the metabolic conversion of cyheptamide to C-10 hydroxylated metabolites, a colorimetric method for these metabolites, based on the formation of a stable chromogen in 30 N H_2SO_4, was developed and applied to the analysis of urine samples of animals or humans. The method is specific and can detect as little as 50 mcg. of lactone (25 mcg. of 5-hydroxy-lactone). Attempts to estimate the levels of 10-hydroxylated metabolites of cyheptamide in the serum of laboratory animals (even at higher doses of cyheptamide) were not successful. This is not surprising in view of the low (1–15 mcg./ml.) serum levels of total cyheptamide metabolites found after administration of labeled material (3).

In the rat, the excretions of C-10 hydroxylated metabolites of cyheptamide were dose dependent, indicating their usefulness as an index of absorption. Fine-particle (micronized) cyheptamide in the same dose range gave a twofold increase in urinary C-10 hydroxylated metabolites, underlining the limited absorption of the coarse material. While the particle size of cyheptamide appears to play an important role in its absorption in the rat, it does not appear to be a critical factor with humans; after oral administration of $^{14}CONH_2$-cyheptamide (particle size not defined but most likely fairly coarse material), as much as 75% of the dose could be accounted for in the urine (3).

In rats pretreated with phenobarbital or primidone, enhanced catabolism (increased urinary C-10 hydroxylated metabolites) of cyheptamide is readily demonstrated. Cyheptamide itself does not possess this property to any significant degree.

Enhancement of drug-metabolizing enzymes by phenobarbital, *etc.*, is known to have profound effects on the circulating levels and clinical effectiveness of many other drugs (9). This fact may be of considerable importance in the clinical evaluation of cyheptamide where it is often administered to patients already receiving anticonvulsant (phenobarbital) therapy.

While the colorimetric determination of urinary C-10 hydroxylated metabolites cannot be used as an absolute measure of cyheptamide absorption, it should be of help in clinical trials to answer several questions. Are patients regularly taking the prescribed medication? Does the bioavailability of cyheptamide vary with different formulations? Is cyheptamide absorption irregular, and can patients be found who require more than the normal therapeutic dose? To answer these questions, it would obviously be preferable to determine cyheptamide (or metabolite) blood levels. At present this is not possible, although preliminary experiments indicated that the lactones do possess some fluorescence in 30 N H_2SO_4 and that this property could be the basis of a blood level method for C-10 hydroxylated metabolites of cyheptamide.

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A Method for Study of Timed-Release Films

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Abstract □ A procedure for the *in vitro* evaluation of timed-release film compositions was investigated. The procedure consisted of measuring release rates of films cast from solutions of selected polymer compositions and physically examining the films. Films with varying proportions of ethylcellulose and hydroxypropyl methylcellulose were used as the model system. The effect of film thickness, film composition, and drying process was investigated. A special film holder was used for release rate studies. A high concentration solution of FD&C Red No. 2 was used as the model solute. Release rate studies were done in a rotating-bottle apparatus. Films were characterized for their release properties by measuring the rate of transport of the dye as the release rate constant, K. Quantitative data on variation in release characteristics as a function of the experimental parameters are presented. Microscopic examination showed maldistribution of hydrophilic polymer under certain drying conditions. However, release rates did not change appreciably with variation in the drying process under the conditions of this study.

Keyphrases □ Timed-release films—*in vitro* release rates, effect of thickness, composition, drying process □ Ethylcellulose films—*in vitro* release rates, effect of thickness, composition, drying process □ Hydroxypropyl methylcellulose films—*in vitro* release rates, effect of thickness, composition, drying process □ Release rates, ethylcellulose and hydroxypropyl methylcellulose films—effect of thickness, composition, drying process □ Film compositions, timed release—effect of thickness, composition, drying process on release rates

The use of barrier films, applied by film coating, is one of the more common methods used to formulate timed-release solid dosage forms. The barrier properties of film coatings are affected by formulation and processing parameters such as film composition, thickness, and drying conditions.

