

Fig. 3.—Solubility of benzoic acid and esters of *p*-hydroxybenzoic acid at 25°C. in a series of *n*-alkanols.

vents for a large number of drugs) and a plot of the data shown in Figs. 1 and 2 may provide values of satisfactory accuracy. It will be rare that the δ value of a drug can be calculated from the Hildebrand equation since energies of vaporization and molar volumes are not ordinarily available.

When mole fraction solubility was plotted against solvent δ values, a peak was observed in the curves. However, a linear relationship existed between the solubility (in grams of solute per gram of saturated solution) and the number of carbon atoms existing in the solvent. This seems to follow a relationship analogous to Traube's rule (15, 16) as observed from Fig. 3. Besides being linear, the lines for the various esters of *p*-hydroxybenzoic acid appear to be nearly parallel to one another, which leads one to believe that the forces involved in dissolution of the various esters in a series of *n*-alkanols are more or less constant from one solute to the next.

CONCLUSION

The Hildebrand equation appears most applicable to hydrogen-bonding solvents whose solubility parameters are quite similar to those of the solutes; in such cases, it will give a fair estimate of the drug solubility even though the system is a polar one. Optimum solubility may be obtained by using a mixture of solvents having a composite δ value equal to that of the solute, but when using a mixed solvent system, the observed solubility will, in general, be somewhat less than that predicted by the Hildebrand equation.

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Factors Influencing the Properties of Films Used for Tablet Coating I

Effects of Plasticizers on the Water Vapor Transmission of Cellulose Acetate Phthalate Films

By LEON LACHMAN and ARGE DRUBULIS

The water vapor transmission of thin plasticized cellulose acetate phthalate films was studied at 90, 76, and 52 per cent relative humidities. The effect of the plasticizers, triacetin, diacetin, diethyl phthalate, dimethyl phthalate, Citroflex-2, Citroflex-A2, and dibutyl tartrate on this property was determined. In general, a decrease followed by an increase in water vapor transmission was observed with increasing plasticizer concentration. The concentration at which the water vapor transmission is at a minimum appears to be the same for all the plasticizers investigated.

THE USE OF polymeric substances, such as cellulose acetate phthalate, for coating tablets and particles has been widely accepted in recent years. The reports that have appeared in the pharmaceutical literature during this time

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have dealt primarily with the development of polymeric substances as film formers (1-6), the formulation of film forming agents for use in tablet and particle coating (7-12), the development of test procedures for film coated tablets (13-15), and the improvement of processes for the application of these agents onto pharmaceutical dosage forms (16-20).

Although work in the above areas has been

TABLE I.—APPARENT WATER VAPOR TRANSMISSION (*WVT*) VALUES (Gm. 24 HR.⁻¹M⁻²) AT 90, 76, AND 52% RELATIVE HUMIDITIES FOR PLASTICIZED CELLULOSE ACETATE FILMS^a

Plasticizer	R.H., ^b %	Plasticizer, %					
		1.0	2.0	3.0	4.5	6.0	9.0
Triacetin	90	62.4	58.6	52.7	97.9	105.6	261.0
	76	44.7	35.5	44.2	67.2	98.9	175.6
	52	45.3	47.0	25.9	44.2	60.5	86.4
Diacetin	90	125.8	77.7	61.9	129.6	162.1	254.1
	76	74.3	50.9	56.6	65.3	94.8	138.2
	52	54.7	42.6	41.3	43.2	45.1	179.5
Diethyl phthalate	90	83.5	94.0	86.4	83.5	118.0	261.0
	76	52.4	51.8	38.8	67.2	95.9	166.9
	52	40.3	25.9	30.7	21.1	79.6	162.1
Citroflex-2	90	75.8	72.9	62.3	87.4	126.8	217.7
	76	48.0	63.3	39.3	62.4	114.1	199.5
	52	36.5	31.3	34.6	50.8	75.8	151.6
Citroflex-A2	90	89.3	77.7	61.4	83.5	126.5	195.9
	76	74.9	66.2	53.7	51.2	121.4	149.8
	52	44.3	36.5	34.0	45.2	88.9	133.2
Dimethyl phthalate	90	94.0	86.4	69.1	75.8	94.0	193.9
	76	44.2	40.3	43.2	60.4	98.8	157.4
	52	42.3	38.4	33.6	54.7	75.8	140.1
Dibutyl tartrate	90	103.7	70.0	64.3	87.4	108.4	162.1
	76	58.6	56.6	54.3	78.7	103.6	165.0
	52	53.7	44.2	52.6	73.9	76.8	111.2

