 2\%$ . A control blank apparatus was included in each batch for the purpose of establishing if any significant change could be attributed to the test apparatus itself. No significant change was noted at any time.

The W.V.T. of a sample was calculated in terms of grams per square inch per 24 hours as follows

$$\text{W.V.T.} = \frac{(g)(24)}{(t)(a)}$$

where  $g$  = weight change in grams,  $t$  = time, in hours, during which weight change occurred, and  $a$  = area of exposed specimen film in square inches.

**Light Stability Test.**—Film samples were cut into 1 × 3 inch strips and placed in open Petri dishes. These were positioned in a light stability cabinet<sup>4</sup> recently described by Lachman and his co-workers (14). The cabinet is constructed so that samples may be placed at various distances from the light source so that light intensity to which samples are subjected may be regulated. By placing the samples at a distance of three feet from the light source, they were subjected to a twentyfold increase in intensity over ordinary light. Samples were studied visually for possible changes in appearance at the end of 4 and 6-week intervals.

## RESULTS AND DISCUSSION

**Effect of Storage on Solubility of Films.**—The four groups of films tested offer a wide degree of solubility characteristics. As had been expected, films of methylcellulose were soluble in the artificial digestive test fluids. No solubility changes were observed in these films upon storage at elevated temperatures for 12 weeks. As had equally been anticipated, films of ethylcellulose were completely insoluble in both gastric and intestinal fluids, and the insolubility of the films was not altered after periods of storage at different relative humidities or temperatures. Different film thicknesses also had no effect on the solubility of these films. Specimen films were considered insoluble when they indicated no

change after 24 hours immersion in the testing apparatus.

The results of the solubility studies on zein films substantiated the properties of this material as being insoluble in gastric fluids but rapidly soluble in intestinal fluids. The rate of solubility in artificial intestinal fluid was directly proportional to the thickness of the film, ranging from 1.5 seconds for test strips of 0.6 mil thickness to 9 seconds for test strips of 1.5 mil thickness. The solubility rates of the zein films were in no way altered by the storage conditions.

The combination of ethylcellulose and polyvinylpyrrolidone proved to be completely insoluble in both gastric and intestinal fluids. The original anticipation that this combination would yield a slowly soluble film due to contributory characteristics of each component did not materialize. The possibility exists that the ethylcellulose completely dominated the film characteristics by coating the polyvinylpyrrolidone molecules, and that different combinations of these materials might reverse this situation.

**Storage Stability of Films.**—The effects of elevated temperatures on the physical characteristics of the film other than its solubility should be noted. Films of ethylcellulose and methylcellulose were found to be completely stable under all temperature conditions. There were no physical changes in these films after 12 weeks. Definite physical changes in the zein films were observed. These changes involved a darkening in color and an increased brittleness. In the case of the thinnest film (0.6 mil) the change became apparent at the 40° temperature level at the end of 8 weeks. At the end of the same period, samples of all thicknesses at 60° had become brown in color and brittle. The cause of this discoloration and increased brittleness was traced to the oleic acid plasticizer used in this film. Oleic acid at 80° has been shown to absorb approximately four atoms of oxygen per molecule with a low yield of peroxide and a considerable evolution of water and carbon dioxide (15). It has also been noted that the oxidation reaction is accelerated by heat and light (16). The long term exposure of the film to the elevated temperature might have caused the acceleration of this oxidation of oleic acid producing a discoloration and a brittleness of the film. The use of other plasticizers such as ethyl lactate, propylene glycol, or sodium lactate might eliminate this problem. No reports could be found in the literature to indicate previous knowledge of such a problem with an oleic acid plasticized zein film.

**Moisture Absorption by Films.**—The method developed for evaluation of the effect of relative humidity on film properties produced results which were uniform and reproducible. In the case of methylcellulose, results indicated that these films absorbed relatively low amounts of moisture, and reached a point of equilibrium at the end of 3 weeks in relative humidities of 10 and 52%. These relative humidities did not produce any apparent physical changes in the films at the end of 12 weeks.

Moisture absorption in the 93% R.H. chamber, however, was so great that the films became soft and gummy within 4 weeks, the point at which maximum absorption was reached. Figure 2 indicates the percentage of moisture absorption for methylcellulose films of 0.5 mil thickness.

<sup>4</sup> The authors are indebted to Ciba Pharmaceutical Products Inc., Summit, N. J., for making available the light stability cabinet used in this study.