The normal course of development of such products requires several experimental products to be prepared

and evaluated. Prior knowledge and experience with specific film formers may enable experienced investigators to reduce the number of needed trials, although probably not for new film-forming agents. Therefore, it seemed desirable to investigate methods of evaluation of film compositions that would permit the number of processing experiments generally required to be reduced. Evaluations of several film-forming compositions, studied as free films, were reported in the literature. These investigations included study of water vapor transmission (1, 2); other physicochemical properties such as oxygen permeability, water absorption, and mechanical, thermal, and photooxidation effects (3); and the effect of plasticizer on water vapor transmission (4).

Most reports in the literature concerning release behavior of timed-release film compositions deal with the release patterns obtained with the finished dosage forms (5, 6). Recently, Fites *et al.* (7) reported a study of the release behavior of several water-insoluble films. The method used by these authors was to mount the selected film in a permeation cell, which was held static in the release medium.

This investigation was concerned with a method of studying the release behavior of film compositions using a film holder designed to simulate a solid dosage form. The holder was designed so that it could be adapted to study of release patterns by the procedure of Souder and Ellenbogen (8), which is widely used for *in vitro* evaluation of timed-release dosage forms. The investigation was directed at applying this method to study the effect of formulations and processing parameters on the release behavior of selected film compositions by studying them as films in an *in vitro* model system. It was felt that this method would also be of help in screening new materials for similar applications.

EXPERIMENTAL

Films of ethylcellulose[1] and hydroxypropyl methylcellulose[2] were used as the model film system. The model solute used was FD&C Red No. 2[3]. The basic procedure employed was to prepare the films, examine them microscopically, measure thickness, and store the films for release rate studies. For release rate experiments, a piece of the film was cut and mounted in the film holder. A highly concentrated solution of FD&C Red No. 2 was instilled into the holder, and the rate of transport of the dye through the film was determined. The parameters investigated were film thickness, film composition, and drying process.

Model Films—Films of ethylcellulose and hydroxypropyl methylcellulose were selected as the model system representing one typical approach of employing a hydrophilic polymer dispersed in a matrix of a hydrophobic polymer. This combination was used previously in the preparation of timed-release solid dosage forms (9–11). With this system, films varying in release pattern could be easily obtained by changing the proportions of ethylcellulose and hydroxypropyl methylcellulose.

Films were prepared from polymer solutions in a solvent of equal parts of methylene chloride[4] and methanol[5]. The solution contained 7.5% w/v of the polymers and 3.25% w/v of propylene glycol[6] as the plasticizer. With this solvent system, it was possible to cast films on a glass substrate that could be easily removed intact from the substrate.

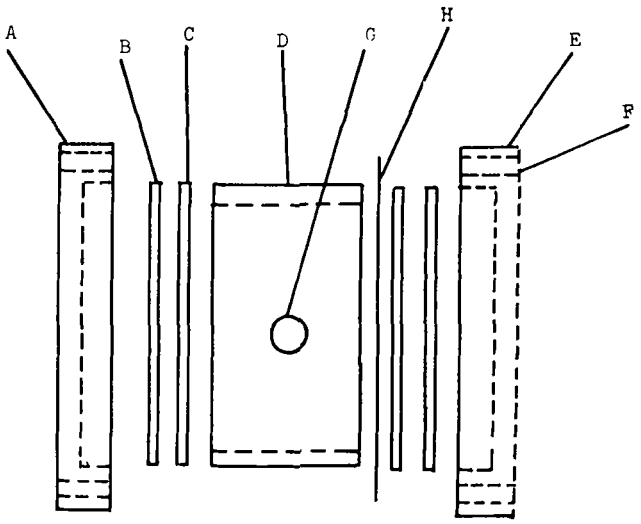

Figure 1—*Film holder used for release rate studies. Key: A, Plexiglas disk (36.0 mm. diameter, 6.0. mm. thick); B, silicone rubber gasket; C, Teflon gasket; D, Plexiglas cylinder (28.0 mm. o.d., 25.0 mm. i.d.); E, Plexiglas ring (36.0 mm. diameter, 6.0 mm. thick); F, holes for stainless steel screws (2.0 mm. diameter); G, hole for delivering dye solution into Plexiglas cylinder (3.0 mm. diameter); and H, test film.*

The method of preparation of film-former solutions was as follows: ethylcellulose was added gradually, with mixing, to the solvent containing propylene glycol. Hydroxypropyl methylcellulose was added gradually, with mixing, after all the ethylcellulose had dissolved. The solution was then allowed to stand for about 30 min. to remove entrapped air.