^a *WVT* values for unplasticized films: 90% R.H. = 142.0; 76% R.H. = 85.7; 52% R.H. = 61.9. ^b Relative humidity.

rather extensive, little has been reported on the evaluation of the critical physical-chemical parameters of these substances and how these parameters may be influenced by the formulations used. Consequently, it has been the practice to develop formulations empirically without any understanding of what these parameters are or how they may be influenced by the other components in the film forming systems. Furthermore, even less is known concerning the effects that changes in these parameters have on the finished coated pharmaceutical product.

Water vapor transmission represents one physical property of considerable significance for film coatings. There is no doubt that the permeation of water vapor through a coating must be considered in the over-all evaluation of the stability of the active drug in a medicinal product. Components added to film forming agents as a part of a formulation may easily affect this property and ultimately alter the stability of the preparation.

The present investigation was designed to study the influence of plasticizers on the water vapor transmission of free cellulose acetate phthalate films. Data have been obtained at three relative humidity conditions for several plasticizers, including phthalates, citrates, glycerol acetates, and a tartrate.

EXPERIMENTAL

Preparation of Cellulose Acetate Phthalate Solutions.—Solutions containing 10% cellulose acetate phthalate and varying amounts of the plasticizers, triacetin, diacetin, diethyl phthalate, dimethyl

phthalate, Citroflex-2,¹ Citroflex-A2,¹ and dibutyl tartrate were prepared on a per cent weight basis in a solvent system containing an equal quantity of acetone and anhydrous ethanol. The solutions were prepared by dissolving the cellulose acetate phthalate in a mixture of the acetone and the plasticizer and adding the alcohol when solution was complete. The finished solutions were passed through several layers of gauze.

Preparation of Cast Films.—The solutions were cast as sheets of 25 mil wet thickness onto highly polished glass plates using a Gardner film casting knife² equipped with a micrometer blade adjustment. The sheets were dried at ambient temperature and stripped from the plates at 18 hours. The resulting films were approximately 2 mils thick.

Determination of Water Vapor Transmission (*WVT*).—The water vapor transmission (*WVT*) was determined by a modification of ASTM method E-96-53T, "Measuring Water Vapor Transmission of Materials in Sheet Form." Ten grams of Drierite, as the desiccant, were placed into a Gardner-Park permeability cup.² A disk of the film under investigation was cut from each sheet and clamped tightly between two polyethylene gaskets under a flat retaining ring. The retaining ring was held in place by a ring cover screwed down onto the cup, resulting in a gas-tight seal. The exposed area of the sample was 25 cm.² The charged cup was weighed and placed into a desiccator containing a saturated solution of either zinc sulfate heptahydrate, sodium acetate trihydrate, or sodium hydrogen sulfate monohydrate to provide the relative humidity conditions of 90, 76, and 52%, respectively. Weighings of the sample cup were made at definite intervals throughout the day.

A preliminary study was undertaken to determine the effect of the quantity of desiccant used, the position of the cup, and the nature of the film surface exposed. Samples were run in which (a)

¹ Marketed by Charles Pfizer & Co., Inc.

² Gardner Laboratory, Inc.

both 10 and 20 Gm. of Drierite were used, (b) the cups were placed in the desiccator in inverted and upright positions, and (c) both surfaces of the film were exposed; *i.e.*, the upper "orange-peeled" and the smooth underside. No appreciable difference in the water vapor transmission values was observed for these conditions. In view of these results, either surface of the film was exposed, 10 Gm. of desiccant was used, and the cups were maintained in an upright position throughout the study.

To determine whether water vapor was sorbed by the film during the water vapor transmission determination, several samples of film disks were weighed before and after the determination. No increase in weight was observed for any of the samples tested. Thus, it was assumed that the weight increase obtained for the sample cup during a determination was due to the water vapor which permeated the film.