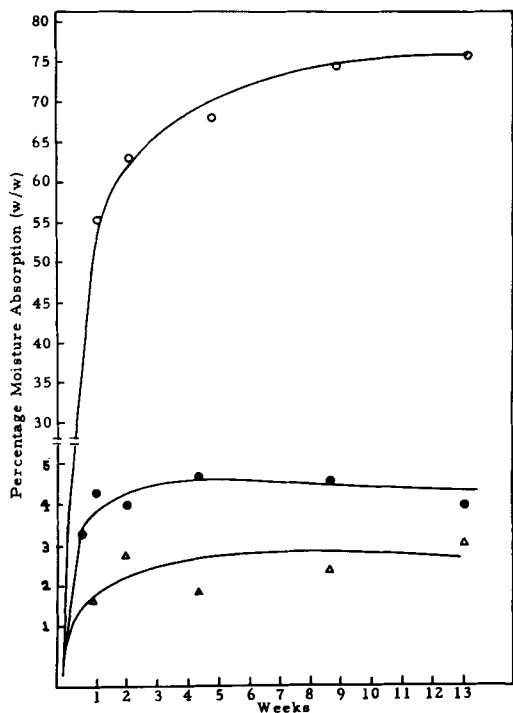


Fig. 2.—Moisture absorption of methylcellulose film of 0.5 mil thickness. O, 93% R.H.; ●, 52% R.H.; Δ, 10% R.H., all at 37.8°.

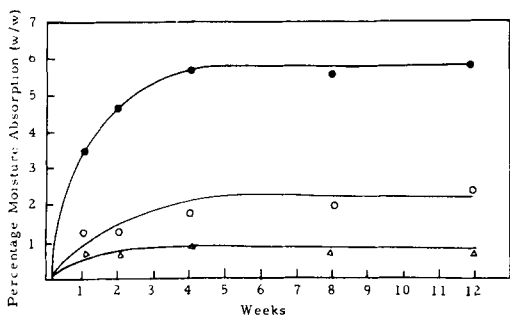


Fig. 3.—Moisture absorption of ethylcellulose film of 1 mil thickness. O, 93% R.H.; ●, 52% R.H.; Δ, 10% R.H., all at 37.8°.

The amount of moisture absorption by the ethylcellulose films reached equilibrium in 3 to 4 weeks (Fig. 3). It was discovered that the percentage of absorbed moisture was not directly proportional to relative humidity. Regardless of thickness, the films consistently absorbed a higher percentage of moisture at 52% R.H. than they did at 93% R.H. This odd phenomenon was not reported anywhere in the literature and no feasible explanation of this can be offered at this time. Relative humidities at the different levels had no visible effect on the physical properties of the ethylcellulose films.

The zein films showed moisture absorption patterns similar to those of methylcellulose. In relative humidities of 10 and 52%, the moisture absorption was 1.5% or less; equilibrium being established within 3 weeks. Films stored at 93% R.H. were

softened considerably by the end of the first week and in some instances the test strips became completely deformed.

The value of studying films produced by a combination of film-forming agents was demonstrated effectively by the moisture absorption rates of the ethylcellulose-polyvinylpyrrolidone films. It has been shown that the moisture content of polyvinylpyrrolidone films is directly related to relative humidity; with the equilibrium percentage of moisture being about one-third of the relative humidity (17). Thus, it could be calculated that if a polyvinylpyrrolidone film was exposed to a relative humidity of 90%, the moisture content at equilibrium would approach 30%. Likewise, at relative humidities of 10 and 52%, the moisture absorption of a polyvinylpyrrolidone film would reach equilibrium at about 3 and 17%, respectively.

Figure 4 indicates that the film composed of a combination of ethylcellulose and polyvinylpyrrolidone absorbed only 0.6% at the 10% R.H. level, and between 3 and 5% moisture at the 52% level. It therefore appears that at the lower levels of relative humidity the ethylcellulose content of the film exercised a major role in the film properties achieved. However, in the 93% R.H. chamber, the same film continued to absorb moisture, and at the end of 12 weeks had absorbed as much as 12%. In this instance it is quite probable that the inherent hygroscopic properties of the polyvinylpyrrolidone overshadowed the effect of the ethylcellulose content. This phenomenon was not observed in ethylcellulose-polyvinylpyrrolidone films of 1.0 mil thickness, in which instance a maximum of 7% absorption of moisture in the 93% R.H. chamber was recorded and this level remained constant after 3 weeks.

