

## Free Films I: Apparatus and Preliminary Evaluation

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**Abstract** □ A method is described for use in the study of free unsupported polymer films. A new apparatus was constructed to permit systematic variations in factors affecting film formation by spraying. The utility and applicability of the proposed methodology were demonstrated in experiments in which the effects of spray rate, spray distance, and film substrate on the tensile strength, modulus of elasticity, apparent density, and water vapor permeability of cellulose acetate films were investigated.

**Keyphrases** □ Films, free, unsupported—method and apparatus for spray formation, evaluation □ Polymer films—method and apparatus for spray formation, evaluation □ Coatings—evaluation of free unsupported polymer films, method and apparatus

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Coatings are applied to pharmaceutical dosage forms to protect them against the environment, to improve their appearance, to mask undesirable taste or odor, to impart enteric properties, and to modulate the release of medicaments. Because of the large selection of film formers, the rapidity with which they can be applied, and the ease with which the coating process can be learned or automated, film coating has assumed an increasingly important role in recent years. Not too surprisingly, a greater need for knowledge on the properties of films is increasingly more evident as greater demands are made on the functionality of film coatings.

The screening and testing of polymers as potential film coatings were the subjects of a number of investigations (1-17). In these studies, films were evaluated on the basis of their performance on film-coated tablets or as free unsupported films. The permeability, solubility, dissolution rate, tensile strength, hardness, adhesiveness, reaction to temperature, and reaction to light of polymer films were investigated. When free films were evaluated, they were invariably prepared by a casting technique. In this method, a solution of the film former is spread evenly over a polished surface or on mercury. The solvent is allowed to evaporate and the free film is then recovered. The purposes of this communication are to point out some shortcomings in evaluating films prepared according to this procedure and to describe and justify the design and construction of a new apparatus for their preparation by a spraying technique. It will be shown that different film properties can be conferred depending on spraying conditions; thus, the proposed methodology permits evaluation of process variables in the coating of pharmaceuticals.

Kanig and Goodman (3) pointed out the advantages of studying the properties of free films, since, after application to dosage forms, erroneous or misleading results due to variables that are not introduced by the film itself may be obtained. In addition, it is more dif-

ficult, if not impossible, to evaluate certain properties of films deposited on dosage forms. After studying the solubility, moisture absorption, water vapor transmission, and reaction to light and temperature of films prepared by a casting technique, they concluded that their testing procedures were meaningful and revealing and suggested further study of free films as opposed to applied films.

Banker *et al.* (10, 11), on the other hand, expressed a somewhat different point of view. They studied the water vapor transmission properties of free polymer films and of films of the same composition applied to tablets. The conclusion reached by these workers was that the results obtained on free films should not be used as the sole criterion for accepting or rejecting potential film coatings. This recommendation was based on the fact that whereas the rate of moisture vapor transmission and film thickness for free films followed a log-log relationship, the thickness of applied films was linearly related to this parameter. Although these results do not contradict the conclusions reached by Kanig and Goodman (3), they do highlight the need for a method of preparing free films which simulates, more realistically, those deposited on dosage forms.

Since Banker *et al.* (10, 11) compared the properties of free films prepared by casting with films applied to dosage forms by conventional spray techniques, the differences observed may not be due solely to the substrate. Undoubtedly, however, a substrate effect is more or less important, depending on the film property under investigation.

A major and obvious difference between sprayed and cast films is that the former is deposited as a series of contiguous layers. It is proposed, also, that at least some particles of spray-dried polymer become entrapped, resulting in discontinuities in the structure of the film. These differences probably become more significant when cohesion between contiguous layers is poor and, in particular, when heterogeneous systems are employed. This latter situation exists when lakes and opacifiers are included in the film. Film solutions may also become heterogeneous as the solvent evaporates and the solubility of one or more components is exceeded. When these conditions exist, segregation may occur during the preparation of cast films, resulting in films consisting of two or more dissimilar layers. This separation does not occur in the film coating of tablets by conventional spray techniques.

These proposed differences between cast and sprayed films could result in serious misinterpretation when

data obtained on cast films are used to evaluate films for use in tablet coating by the spray method. Therefore, it seemed reasonable to design an apparatus for the production of free films by a spraying technique under accurately controlled conditions. Provisions were included in the design so that factors likely to influence the formation of sprayed films, *i.e.*, process variables, can be studied in a systematic fashion.

