Effect of Plasticizers on Some Physical Properties of Cellulose Acetate Phthalate Films

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Abstract □ The effects of several plasticizers on the following properties of cellulose acetate phthalate films were studied: water vapor transmission rate, moisture absorption, enteric coating performance (minimum coating required on tablets to prevent gastrodisintegration), tablet-disintegration time, and water permeation. The addition of plasticizers generally lowered the water vapor transmission rate, moisture absorption, and water permeation but had little effect on tablet-disintegration time. However, addition of most plasticizers resulted in poorer enteric coating performance. Significant differences among the plasticizers were observed, and no one plasticizer was found to be superior overall.

Keyphrases □ Cellulose acetate phthalate films, physical properties—effect of plasticizers □ Plasticizers—effect on cellulose acetate phthalate films, physical properties □ Films, cellulose acetate phthalate—effect of plasticizers on physical properties

A polymeric system such as one containing cellulose acetate phthalate usually contains a plasticizer, a component that would be expected to alter one or more physical properties of the polymer. Since cellulose acetate phthalate was first suggested as an enteric coating (1), the material has been widely used in the pharmaceutical industry. However, only a limited amount of work has been reported concerning the effect of plasticizers on cellulose acetate phthalate. Malm *et al.* (2) studied the effect of various plasticizers on ion (sodium chloride) and dilute acid (hydrochloric) permeation and concluded that diethyl phthalate was a preferred plasticizer. Water vapor permeation data were obtained on unplasticized cellulose acetate phthalate (3) and on cellulose acetate phthalate plasticized with polyethylene glycol (4) or with several water-insoluble plasticizers at low levels (5). In the two latter studies, the authors found a decrease followed by an increase in water vapor transmission rate as the plasticizer level was increased.

This study was designed to: (*a*) obtain information on the effect of various plasticizers on some properties of free films of cellulose acetate phthalate, and (*b*) examine the effect of these plasticizers on cellulose acetate phthalate when coated on tablets. Specifically, the following properties were studied: (*a*) water vapor transmission rates of thin films, (*b*) moisture absorption of thin films, (*c*) enteric coating performance, defined as the minimum amount of coating required to protect tablets from disintegrating in gastric fluid, (*d*) disintegration time, *in vitro*, of coated tablets, and (*e*) liquid water permeation of coated tablets.

Seven plasticizers were selected for study: diethyl phthalate, triacetin, fully acetylated monoglycerides,[1] butyl phthalyl butyl glycolate,[2] tributyl citrate, partially acetylated monoglycerides,[3] and castor oil.

[1] Myvacet, distilled acetylated monoglycerides type 9-40, Eastman Chemical Products, Inc., Kingsport, Tenn.
[2] Santicizer B-16, Monsanto Co., St. Louis, Mo.
[3] Myvacet, distilled acetylated monoglycerides type 5-07, Eastman Chemical Products, Inc., Kingsport, Tenn.

Table I—Water Vapor Transmission Rate with Different Plasticizers

Plasticizer[a]	Water Vapor Transmission Rate[b]
None	0.520
Diethyl phthalate, %	
10	0.359
20	0.315
30	0.307
Triacetin, %	
10	0.311
20	0.327
30	0.327
Castor oil, %	
10	0.524
20	0.489
30	0.504
Fully acetylated monoglycerides, %	
10	0.504
20	0.382
30	0.425
Butyl phthalyl butyl glycolate, %	
10	0.288
20	0.307
30	0.276
Tributyl citrate, %	
10	0.386
20	0.351
30	0.386

[a] Plasticizer level as percent of cellulose acetate phthalate. [b] g. × cm./m.²/24 hr.

EXPERIMENTAL

Preparation of Cellulose Acetate Phthalate Solutions—Solutions were prepared in acetone to contain 15% w/w total solids. The appropriate amounts of cellulose acetate phthalate and plasticizers were dissolved in a portion of the acetone. The remainder of the solvent was added to complete the preparation.

Preparation of Thin Films—The solutions were poured onto glass plates, and films were drawn with a doctor blade adjusted so that dried films of about 0.0033-cm. thickness were obtained. After about 1 hr., the films were stripped from the glass and dried for 24 hr. under ambient conditions before use.