**Water Vapor Transmission.**—Ethylcellulose films showed a W.V.T. rate which varied inversely with the thickness of the film. Figure 5 indicates that the W.V.T. decreased almost linearly with an increased thickness of film. Figure 6 demonstrates that methylcellulose films exhibited W.V.T. charac-

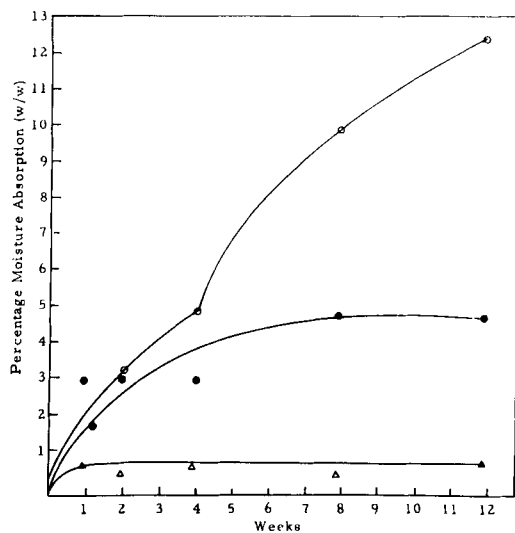


Fig. 4.—Moisture absorption of ethylcellulose-polyvinylpyrrolidone film of 1.5 mil thickness. O, 93% R.H.; ●, 52% R.H.; Δ, 10% R.H., all at 37.8°.

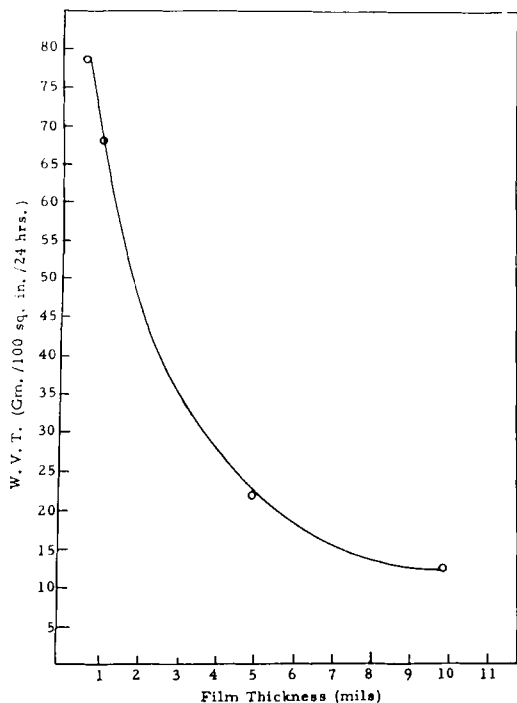


Fig. 5.—Water vapor transmission of ethylcellulose films, 91% R.H. at 37.8°.

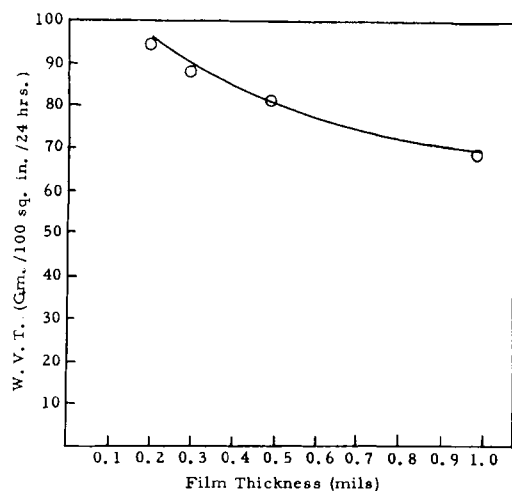


Fig. 6.—Water vapor transmission of methylcellulose films, 91% R.H. at 37.8°.

teristics which were very similar to those of ethylcellulose films, even though the former material is completely soluble in water while the latter is insoluble.

Zein films (Fig. 7) manifested the lowest W.V.T. rates of all the tested films. These films should, therefore, offer good protection qualities against moisture when applied to dosage forms. It has been shown that the major factors controlling the W.V.T. of a film are: chemical structure, polarity, symmetry, and the size of the polymers or molecules making up the film (13, 18). A recent study (19) has demonstrated that the films containing more polar group-

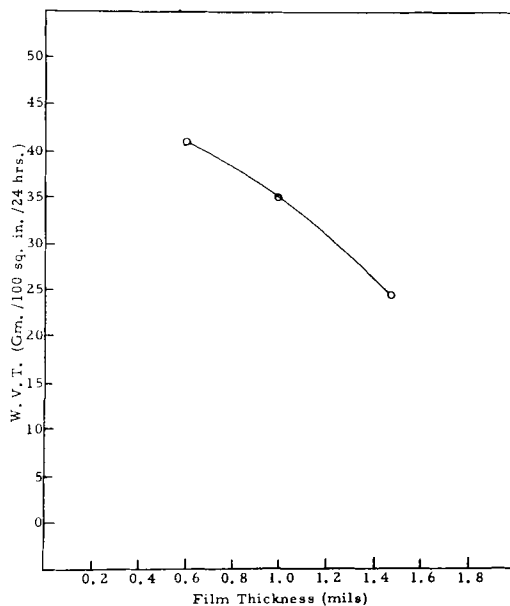


Fig. 7.—Water vapor transmission of zein films, 91% R.H. at 37.8°.