Preparation of Films—Films of three different thicknesses were prepared. The films were cast on a glass substrate[7]. Three different wet film thickness values were obtained by casting films at three gap openings (5, 10, and 25) of the applicator. The glass substrate used consisted of TLC plates, 20 cm. square. The technique used was essentially that of Kanig and Goodman (1).

Drying Process—Films prepared for evaluating the effect of thickness and composition were dried at room temperature for 30–45 min. In addition, a study was done to evaluate the effect of the drying process on release rates. For this phase of the study, the films were prepared as previously described and were dried using one of three drying processes: (*a*) drying at room temperature for 30–45 min., (*b*) drying in an oven at 45° for 10 min., and (*c*) drying with a heat gun[8]. In this latter process, the heat gun was fixed 37.2 cm. (14.5 in.) above the wet film on the glass plate and drying was carried out for 10 min. The air temperature at this distance was 45°. The dried films were stored in a vacuum desiccator over silica gel until used.

Measurement of Film Thickness—Film thickness was measured using a 0–2.54-cm. (0–1-in.) range micrometer. The measurement was recorded as the average of six readings taken over an area of about 16.1 cm.^{2} (2.5 in.^{2}). It was found that the thickness of the films cast at one gap setting was essentially the same for films of all compositions.

Film Holder—The film holder design was similar in principle to the diffusion cell of Garrett and Chemburkar (12). It consisted of a circular Plexiglas disk (36 mm. diameter, 6 mm. thick), a matching Plexiglas ring, a Plexiglas cylinder (10 mm. long) with a small hole for introducing the solution, two Teflon gaskets, two silicone rubber gaskets, and three stainless steel screws and nuts. The order of assembly of the holder with the film is shown in Fig. 1. When the film was mounted in the film holder, the diameter of the exposed

[1] Ethylcellulose NF; Ethocel, 100 cps.; Dow Chemical Co., Midland, Mich.
[2] Hydroxypropyl methylcellulose NF; Methocel-HG 60, 50 cps.; Dow Chemical Co., Midland, Mich.
[3] H. Kohnstamm and Co., New York, N. Y.
[4] Methylene chloride, "industrial use," Missouri Solvent and Chemical Co., St. Louis, Mo.
[5] Methyl alcohol, ACS; Matheson, Coleman & Bell Co., East Rutherford, N. J.
[6] Propylene glycol USP, Ruger Chemical Co. Inc., New York, N. Y.
[7] Using a Gardner Ultra Applicator No. 186, range 5–25 mil wet film thickness, Gardner Laboratory Inc., Bethesda, Md.
[8] Heat gun, model HG-201, Master Appliance Corp., Racine, Wis.