### FREE FILM APPARATUS

The apparatus for preparing free films is shown in Fig. 1. The major elements are a vertically reciprocating spray nozzle mounted opposite a revolving cylinder. The cylinder is 15.24 cm. (6 in.) high and 30.48 cm. (12 in.) in diameter; it is coated with Teflon and fitted with a clamping device for attaching other substrates to its surface. The spray nozzle is of the air-liquid type, where the liquid pumped through the nozzle is atomized by a stream of air under pressure.

The length of stroke, the number of strokes per minute, and the distance of the spray nozzle to the cylinder can be varied, as can the revolutions per minute of the rotating cylinder.

Heated drying air, the linear velocity and temperature of which can be controlled, is supplied to the cylinder surface through a 3.81-cm. (1.5-in.) diameter duct.

Films were prepared in the following manner. After adjusting the apparatus to set the desired conditions for each run, an obstacle such as a piece of cardboard was placed between the spray nozzle and the cylinder. The pump that delivered the polymer solution to the nozzle at a predetermined rate was then activated. The obstacle was removed when a steady spray rate was achieved. After spraying for the specified time for each run, the obstacle was again placed between the spray nozzle and the receiving surface before stopping the apparatus. The film was then separated from the substrate for study. In preparing free films with this apparatus, the length of stroke is adjusted so that film deposited at the point when the spray nozzle is stationary (top or bottom of stroke) does not constitute part of the recovered film.

### PRELIMINARY EVALUATION

The apparatus was conceived so that properties of sprayed films can be systematically examined in relation to factors influencing their formation. Preliminary experiments intended only to demonstrate the applicability and the suitability of the proposed concept and methodology are reported here.

Some general remarks regarding the nature and the design of these initial experiments seem appropriate. From its conception, the possibility of potential interaction between film and substrate resulting in artifacts has been a source of great concern. While every effort can be made to choose substrates on the basis of their inertness, there is no certainty that their influence on any given film property is excluded. Hence, the effect of substrate deserves immediate attention. It is also evident that the number of known variables in film formation by spraying is formidable, even when all are amenable to control. Within the range over which such control can be exercised, and recognizing the existence of variables not immediately evident, can films be sprayed with sufficient reproducibility so that factors affecting their formation can be discerned with a reasonable degree of clarity? To attempt an evaluation of the proposed technique, executions of the film-forming process and of the subsequent measurements on film properties should contribute only minimally (hopefully insignificantly) to the experimental outcome and its interpretation. These considerations and the lack of prior knowledge concerning sprayed films constitute the rationale for these preliminary experiments.

The system chosen for evaluation was cellulose acetate<sup>1</sup> sprayed as a 3% w/v solution in acetone. This system was selected for its simplicity in composition and because of its Newtonian properties with respect to flow. Variables in film formation chosen for study were

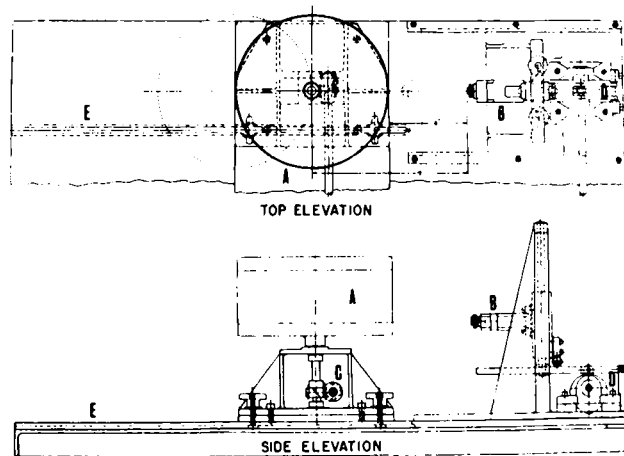


Figure 1—Spray apparatus. Key: A, cylinder; B, spray nozzle; C, right angle drive; D, cam; and E, track.

the film substrate material (*S*), the spray rate (*V*), and the distance (*D*) between the spray nozzle and the rotating cylinder. All other known factors in the film-forming process were held constant throughout. A summary of the experimental conditions is shown in Table I. All equipment used in this study, including sources of air for drying and atomizing, are those actually employed in film coating of dosage forms. All combinations of variables at all levels were studied in duplicate in accordance with a factorial design. The resulting films were studied with respect to their apparent density, tensile strength, modulus of elasticity, and water vapor permeability.