Water Vapor Transmission Rates—Two-ounce flint-glass bottles were uniformly filled with a commercial desiccant[4] to within 5 mm. of the top. Disks punched from the cured films (3.2 cm.) were sealed to the bottle lips with silicone grease. Caps, from which 2.5-cm. disks had been removed, were then placed on the bottles.

The bottles were placed in a desiccator containing water saturated with ammonium nitrate at 25° (63% R.H.). The bottles were periodically weighed, and plots were made of weight increase *versus* time. Water vapor transmission rates were calculated from the formula:

$$\text{rate} = \frac{WL}{S} \qquad \text{(Eq. 1)}$$

where W = weight increase/24 hr., g./24 hr., from the straight-line portion of weight gain *versus* time; L = film thickness, centimeters, measured with an Ames dial comparator after W was determined; and S = area of the exposed film in square meters.

Moisture Absorption—Strips, 2.5 × 7.6 cm., were cut from the cured film and dried under vacuum in the presence of the commercial

[4] Drierite, W. A. Hammond Drierite Co., Xenia, Ohio.

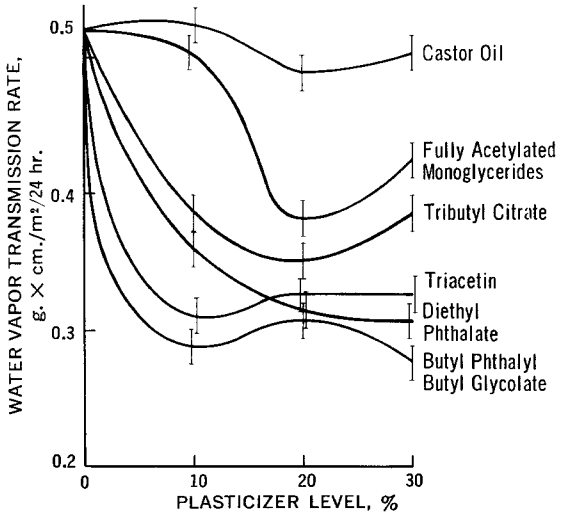

Figure 1—*Water vapor transmission rates of plasticized cellulose acetate phthalate. (Vertical lines represent estimated standard deviation of the measurements.)*

desiccant to constant weight. The strips were placed under 25°/63% R.H. conditions until a constant weight was again obtained. The moisture absorption was calculated as follows:

$$\% \text{ absorption} = \frac{\text{conditioned weight} - \text{dry weight}}{\text{dry weight}} \times 100 \quad \text{(Eq. 2)}$$

Tablet Coating—Fifteen pounds of tablets [dicalcium phosphate, 300 mg., 0.87 cm. ($^{11}/_{32}$ in.) deep concave punches; lactose, 230 mg., 0.87 cm. ($^{11}/_{32}$ in.) deep concave punches] were coated per run in a 40.64-cm. (16-in.) spherical coating pan. Coating solutions were prepared using 10% w/w cellulose acetate phthalate plus plasticizer in acetone. The tablets were spray coated with the solutions, using an airless unit[5] with a 1-sec. spray/10-sec. dry sequence. Samples of the tablets were removed at 5-min. intervals for testing.

Tablet-Disintegration Time—Tests were performed according to the USP XVII Tablet-Disintegration Test, except that the simulated intestinal fluid contained no pancreatin.

Percent Coating Weight—Ten coated tablets were placed in acetone to remove the coatings. The tablets were dried for 16 hr. at 37°, and the average core weight was determined. The coated weights of the tablets were obtained as described under *Liquid Water Permeation*. The percent coating weights were calculated as follows:

$$\% \text{ weight} = \frac{\text{coated weight} - \text{core weight}}{\text{core weight}} \times 100 \quad \text{(Eq. 3)}$$

Liquid Water Permeation—Ten coated tablets (lactose) were dried for 16 hr. at 37°. The tablets were weighed, immersed in distilled water, and reweighed after 1 and 4 hr. Since tablets of identical size were used, water permeation was proportional to percent weight increase, which was calculated as follows:

$$\% \text{ weight increase} = \frac{\text{wet weight} - \text{dry weight}}{\text{dry weight}} \times 100 \quad \text{(Eq. 4)}$$

RESULTS AND DISCUSSION

Water Vapor Transmission Rate—The results summarized in Table I show that the selection of plasticizer was more important than the level. Castor oil, for example, had essentially no effect on the water vapor transmission rate, but the use of butyl phthalyl butyl glycolate resulted in a rate less than 60% that of unplasticized cellulose acetate phthalate. Conversely, the level of plasticizer (10–30%) had considerably less effect on the rate. These data are illustrated in Fig. 1. Minimum water vapor transmission rates were found for five of the six plasticizers. The minima for three of these

[5] Versa-Spray, Nordson Corp.