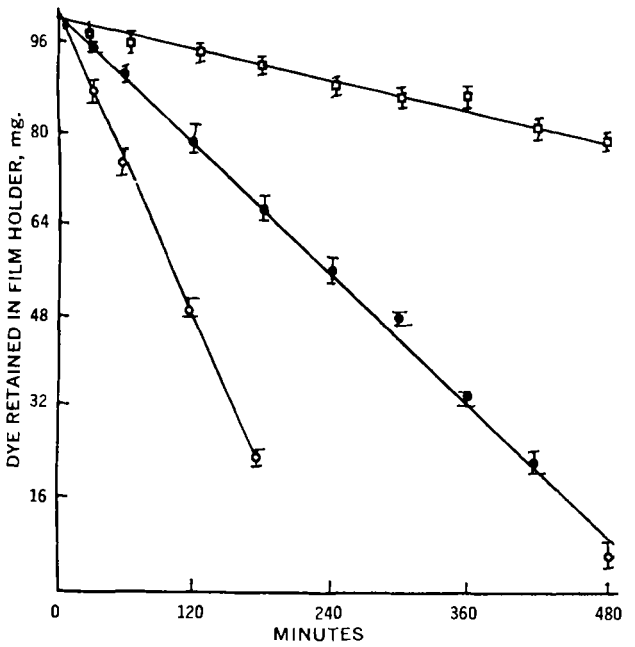

Figure 2—*Release rate of FD&C Red No. 2 through films of varying hydroxypropyl methylcellulose content and film thickness. Key: % w/w hydroxypropyl methylcellulose and thickness, mm.: ●, 10, 0.24; □, 15, 0.051; and ○, 20, 0.032.*

film was 25 mm. A silicone rubber closure was used to close the hole in the holder. The volume capacity of the film holder was about 5 ml.

Procedure for Release Rate Studies—Release rates were determined at 37 ± 1°, essentially by the method of Souder and Ellenbogen (8), using distilled water as the release medium. A piece of the test film, about 16.1 cm.² (2.5 in.²), was mounted in the film holder. Then 1.0 ml. of a solution of FD&C Red No. 2, 100 mg./ml., was introduced in the cylinder of the film holder, and a silicone rubber closure was applied to close the cylinder. The film holder was dropped into a wide-mouth, round, 240-ml. (8-oz.) polypropylene screwcap bottle containing 200.0 ml. of distilled water, previously mounted on the rotating-bottle apparatus in a water bath, and equilibrated at the test temperature. The dimensions of the bottles were as follows: 38-mm. openings, 62 mm. diameter, and 125 mm. long. Each measurement was done in triplicate. An equal number of bottles containing distilled water were also mounted in the rotating-bottle apparatus. The bottles were rotated end-over-end 25 times/min.

Samples of 10 ml. were withdrawn at various time intervals and replaced with an equal amount of distilled water. The samples were analyzed spectrophotometrically at 520-nm. wavelength, using distilled water as the blank. Release rates were determined over an 8-hr. period.

Table I—Film Release Rate Constant, *K*, as a Function of Thickness and Film Compositions

Hydroxypropyl Methylcellulose in Dry Film, %	*K*, mg./min. Film Thickness, mm. 0.024 ± 0.002	0.032 ± 0.001	0.051 ± 0.002
2	0.052	0.019	—[a]
4	0.079	0.017	—[a]
6	0.113	0.024	—[a]
8	0.129	0.114	—[a]
10	0.189	0.152	0.018
15	0.649	0.214	0.038
20	1.166	0.434	0.189
25	—[b]	0.469	0.434

[a] No release. [b] Film ruptured.

Table II—Film Release Rate Constant, *K*, as a Function of Drying for Average Film Thickness 0.032 mm. for Various Film Compositions

Hydroxypropyl Methylcellulose in Dry Film, %	*K*, mg./min. A[a]	B[b]	C[c]	Average
10	0.140	0.130	0.149	0.139
15	0.198	0.210	0.195	0.201
20	0.423	0.401	0.418	0.414
25	0.458	0.427	0.460	0.448

[a] A = drying at room temperature, 25°. [b] B = drying with a heat gun for 10 min. [c] C = drying in an oven at 45° for 10 min.

It was separately determined that the dye solution did not undergo any decomposition during the test period and that the spectrophotometric assay was not affected by pH changes in the range of 1.0–7.8.

RESULTS AND DISCUSSION

The eight compositions investigated were selected on the basis of showing complete release in 1 hr. to incomplete release in 8 hr., as determined by preliminary experiments. Plots of milligrams of dye retained in the holder against time were linear, indicating a zero-order relationship. Typical data obtained are shown in Fig. 2.