RESULTS AND DISCUSSION

The water vapor transmission values for cellulose acetate phthalate films plasticized with the varying concentrations of the plasticizers studied are presented in Table I. The values were obtained from the slopes of the plots of weight increase of the sample cup *versus* time, using

$$WVT = \frac{[g] [24]}{[t] [a]}$$

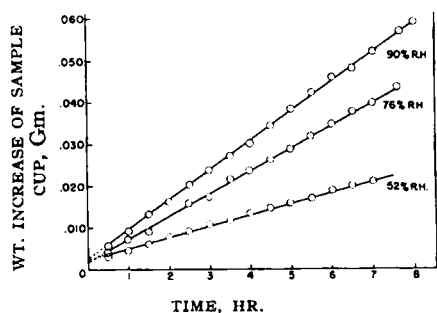


Fig. 1.—Water vapor permeation as a function of time for the diethyl phthalate plasticized films. Cellulose acetate phthalate: 1% diethyl phthalate.

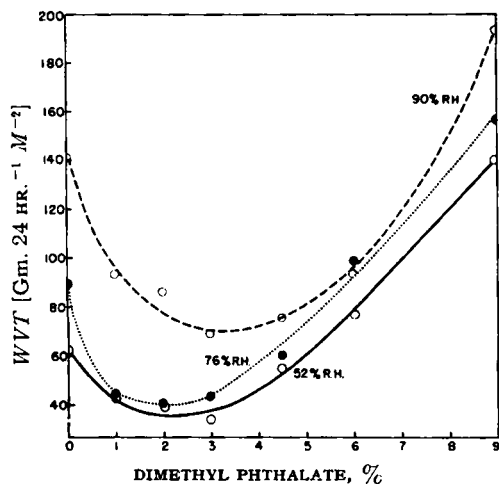


Fig. 2.—Effect of plasticizer concentration on WVT for the dimethyl phthalate plasticized films.

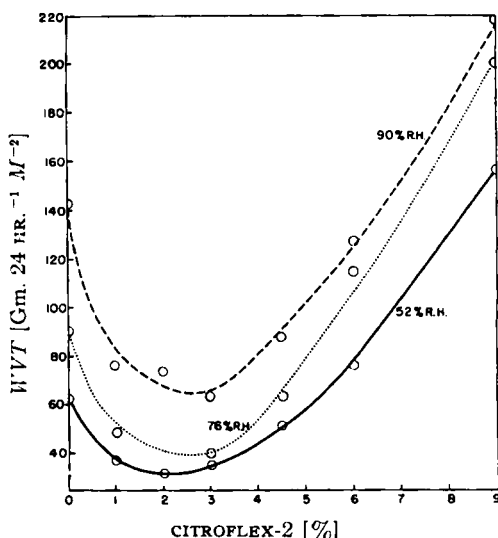


Fig. 3.—Effect of plasticizer concentration on WVT for the Citroflex-2 plasticized films.

where WVT = "apparent" water vapor transmission in grams 24 hours⁻¹M⁻², g = weight gain in grams, t = time in hours during which the gain was observed, and a = exposed area of the specimen in square meters (M.²).

Typical plots from which these values were calculated for films plasticized with 1% diethyl phthalate are shown in Fig. 1.

The WVT values obtained in this study should by no means be considered as absolute, but rather as relative for the experimental conditions. This limitation is necessary because the relative humidity conditions obtained with saturated salt solutions contained in desiccators change as the samples are removed and actually are not at the theoretical values for the entire sample time.

As a check, samples were tested under conditions in which the salt solutions were continuously stirred to allow the humidities within the desiccators to reach equilibrium quickly once the samples were replaced after weighing. The length of time between weighings was also increased severalfold. Under these conditions, the samples were at relative humidity conditions closer to the theoretical values for a longer period of time. The results obtained for these samples were of a different magnitude, but of the same relative order as the data presented above. In view of these results, it would appear that the findings of this investigation, in general, are indicative of what occurs in these plasticized films.