ings permit larger amounts of moisture vapor to pass through them. The low W.V.T. of the zein films, therefore, may be attributed to the large number of nonpolar side chains making up the polymer units.

**Light Stability of Films.**—Samples of all films exposed for a period of 6 weeks in the light stability cabinet indicated complete physical stability with the exception of zein, which underwent a change from an initial light tan color to almost colorless in this period of time. The brittleness of the film was increased at the same time and may have been caused by the oxidation of the oleic acid plasticizer as previously noted in the effects of high temperatures on the same film. The discoloration of the film was probably due to a bleaching of the color constituents of zein. These observations suggest the necessity of the use of other plasticizers, and the addition of ultraviolet light-absorbing agents in those instances where bleaching of films is undesirable.

## SUMMARY

1. Meaningful testing procedures have been developed or adapted for the rapid evaluation of film-forming agents for pharmaceutical use.

2. The testing procedures developed were used to evaluate several free films, and the results obtained either substantiated expected results or indicated properties which might not have been revealed in an applied film.

3. Data on the physical properties observed as a result of the evaluation of free films not only indicate the validity of the testing procedures but also point out the need for further study of free films in contrast to the current methods of evaluation of applied films.

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## Notes

## Toxicity and Central Depressant Activity of D-1-Phenyl-2-ureidopropane

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D-1-Phenyl-2-ureidopropane was prepared by the method of Toritaku and alternatively, by reacting 1-phenyl-2-aminopropane directly with urea. The LD<sub>50</sub> of this ureide was found to be 840 mg./Kg. The compound was found to act as a central nervous system (CNS) depressant rather than as a sustained action CNS stimulant, as suggested by Toritaku. Comparison of the structural formula of 1-phenyl-2-ureidopropane with that of the barbiturates and hydantoins supports the experimental evidence that this compound acts as a barbiturate-like central nervous system depressant.

THE PREPARATION of sustained release amphetamine compositions has depended principally upon three approaches: (a) the preparation of beads of active ingredient coated with shellac, wax, or other insoluble substance, (b) the formation of a complex between amphetamine and an ion exchange resin, and (c) the formation of insoluble salts of amphetamine, such as the tannate, which are then slowly converted to soluble amphetamine salts in the acid stomach.

Our attention has been directed toward the search for new amphetamine compounds which would hydrolyze to give sustained amphetamine action or which, in themselves, would provide prolonged stimulation of the central nervous system.

Toritaku (1) has indicated that the urea derivative of amphetamine hydrolyzes *in vivo* to give a sustained amphetamine action. Toritaku's patent described the preparation of the compound but reported no biological tests to demonstrate the amphetamine action. This study was therefore initiated to determine the toxicity and duration of action of D-1-phenyl-2-ureidopropane.

## EXPERIMENTAL

**Synthesis.**—D-1-Phenyl-2-ureidopropane was prepared from D-1-phenyl-2-aminopropane sulfate and potassium cyanate as described by Toritaku (Fig. 1).

D-1-Phenyl-2-aminopropane sulfate, 60 Gm. and potassium cyanate, 30 Gm., were placed in 350 ml. distilled water and boiled for 30 minutes. After three recrystallizations from water, white needles were obtained which melted at 138.5 to 139°, which agrees with previously reported data (2, 3). The actual yield from the reaction was 55 Gm. or 90% of the theoretical yield, 58 Gm.

D-1-Phenyl-2-ureidopropane was also prepared by the reaction of D-1-phenyl-2-aminopropane with urea (Fig. 2.). This method was abandoned because of low yield.

**Biological Examination.**—The intraperitoneal LD<sub>50</sub> of this compound was determined by the method of Hagan (4). White rats, 200 Gm., both male and female, were used as experimental animals. Following determination of the intraperitoneal LD<sub>50</sub>, the compound was administered orally to 200-Gm. rats, both sexes, at a dose of twice the intraperitoneal LD<sub>50</sub>. The experimental animals were compared to the controls by visual examination.

**Results.**—The data from the intraperitoneal

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