The slopes of the zero-order plots yield the release rate constant, *K*, characterizing the film. The dye concentration in the holder was considerably higher than in the release medium in most cases, indicating that transport would be expected from the inside to the outside. The values of release constants *K*, calculated by the method of least squares, are shown in Table I for films of various thickness values and compositions. Plots of release constant *versus* concentration of hydroxypropyl methylcellulose are shown in Fig. 3.

The amount of dye released from the dye solution placed in the film holder was, in many cases, in excess of 50% of the initial quantity placed within the holder. The zero-order relationship of release rates observed is not typical of transport through membranes under these conditions. It suggests that the film is probably increasing in permeability with time. This type of behavior was reported by Goldman (13) for controlled-release coatings applied to sustained-release pellets. A review of the release rate data, and the zero-order relationship of release rates, suggest a possible mechanism of release operating in films of ethylcellulose and hydroxypropyl methylcellulose. Since the film is a matrix of ethylcellulose with

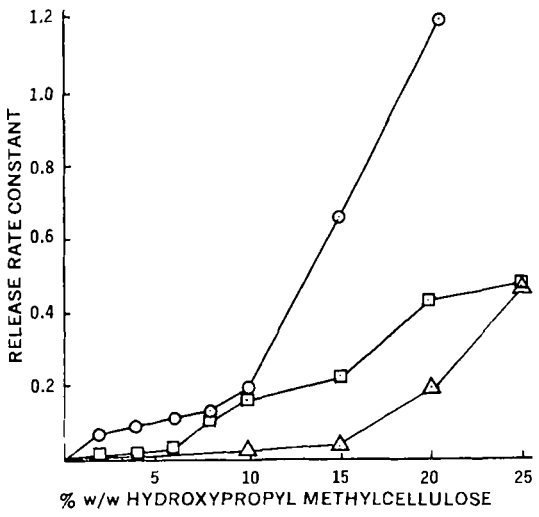

Figure 3—*Plots of release rate constant*, K, versus % *w/w hydroxypropyl methylcellulose in film. Key: thickness, mm.: ○, 0.024; ⊡, 0.032; and △, 0.051.*

hydroxypropyl methylcellulose dispersed in it, solute transport would be expected to occur through channels formed due to the dispersed hydroxypropyl methylcellulose.

It is suggested that two factors might be operating in these films, resulting in the formation of two types of channels or pores to permit transport. One would be hydration and dissolution of the hydroxypropyl methylcellulose to leave pores in the film. The other would be for the hydrated hydroxypropyl methylcellulose to be retained in the film as a barrier. This would require diffusion of the solute through the hydrated film for transport to occur, thus considerably reducing the transport rate. While the formation of the hydrated film would be the first step in formation of a transport channel, the retention time of the hydrated hydroxypropyl methylcellulose as a barrier film would be a function of the thickness of the film and the concentration of hydroxypropyl methylcellulose in the film. In thicker films, longer retention times might be expected. Or in the case where there is less hydroxypropyl methylcellulose in the film, a comparatively longer retention time might also be expected due to the support provided by the hydrophobic ethylcellulose matrix. The observed rate of transport would then be a function of the balance of the two operating factors. With time, retained hydrated hydroxypropyl methylcellulose would tend to dissolve to permit an increase in the transport rate. Such a mechanism would be consistent with the suggestion of increased permeability with time.

Another factor to be considered would be that only the dispersed hydroxypropyl methylcellulose particles exposed to the action of the release medium would be expected to lead to formation of transport channels. The exact effect of this factor is difficult to evaluate, except that it would be more significant in films of low hydroxypropyl methylcellulose concentration.

Composition and Thickness—As might be expected, the release rate is increased as the hydroxypropyl methylcellulose level is increased and also as film thickness is reduced. The only exception to this pattern is the value of the release rate constant for the 0.032-mm. film containing 4% hydroxypropyl methylcellulose. However, the release rate constant values for the 0.032-mm. films containing up to 6% hydroxypropyl methylcellulose are quite low. In view of the very low degree of release obtained with these films of low hydroxypropyl methylcellulose content, the deviation is felt not to be significant.