Table II—Moisture Absorption with Different Plasticizers

Plasticizer	Moisture Absorption, %
None	2.8
Diethyl phthalate, %	
10	2.1
20	1.6
30	0.3
Triacetin, %	
10	1.2
20	−1.6
30	−6.8
Castor oil, %	
10	1.1
20	1.2
30	1.2
Fully acetylated monoglycerides, %	
20	1.7
30	1.8
Butyl phthalyl butyl glycolate, %	
10	1.0
20	1.3
30	2.0
Tributyl citrate, %	
20	2.4
30	2.8

(castor oil, fully acetylated monoglycerides, and tributyl citrate) occurred at a 20% level and for the remaining two (triacetin and butyl phthalyl butyl glycolate) at 10%. Also, it appeared that the rate for butyl phthalyl butyl glycolate may have had more than one point of inflection.

Moisture Absorption—In addition to the water vapor transmission rate, the moisture absorption of cellulose acetate phthalate was affected by the choice of plasticizer (Table II). The level of plasticizer was also an important factor. Interesting, too, are the different effects of the plasticizer level. As the level of diethyl phthalate, for example, was increased, the moisture absorption, as perhaps expected, decreased (from 2.1% at 10% to 0.3% at 30%). The opposite occurred, however, with butyl phthalyl butyl glycolate; the minimum absorption was found at a level of 10% or lower. The third type of effect, that of insensitivity toward plasticizer level, was noted with castor oil. The unexpected results for triacetin warrant some mention; a loss in weight rather than an increase was observed. This is not understood but it may reflect hydrolysis to, and evaporation of, acetic acid and would predict low plasticizer permanence.

The lowest moisture absorption was found with 30% diethyl phthalate. The low value for unplasticized cellulose acetate phtha-

Table III—Tablet-Coating Performance

Plasticizer	Percent Weight of Coating—Uncorrected[a] Lactose	Uncorrected[a] Dical	Corrected[b] Lactose	Corrected[b] Dical	Disintegration Time (min.) in Intestinal Fluid—Lactose	Intestinal Fluid—Dical
None	7.8	2.3	7.8	2.3	14	6
Diethyl phthalate, 25%	12.3	4.6	9.8	3.7	10	6
Triacetin, 20%	18.8	2.6	15.7	2.2	18	6
Fully acetylated monoglycerides, 20%	5.3	3.7	4.4	3.1	12	6
Partially acetylated monoglycerides						
10%	12.3[c]	1.6	11.2[c]	1.5	—	3
30%	12.7[c]	2.0	10.6[c]	1.5	—	4
Butyl phthalyl butyl glycolate						
10%	5.6	3.6	5.1	3.3	12	6
20%	8.3	3.8	6.9	3.2	14	5
30%	8.5	4.0	6.5	3.1	13	7
Tributyl citrate, 20%	12.7	2.8	11.6	2.3	16	4

[a] Total minimum amount of coating. [b] Amount of cellulose acetate phthalate only. [c] A spray nozzle of reduced capacity was required for the formula containing partially acetylated monoglycerides. This run was discontinued after an inordinately long coating time (5 hr. *versus* 3 hr. in the case of the other runs). These tablets disintegrated in simulated gastric fluid.

Table IV—Liquid Water Permeation of Coated Lactose Tablets

Plasticizer	Percent Weight Gain after 1 hr.	4 hr.
None	1.9	5.9
Diethyl phthalate, 25%	0.73	1.3
Triacetin, 20%	1.9	6.1
Fully acetylated monoglycerides, 20%	0.95	2.4
Butyl phthalyl butyl glycolate		
10%	1.0	2.4
20%	1.1	2.6
30%	0.47	1.0
Tributyl citrate, 20%	0.81	2.9

late, however, suggests that this parameter normally need not be a prime criterion in selecting a plasticizer.