Table I shows that the permeation of water vapor for all the systems studied is similarly dependent on the concentration of the plasticizer in the film. Figures 2 and 3, respectively, are plots of WVT *versus* per cent plasticizer for the dimethyl phthalate and the Citroflex-2 plasticized systems. The dependency appears to be one that shows a decrease in permeation for increasing plasticizer concentration up to about 3% and an increase in permeation with increasing plasticizer concentration beyond this point.

In general, this dependency, exhibiting a minimum WVT value, is similar to that obtained by Kirk-

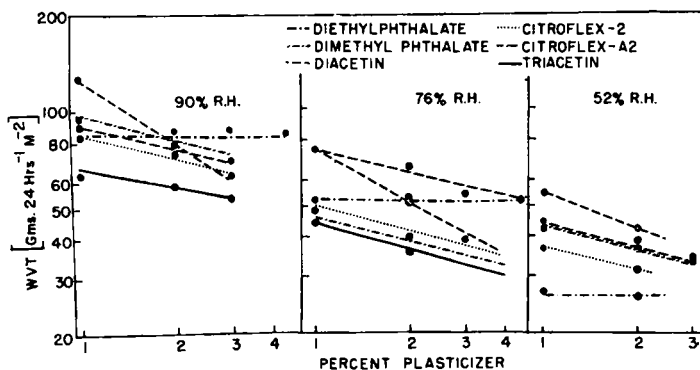


Fig. 4.—Effect of plasticizer concentration on WVT for lower concentrations.

patrick (21) for cellulose acetate films plasticized with certain sulfonamides and phthalates. It may possibly be explained if the plasticizer is considered as an integral part of the film distributed within the interstices of the polymer. If the permeation of water vapor through the film is primarily by passage through the interstices, then it would be expected that as these spaces become filled with plasticizer the rate of water vapor permeation would decrease.

The rate at which the water vapor permeation decreases for plasticizer concentrations between zero and 3% can readily be seen when the logarithm of WVT is plotted against the logarithm of per cent plasticizer, as shown in Fig. 4. It is evident from the slopes of these plots that the change in permeation is greatest for diacetin, while essentially no change in permeation occurs with increasing concentrations of plasticizer for diethyl phthalate. For the other plasticizers studied, the change in permeation with plasticizer concentration is approximately the same, as indicated by the parallel lines in Fig. 4.

It would seem that the change of WVT with respect to plasticizer concentration at these lower concentrations is specifically dependent on some physical property of the plasticizers, and that this property is approximately the same for dimethyl phthalate, triacetin, Citroflex-2, Citroflex-A2, and dibutyl tartrate, but different for diacetin and diethyl phthalate. Of the properties for these plasticizers listed in Table II, the water solubility correlates with the data presented.

Thus, diacetin with an infinite water solubility exhibits the greatest influence on the rate at which WVT changes with respect to plasticizer concentration. The water insoluble diethyl phthalate, on the other hand, apparently does not exhibit any influence on the rate at which WVT changes with plasticizer

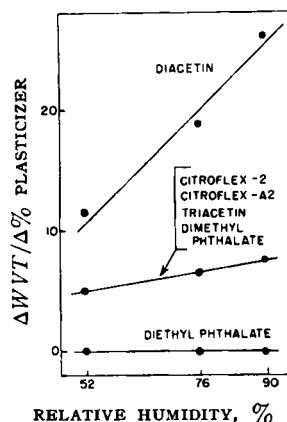


Fig. 5.—Relative humidity dependency of the rate of change of WVT with respect to plasticizer concentration for lower concentrations.

concentration. This is indicated by the resulting lines of zero slope. The effects of triacetin, dimethyl phthalate, Citroflex-2, and Citroflex-A2 appear to be intermediate. The tenfold difference in water solubility between Citroflex-A2 and triacetin, for example, apparently is not sufficient to influence the permeation; thus the rate at which WVT changes is the same for these plasticizers.

The relationships presented above appear to hold for these systems at the three relative humidity conditions studied. Furthermore, a plot of the change of WVT with respect to per cent plasticizer ($\Delta WVT/\Delta\%$ plasticizer) versus per cent relative humidity shown in Fig. 5 indicates that in all probability the influence of the plasticizer on the water vapor permeation or transmission is linearly dependent on the relative humidity.