In the case of the thin film of this study (Fig. 3), a sharp increase in release rate is seen when the hydroxypropyl methylcellulose level is increased to more than 10%. At the hydroxypropyl methylcellulose level of 25%, this film was found to rupture, causing total release of dye in a very short time. This behavior suggests a large increase in the formation of pores or considerably reduced retention of hydrated hydroxypropyl methylcellulose. The thicker films, on the other hand, show gradual increase in release rates within the range of the hydroxypropyl methylcellulose levels used in this study.

It is more interesting to note thickness–composition interaction. Theoretically, these two parameters might be manipulated to achieve the desired release pattern. The data indicated that the rate of change or release pattern as a function of composition (or hydroxypropyl methylcellulose level) is more pronounced with thin films. Therefore, it would seem likely that an appropriate balance of a thicker film with more hydroxypropyl methylcellulose might result in a film coating with less variation due to batch-to-batch processing differences in coating. Use of less permeable but thinner films would, on the other hand, require greater process control.

Drying Conditions—Early in the study, it was observed, with several systems of an insoluble matrix with a soluble agent dispersed in it, that wide variation in the distribution of the soluble agent in the matrix could occur. The resulting films were found to have the soluble agent either uniformly dispersed or distributed unevenly in clusters. This finding suggested the possibility of variation in the nature and distribution of transport channels formed. The occurrence of maldistribution was noted by microscopic examination and, in many cases, was readily apparent on visual inspection. In some films with maldistribution of the water-soluble agent, larger pinholes were observed on examination of the film after release rate measurement. Differences in distribution were observed with variation in drying conditions, with films dried slowly showing more uniform distribution.

As a result of these observations, the effect of three drying processes was investigated. This phase of the study was carried out with films of three thickness values and four film compositions. The release rates obtained for films dried under the three conditions were found to be essentially similar. Values for the release rate constant, K, for 0.032-mm. films are shown in Table II. Similar results were obtained for films of different thickness values (0.024 and 0.051 mm.) and the same compositions. Thus, although the film appearance did change, this apparently did not affect release rates within the range of drying conditions of this study.

Solvent Effects—The observed differences in distribution would appear to be due to differences in the rate of precipitation of the two solutes as drying proceeds. Since organic solvents are usually employed in film coating, it seems likely that the precipitation of the hydrophilic component of the film would be affected to a greater extent. In general, a shift to a more polar solvent might result in more rapid precipitation of the hydrophilic agent. Shifts in solvent polarity would also influence such factors as solvation of polymers and viscosity of resulting solution. For example, it was observed with films of ethylcellulose and polyethylene glycol 6000, during preliminary experiments, that the use of a more polar solvent caused the film to adhere to the substrate so that it could not be removed intact from the substrate. Similarly, for the composition investigated in this study, it was found that rendering the solvent more polar by increasing the proportion of methanol resulted in a considerable increase in the viscosity of the polymer solution. In this study, the basic criteria for selection of solvent were the solubility of the polymers in the solvent system and the ability to remove the film intact from the glass substrate.

Solvent effects on distribution of the hydrophilic agent were not investigated in this study. However, the observations of this investigation suggest a mechanism to explain the basis of solvent selection for such compositions, which was done in the past by experience and intuition.

SUMMARY AND CONCLUSIONS

A method was developed for evaluation of transport characteristics of timed-release film compositions investigated in the form of free films. Films of ethylcellulose and hydroxypropyl methylcellulose were used as the model film system. The model solute used was FD&C Red No. 2. Parameters investigated were film composition, film thickness, and drying process.

Transport of the dye through the films was found to follow a zero-order relationship, suggesting that these films may be increasing in permeability with time during the test procedure. Quantitative data were obtained on variation in release characteristics as a function of the experimental parameters. It was suggested that this type of data can be useful in development studies of timed-release products in providing direction as to desired formulation and processing conditions, thus reducing the number of processing experiments needed.

Changes in drying conditions caused variation in the physical appearance of the film but were found not to affect release rates under the conditions of this study. Some observations as to the basis of solvent selection in film coating were presented.