### EXPERIMENTAL

**Film Formation**—As shown in Table I, there are 12 possible combinations of the three variables chosen for investigation. Each combination was sprayed in duplicate; hence, there were 24 separate

Table I—Experimental Conditions in Film Formation

Spraying Conditions	Setting	Observed Range
Spray nozzle <sup>a</sup> :		
Liquid	2850	—
Air	120	—
Spray head movement:		
Strokes per minute	47	—
Stroke length	12.7 cm. (5 in.)	—
Cylinder speed	120 r.p.m.	—
Atomization pressure	6 p.s.i.g.	—
Spray solution:		
Concentration	3% w/v	—
Temperature	R.T.	21.5–24.0°
Drying air:		
Temperature	50°	48–52°
Velocity [3.81-cm. (1.5-in.) dia.]	243.8 m./min.	237.7–254.5
Film thickness	0.040 mm.	0.038–0.042mm.
Spraying time	—	6–8 min. and 3.75–4.25 min. 120–190 ml.
Solution consumed	—	
Spray rate (variable)		
I	20 ml./min.	—
II	40 ml./min.	—
Spray distance (variable)		
A	5.08 cm.	—
B	12.7 cm.	—
Substrate (variable)		
1	Teflon <sup>b</sup>	—
2	Aclar <sup>c</sup>	—
3	Aluminum <sup>d</sup>	—

<sup>a</sup> Spraying Systems Co., Bellwood, Ill. <sup>b</sup> Teflon Tape, Kaufman Co., Wilmington, Del. <sup>c</sup> Aclar 33C, Allied Chemicals, New York, N. Y. <sup>d</sup> Aluminum foil, 0.0038 cm. (0.0015 in.), Joseph Frankel, Philadelphia, Pa.

<sup>1</sup> Cellulose acetate, type D398-10, Eastman Chemical, Kingsport, Tenn.

**Table II—Summary of Analyses of Variance on the Effect of Factors in Spraying on the Physical and Mechanical Properties of Cellulose Acetate Films (Mean Square Values)**

Sources of Variation	Tensile Strength	Modulus of Elasticity	Film Density	Water Vapor Permeability
Spray rate ( <i>V</i> )	675,362 <sup>a</sup>	33,638 <sup>a</sup>	21,027,769 <sup>a</sup>	12,192 <sup>a</sup>
Spray distance ( <i>D</i> )	2,180,449 <sup>a</sup>	130,169 <sup>a</sup>	78,438,533 <sup>a</sup>	25,808 <sup>a</sup>
Substrate ( <i>S</i> )	37,934	802	2,684,468	1,640
<i>V</i> × <i>D</i>	562,121 <sup>a</sup>	24,352 <sup>a</sup>	14,335,788 <sup>a</sup>	9,718 <sup>a</sup>
<i>V</i> × <i>S</i>	40,392	68	1,840	3,192 <sup>b</sup>
<i>D</i> × <i>S</i>	13,424	294	3,195	182
<i>V</i> × <i>D</i> × <i>S</i>	2,392	330	382,084	1,098
Film replication ( <i>R</i> )	24,505 <sup>a</sup>	859 <sup>c</sup>	887,397 <sup>a</sup>	596
Residual	7,775	291	34,140	768

<sup>a</sup> Statistically significant,  $p < 0.001$ . <sup>b</sup> Statistically significant,  $p < 0.025$ . <sup>c</sup> Statistically significant,  $p < 0.005$ .

experiments in film formation. The order in which the experiments were performed was determined by a random process. Several attempts were sometimes required before a film having the specified thickness was achieved. As each film strip was formed, it was separated from its substrate and stored in a desiccator over dried silica gel. The storage position of each film in relation to all other films within the desiccator had been fixed by random assignment and maintained for the duration of this study. No measurement of film properties was undertaken until all 24 film strips had been formed.

**Tensile Strength Measurements**—Tensile strength measurements were made on a tensile strength apparatus<sup>2</sup> which had been modified. The spring for recording the force was replaced by a transducer<sup>3</sup>, the voltage output from which was recorded continuously on a strip-chart recorder. Inasmuch as the rate of strain was constant at 1.06 cm./min., film elongation was directly related to time and, therefore, could be easily estimated from the recorder chart.