As indicated above, the WVT values for all systems studied go through a minimum as the concentration of plasticizer is increased from zero to 9%. Apparently, any plasticizer added beyond the concentration present at the point of minimum WVT can no longer be held as an integral part of the film and thus may be "squeezed out" and may separate as a thin layer on the surface of the film. It is at this point that an increase in water vapor permeation with increasing plasticizer concentration is observed. It appears that, although the absolute permeation may be dependent on the specific thin layer of plasticizer present on the surface of the film, the over-all change in WVT with respect to

TABLE II.—PHYSICAL PROPERTIES

Plasticizer	Mol. wt.	B.p., °C.	Soly. in H ₂ O, Gm./100 ml.
Triacetin	218.20	259	7.17
Diacetin	176.17	176	∞
Diethyl phthalate	222.2	296.1	insol.
Citroflex-2	276	127	6.5
Citroflex-A2	318	132	0.72
Dimethyl phthalate	194.18	282	0.5
Dibutyl tartrate	262.30	203	0.49

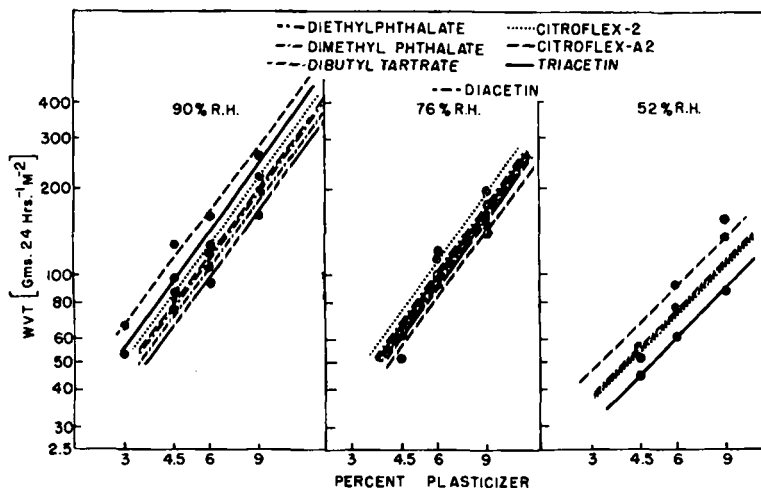


Fig. 6.—Effect of plasticizer concentration on WVT for higher concentrations.

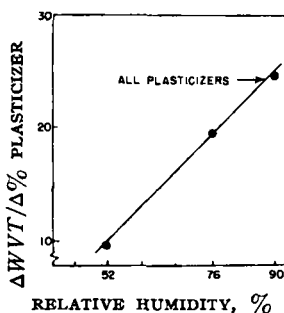


Fig. 7.—Relative humidity dependency of the rate of change of WVT with respect to plasticizer concentration for higher concentrations.

plasticizer concentration is not dependent on the specific plasticizer used. An explanation that can be offered is that once the plasticizer has filled the interstices of the polymer, further addition of plasticizer has only a dilution effect on the polymer. As the polymer is diluted, the permeation of water vapor would be expected to increase. Furthermore, since the plasticizers studied are of reasonably similar molecular mobility, they would tend to affect the permeation in a similar manner. This can be seen from the logarithmic plots in Fig. 6, where the slopes of the graphs of WVT versus per cent plasticizer for higher concentrations of plasticizer are the same for all the plasticizers studied.

As in the case of the lower plasticizer concentrations, when the change in WVT with respect to per cent plasticizer is plotted against the per cent relative humidity, a linear relationship results. The dependency can be seen in Fig. 7. Again, this shows that the influence of the plasticizer on the water vapor transmission is dependent on the relative humidity.

SUMMARY

The effects of several plasticizers on the water vapor transmission of cellulose acetate phthalate films have been presented. The data tend to indicate that for all the plasticizers studied (a) a decrease in water vapor permeation occurs with increasing plasticizer concentration up to about 3%, followed by an increase in permeation with further increase in plasticizer concentration, (b) the rate at which WVT changes with respect to plasticizer concentration is dependent on the specific plasticizer used for the lower concentrations, but not for the higher concentrations, and (c) that this rate is linearly dependent on relative humidity for both low and high plasticizer concentrations.

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