Enteric Coating Performance—Table III summarizes the comparison of tablet coating performance among the plasticizers. The uncorrected columns report the minimum amount of total coating weight required to prevent tablet disintegration for 1 hr. in simulated gastric fluid. The corrected columns report the same data calculated in terms of cellulose acetate phthalate only.

Overall, considerably more coating was required to protect the lactose tablets. While this may be due in part to a difference in tablet porosity, the large differences for most plasticizers suggest that the type of tablet base is indeed of significance.

Greater amounts of coating generally were required when plasticizers were added to cellulose acetate phthalate. Among the six plasticizers tested on lactose, only fully acetylated monoglycerides and butyl phthalyl butyl glycolate performed better than unplasticized cellulose acetate phthalate. On dicalcium phosphate, only partially acetylated monoglycerides performed better.

Furthermore, the plasticizers that promoted good performance on one type of tablet base performed poorly on another base. Partially acetylated monoglycerides, for example, performed excellently on dicalcium phosphate but poorly on lactose. Similar (though opposite) results were found for fully acetylated monoglycerides.

These data show that a plasticizer may be carefully chosen to promote good performance on a given tablet substrate and yet may not perform well on a different substrate.

Tablet-Disintegration Time—Table III also summarizes the disintegration times in simulated intestinal fluid and shows that the plasticizers had little effect.

Liquid Water Permeation—Most enteric coated tablets are finished with sugar coatings. During this operation, the cellulose acetate phthalate film is most likely in contact with water. Transport through the film is therefore by means of liquid water in addition to water vapor permeation. Table IV illustrates the weight increases of lactose tablets after immersion in water (the values again reflect data on tablets coated with the minimum amounts of coating to resist disintegration in simulated gastric fluid for 1 hr.).[6] Varying amounts of water permeation were observed; diethyl phthalate and 30% butyl phthalyl butyl glycolate contributed to the most effective barriers.

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[6] The results would, of course, be inaccurate if some lactose was lost by diffusion through the coating. It was determined by reweighing tablets, dried for 16 hr. at 37° after exposure to water (25°) for 6 hr., that this did not occur.

Facile Isolation of Phenylephrine from Syrups

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Abstract □ Although phenylephrine HCl is easily isolated from most of its dosage forms, the high water solubility of both the base and salt forms often makes its isolation from syrups and elixirs difficult. The partition coefficient for extraction of phenylephrine from water to *n*-butyl alcohol is unfavorable, but the drug can be salted into the organic solvent with an excess of sodium chloride and recovered from butanol by extraction with aqueous alkali. Interference to spectrophotometric determination caused by certain coal tar dyes can be circumvented by preliminary extraction of them as ion pairs with quaternary salts. Recovery of at least 98.0% and excellent precision were obtained in trials of the procedure with syrup USP and an elixir placebo as the test vehicles.

Keyphrases □ Phenylephrine—isolation from syrups □ Syrups—separation, isolation of phenylephrine □ UV spectrophotometry—analysis

Phenylephrine HCl is extensively formulated with other drugs in a variety of liquid and solid dosage forms. Because both the free base and salt forms of the drug are very water soluble, its isolation from excipients and many coformulated drugs often can be accomplished by simple solvent extraction of interferences from a dilute acid or base extract of the product. With syrups and elixirs, however, separation of phenylephrine to provide an unaltered UV spectrum is often difficult.

Several chromatographic methods have been described for isolation of phenylephrine from its dosage forms. Schriftman separated it by paper chromatography (1) and electrophoresis (2). Kelly and Auerbach (3) and Montgomery *et al.* (4, 5) used ion-exchange chromatography. Clark and Rosenberg (6) eluted phenylephrine as its diacetyl derivative, formed on a partition chromatography column, and then determined it spectrophotometrically after hydrolysis of the acetyl functions. Levine and Doyle (7) described the partition chromatographic separation of phenylephrine as its ion pair with di-(2-ethyl)hexylphosphoric acid. Ponder (8) exploited the observation that phenyl-