Test strips were cut from the films with the aid of a rectangular template having dimensions of  $1.07 \times 12$  cm. Test strips were always taken such that their longer dimension was parallel to that of their parent. In other words, in relation to the film-formation process, the tensile strengths reported here are those along the direction perpendicular to the motion of the reciprocating spray nozzle. These strips were mounted in the tensile strength apparatus so that the length of film between the jaws was initially 10 cm. Where breakage occurred at the jaw, which was infrequent, the result was considered invalid and the test was repeated on another strip. Four tensile strength measurements were taken on each film. Each of the 96 measurements was considered a separate experiment, and the order in which they were performed was randomly assigned. A correction was made to account for changes in cross-sectional area resulting from elongation. Hence:

$$\text{tensile strength} = \frac{\text{break force}}{ab} \left( 1 + \frac{\Delta L}{L} \right) \quad (\text{Eq. 1})$$

where  $L$ ,  $b$ , and  $a$  are the length, width, and thickness of the test strip, respectively; and  $\Delta L$  is the elongation at break.

**Modulus of Elasticity Measurements**—Estimates of the modulus of elasticity (Young's modulus) were also obtained from the slopes of the stress-strain relationships recorded during the tensile strength measurements. Again, area corrections were made:

$$\text{modulus of elasticity} = \frac{\text{corrected stress}}{\text{strain}} \quad (\text{Eq. 2})$$

**Film Density Measurements**—Film densities were estimated by weighing test strips used in tensile strength measurements.

**Water Vapor Transmission Measurements**—Five milliliters of a saturated solution of ammonium monophosphate, together with an excess of solid, was placed inside aluminum permeation cells. The design of these cells is similar in principle to those reported by other workers (4, 10). Openings of the cell were covered with circular portions of the test films. The assembled cells were weighed and placed in a desiccator over dried calcium chloride at room temperature. The rate of moisture loss through the films was determined by

weighing the cells periodically over about 24 hr. These 48 experiments were performed sequentially in groups of six by random assignment. Relative positions of the six cells within each group were again randomized. The permeability coefficient,  $P$ , is defined by:

$$P = \frac{aR_{wvt}}{A \Delta p} \quad (\text{Eq. 3})$$

where  $R_{wvt}$  is the rate of water vapor transmission in milligrams per minute,  $a$  is the film thickness in millimeters,  $\Delta p$  is the pressure difference across the membrane in mm. Hg, and  $A$  is the area of film through which transmission takes place. Since values of  $A$  and  $\Delta p$  were constant throughout, comparisons of films made under different spraying conditions were made on the basis of:

$$P' = PA \Delta p = aR_{wvt} \quad (\text{Eq. 4})$$

Moisture loss through cellulose acetate films was found to be a linear function of time. Values of  $R_{wvt}$  were obtained from the slopes of least-squares lines forced through the origin.

## RESULTS

The results obtained for tensile strength, modulus of elasticity, film density, and water vapor permeability were subjected to the appropriate analysis of variance. Statistically significant effects are summarized in Table II. With respect to each film property, if film replication effects ( $R$ ) were found to be statistically significant against the residual, all other effects were then tested against  $R$ . Otherwise, the variability associated with film replication was combined with the residual to form a pooled estimate of experimental error against which all other factors were tested.

Results on the physical and mechanical properties of cellulose acetate films formed as a result of spraying under various experimental conditions are summarized in Tables III–VI. Each entry in a table represents an average value resulting from measurements made on test strips taken from the same film. Duplicate entries shown for each set of spraying conditions correspond to values obtained for films prepared on two separate occasions.

Average results on tensile strength, modulus of elasticity, and apparent film density are shown in Tables III, IV, and V, respectively. It is evident that films formed as a result of spraying at the

**Table III—Tensile Strength of Cellulose Acetate Films Formed by Spraying under Various Conditions, kg.-mm.<sup>-2</sup>**

Spray Rate, ml./min.	Spray Distance, cm.	Substrate		
		Teflon	Aclar	Aluminum
20	5.1	3.67	4.07	4.28
		3.44	3.21	3.93
20	12.7	1.28	1.17	1.90
		1.33	1.06	1.94
40	5.1	3.38	3.58	3.69
		4.16	4.26	3.97
40	12.7	3.82	3.26	3.17
		2.73	2.54	2.98

<sup>2</sup> Gardner Laboratory, Inc., Bethesda, Md.

<sup>3</sup> Model GI-80-350, Satham Instrument, Inc., Los Angeles, Calif.