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Effects of Structure on Permeability of Substituted Anilines from Aqueous Solutions through Polyethylene

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Abstract □ Permeation studies were undertaken with aqueous solutions of aniline and various substituted anilines to ascertain the effect of chemical structure on the permeation of these agents through polyethylene. The permeation studies permitted the estimation of steady-state rates of permeation and calculation of the permeability constants. Permeability constants varied from a low of 1.61×10^{-9} cm.²/sec. for 2-anilinoethanol to a high of 3.58×10^{-6} cm.²/sec. for *N,N*-dimethylaniline. When the permeability constants of the compounds were compared with their hexane–water partition coefficients, a very high correlation resulted, leading to an empirical expression which may be useful in predicting the permeability constants of similar types of compounds having partition coefficients in the range of the values reported.

Keyphrases □ Permeability constants, substituted anilines—from aqueous solution through polyethylene, effects of different aniline structures, correlated with hexane–water partition coefficients □ Anilines, substituted—effects of structure on permeability, from aqueous solution through polyethylene, correlated with hexane–water partition coefficients □ Plastics—effect of aniline structure on its permeability, hexane–water partition coefficient correlated with structure of aniline □ Polyethylene—effect of structure of substituted anilines on permeability, correlated with hexane–water partition coefficient

One of the most used plastics for containers and packaging systems for all types of drug, cosmetic, and household products is polyethylene. The excellent moisture-vapor barrier properties of polyethylene have encouraged the use of this specific plastic by the pharmaceutical and cosmetic industries as well as by the hospital pharmacist for the packaging of a host of aqueous products. Salame and Pinsky (1) contributed a great deal of information concerning the permeation of a large number of organic liquids stored in polyethylene containers. They developed a method (permachor method) for predicting the permeation of an organic solvent from the structure of the compound.

Much less information on the permeability of solutes in aqueous systems stored in polyethylene containers is available. Polack *et al.* (2) formulated a method for predicting the permeation of selected solutes in aqueous systems when the products (in polyethylene containers) were autoclaved. Gonzales *et al.* (3) studied the permeation of aqueous solutions of selected compounds through polyethylene and reported that structure influences the permeability constant. Other investigators (4–7) studied the permeation of solute molecules through different types of polymeric materials.

The loss of an ingredient from a drug product can lead to a decrease in the potency of the product or render the product pharmaceutically unacceptable. A definite need, therefore, exists to generate qualitative and quantitative permeation data for groups of solutes to guide the pharmaceutical scientist and packaging engineer in deciding which of a number of polymeric materials might be the most useful for a specific packaging application.

This report concerns a permeation study of aqueous solutions of aniline and various substituted anilines using polyethylene film as the specific plastic. The primary objectives of this study were to discern what effects the structure of solutes have on permeation and to see to what extent permeability through polymeric films can be correlated with partition coefficients obtained in a convenient solvent system such as hexane–water. In the ideal case the mechanics of the diffusional process within a polymeric barrier are unaffected by the nature of the adjacent phases and, therefore, basic data obtained from a liquid–membrane–liquid model system may be applicable to the packaging system in which one surface is in contact with air.

EXPERIMENTAL

Materials—The polyethylene film[1] had a 0.0127-cm. thickness and a 0.924 density. All chemicals employed in this study were analytical reagent grade or the highest available purity. Table I lists the compounds studied along with their structures and molecular weights.

Analytical Methods—The absorbance of aqueous solutions was determined with a spectrophotometer[2] at the wavelength of maximum absorption for each compound. The concentration of each solution was calculated from Beer's law plots prepared for each compound under study.

Conditioning of Film—The polyethylene film was cut into 10 × 10-cm. squares and soaked in 95% ethanol for 24 hr. The film was rinsed with distilled water and further soaked in 50% ethanol for

[1] Obtained from Gulf Oil Corp., Chemicals Department, Orange, Texas.

[2] Hitachi-Perkin-Elmer model 139.