**Table IV**—Modulus of Elasticity of Cellulose Acetate Films Formed by Spraying under Various Conditions, kg.-mm.<sup>-2</sup> × 10<sup>-3</sup>

Spray Rate, ml./min.	Spray Distance, cm.	Substrate		
		Teflon	Aclar	Aluminum
20	5.1	1.21	1.26	1.26
		1.14	1.23	1.20
20	12.7	0.65	0.74	0.65
		0.64	0.61	0.74
40	5.1	1.14	1.23	1.22
		1.24	1.28	1.35
40	12.7	1.13	1.12	1.02
		0.96	0.93	1.02

slower rate from the greater distance are mechanically weaker, less elastic, and less dense. Statistical analyses (Table II) indicate that the effect of this particular combination of spraying variables is most probably real, even though the variability associated with film replication is great with respect to each of these film properties. Individual effects of spray rate alone and of spray distance alone are also statistically significant. This is to say that the tensile strength, the modulus of elasticity, and the apparent density of cellulose acetate films are sensitive to changes in spray rate and spray distance and that combinations of these can be found to yield films which are optimal with respect to these film properties. There is no evidence that any of the three substrates selected for investigation behaves differently in its influence on each of these cited film properties.

Results on water vapor permeability are shown in Table VI. The combination of low spray rate and a greater distance is again the major factor resulting in films more permeable to water vapor. Films more or less impervious to water vapor can be obtained by variations in spray rate alone or in spray distance alone. In addition, the interaction of spray rate with substrate ( $V \times S$ ) is also statistically significant at the 97.5% level. This interaction is associated with the fact that there is apparently a difference in film permeability between high and low spray rates except when aluminum is the film substrate. Examination of the individual data indicates that the greatest variability between duplicate water vapor permeability measurements is found in cases involving the aluminum substrate and the greater spray distance. Results on water vapor permeability also differ from other film properties in that film replication is not statistically significantly different.

### DISCUSSION

In these preliminary experiments, it was demonstrated that the apparatus described is useful for preparing free unsupported films for further study. Furthermore, the results obtained clearly indicate that processing conditions can have dramatic effects on the properties of sprayed films. It follows, therefore, that cast films must possess properties generally different from some sprayed films, which have been shown to differ depending on spraying conditions.

The fact that the tensile strength and Young's modulus data generated in this study are in agreement with literature values (18) lends credence to both the testing procedure and the method of film preparation. The applicability of the methodology developed in

**Table V**—Apparent Density of Cellulose Acetate Films Formed by Spraying under Various Conditions, g.-cm.<sup>-3</sup>

Spray Rate, ml./min.	Spray Distance, cm.	Substrate		
		Teflon	Aclar	Aluminum
20	5.1	1.0144	1.0514	1.0970
		0.9710	1.1024	1.0988
20	12.7	0.6818	0.7634	0.6477
		0.6388	0.6260	0.7876
40	1.5	1.0740	1.0430	1.0412
		1.0336	1.1162	1.1656
40	12.7	0.9236	1.0342	0.9483
		0.8140	0.8770	0.9983

**Table VI**—Water Vapor Permeability ( $P'$ ) of Cellulose Acetate Films Formed by Spraying under Various Conditions, mg.-cm.-min.<sup>-1</sup> × 10<sup>3</sup>

Spray Rate, ml./min.	Spray Distance, cm.	Substrate		
		Teflon	Aclar	Aluminum
20	5.1	2.96	2.58	2.83
		3.04	2.76	2.85
20	12.7	3.78	3.42	3.68
		4.04	3.38	3.22
40	5.1	2.84	2.65	2.98
		2.70	3.00	2.65
40	12.7	2.84	2.84	3.04
		2.86	2.88	3.42

this study and the validity of the conclusions are unaffected by the apparent poor reproducibility of films as measured by tensile strength, Young's modulus, and film density. It is postulated that reproducibility is a function of the levels at which each variable is studied; thus, it depends on the particular set of conditions chosen for film preparation. The substrate effect of aluminum foil on moisture vapor transmission was not altogether unexpected, since much difficulty was experienced in handling this substrate without introducing creases and other imperfections. Minor imperfections in the film are also more likely to be demonstrated in water vapor transmission measurements than in the other properties studied.

The properties of free films reported in the pharmaceutical literature include water vapor transmission, solubility, dissolution rate, mechanical properties such as tensile strength and hardness, stability to light and temperature, permeability to gases, and moisture absorption. In addition to these properties, this new apparatus will allow the cohesiveness of contiguous layers of film to be studied. The adhesion of one film to another or to any substrate can also be evaluated. In this connection, it should be mentioned that Wood and Harder (19) investigated methodology for measuring the adhesion of sprayed film coatings to tablet surfaces. A further use for this apparatus is the rapid screening of opacifiers and colorants as a function of concentration and film thickness.

These and other applications of the apparatus are being investigated. Hopefully, this technique will provide information on films complementary to that derivable from casts.

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## NOTES

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# Concurrent Water and Drug Absorption in the Rat Intestine

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**Abstract** □ The absorption of water from the rat small intestine during drug absorption experiments was studied. The data indicated that approximately 4 ml. of water was lost from the intestine during 60 min.

**Keyphrases** □ Drug absorption—concurrent loss of water, in rat intestine □ Water absorption, rat intestine—effect on drug absorption profiles □ Absorption, water—effect on drug absorption rates in the intestine

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In these studies involving drug absorption and pharmacokinetics, an unusual trend was noted which may be a consequence of water absorption. Approximately 1 hr. into the experiment, a rise in the luminal drug concentration was observed. Enterohepatic circulation was considered, but cannulation of the bile duct failed to prevent the drug concentration rise. Return from circulation of metabolized steroid was investigated and found to be extremely low. Water absorption was evaluated next.

In 1932, Heller and Smirk (1) showed that approximately 5 ml. of water/hr. was absorbed from the small intestine of an unanesthetized rat. More recently, Miller and Schedl (2), using phenol red, polyethylene glycol 4000, and inulin-<sup>14</sup>C indicators with the intestinal perfusion method, found approximately 13% (6 ml.) net water absorption in the rat intestine during 60 min. In drug absorption studies on the rat intestine, Doluisio *et al.* (3) reported  $\pm 10\%$  (1 ml.) changes in phenol red concentration and concluded that water absorption was not significant in their studies. However, Bates and Gibaldi (4), using the Doluisio intestinal preparation, found particularly significant water absorption in experiments extending beyond 30 min. Our drug absorption data indicated approximately 30–40% (4 ml.) net water absorption per hour. Phenol red and tritiated water experiments confirmed the 4-ml. water loss from

the intestine to be the major contributing factor to the rise in drug concentration in the lumen.

## EXPERIMENTAL

**Solution**—The instillation fluid was a 10% solution of ethanol and isotonic Sørensen's buffer at pH 6.24. The drug, norethindrone, was made radioactive by coprecipitation in cold acetone with tritiated norethindrone. This steroid was dissolved in the buffer solution; then phenol red was added to a concentration of 5 mg./ml. of buffered drug solution. Ten milliliters of the solution (100 mcg. norethindrone) was then instilled into the duodenum of each rat.

The second instillation fluid was isotonic Sørensen's buffer (pH 6.24) made with tritiated water; 2.5- and 5-ml. samples were instilled into the rat's duodenum.

**Animal Preparation**—Sprague-Dawley female rats, weighing 200–250 g., were fasted 18 hr. with water *ad libitum* prior to the experiment. The animals were anesthetized with sodium pentobarbital<sup>1</sup>, 50 mg./kg. An abdominal incision exposed the intestine and bile duct. While paying particular attention not to tie off major vessels of the gut, the pylorus and the jejunoileal junction were ligated. The bile duct was cannulated with polyethylene tubing<sup>2</sup>. The buffered solution was injected into the duodenum using a 23-gauge needle.

The bile samples taken were the total bile flow over 5-min. periods (~0.1 ml.). Intestinal samples of 0.1 ml. were taken along the length of the ligated section with a 27-gauge needle and disposable syringe. Blood samples were taken from the carotid artery, and plasma was obtained after centrifugation at 4000 r.p.m.

**Assay Method**—For phenol red solution data, lumen and bile samples were divided into 50- $\mu$ l. portions: 50  $\mu$ l. was placed in 10 ml. of Bray's solution (5) and counted<sup>3</sup>, and 50  $\mu$ l. was diluted with 1 *N* NaOH and the absorbance was read at 500–560 nm. on a scanning spectrophotometer<sup>4</sup>. Numerically, the intestinal lumen sample was added to the bile sample as though the phenol red had been returned to the intestine. The radioactive norethindrone was used to follow the absorption of the drug. The absorbance was used to estimate water movement using the following equation:

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<sup>1</sup> Nembutal.

<sup>2</sup> PE 50 Intramedic, Clay Adams.

<sup>3</sup> On a Nuclear Chicago Unilux II.

<sup>4</sup> Beckman model DU.