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PLASTICIZATION OF CELLULOSE ESTERS USED IN THE COATING OF SUSTAINED RELEASE SOLID DOSAGE FORMS

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ABSTRACT

Plasticizer/polymer interactions have been studied by measuring intrinsic viscosity of six cellulose esters in a series of dialkyl phthalates and glyceryl triacetate. Mechanical properties (tensile strength and modulus of elasticity) of cast films were also measured. In general, high values for the reciprocal of modulus of elasticity and low tensile strength correlated with high intrinsic viscosity values. Among the plasticizers tested, dimethyl phthalate and glyceryl triacetate were most efficient.

INTRODUCTION

Film formers such as cellulose esters are extensively used in the coating of solid dosage forms to control drug release. Plasticizers are added to these polymers in order to change their physical properties and enhance their film-forming characteristics. To be effective, a plasticizer must interpose itself between the polymer chains and interact with them thereby extending and softening the polymer matrix. This phenomenon becomes evident in reduced modulus or stiffness and increased elongation and flexibility.

There is scattered information in the literature concerning the interaction of these polymers with plasticizers. Some data on the effect of glyceryl triacetate on mechanical properties of a series of cellulose acetates and acetate butyrates have been compiled (1, 2) FMC booklets 1 and 3. Phthalates represent by far the largest plasticizer group because of their performance and economy. However, the interaction of phthalates with cellulose acetates and acetate butyrates has not been described.

A convenient way of assessing the degree of polymer/plasticizer interaction is to measure the intrinsic viscosity of the polymer dissolved in the plasticizer (3). Entwhistle Although the polymer is the major component in typical polymer-plasticizer systems, it is possible to use the viscosity of dilute polymer solutions as a measure of the solvent power of the liquid for the polymer. Thus, a liquid with high solvent power for the polymer is expected to cause chain molecules to expand, whereas a liquid with low solvent power would be less effective or possibly cause the chains to coil up. This is because in the liquid with low solvent power, the polymer segments prefer to stay close to each other while in a good solvent, they stretch and interact with the solvent molecules. Therefore the resulting solution has high viscosity where interaction between polymer segments and solvent molecules is preferred.

The effect of aging on water permeability and mechanical properties of cellulose acetate was recently reported (4). Sinko Fordyce and Meyer performed visual evaluation of the suitability of a number of plasticizers with cellulose acetate and cellulose acetate phthalate (5). The incorporation of several plasticizers in free films of cellulose acetate phthalate resulted in a reduction in water vapor transmission at low concentrations, followed by an increase as plasticizer concentration beyond about 3% (6). Bindschaedler and co-workers compared the physical and mechanical properties of cellulose acetate films containing various plasticizers and produced from aqueous latices and organic solutions (7).

In this work, mechanical measurements have been made for six different cellulose esters combined with a series of liquid phthalates. The results were compared to intrinsic viscosity measurements.

Designation	**Acetyl Content (Weight %)**	**Butyryl Content (Weight %)**	**Hyroxyl Content (Weight %)**
CA 320S	32	0	9.0
CA 398-10	39.8	0	3.4
CA 435-75S	43.5	0	0.9
CAB 171-15S	29.5	17.1	1.5
CAB 381-2	13.0	38.1	1.5
CAB 500-1	5.0	50	0.5

METHODS AND MATERIALS

All cellulose esters were supplied by FMC Corporation (Philadelphia PA). The nomenclature and nominal composition are summarized in Table 1. Dimethyl phthalate, diethyl phthalate, dibutyl phthalate, glyceryl triacetate, methanol and methylene chloride were used as received (Fisher Scientific, Springfield, NJ).

Intrinsic Viscosity

Viscosity of plasticizer and solutions of known concentration of the polymer in plasticizer (usually between 0.1% and 0.5% w/w) was measured using a capillary viscometer at 20 °C.

The reduced viscosity, defined as $\frac{(\eta-\eta_o)}{\eta_o C}$, where η is viscosity of the polymer solution, η_o is plasticizer viscosity and C

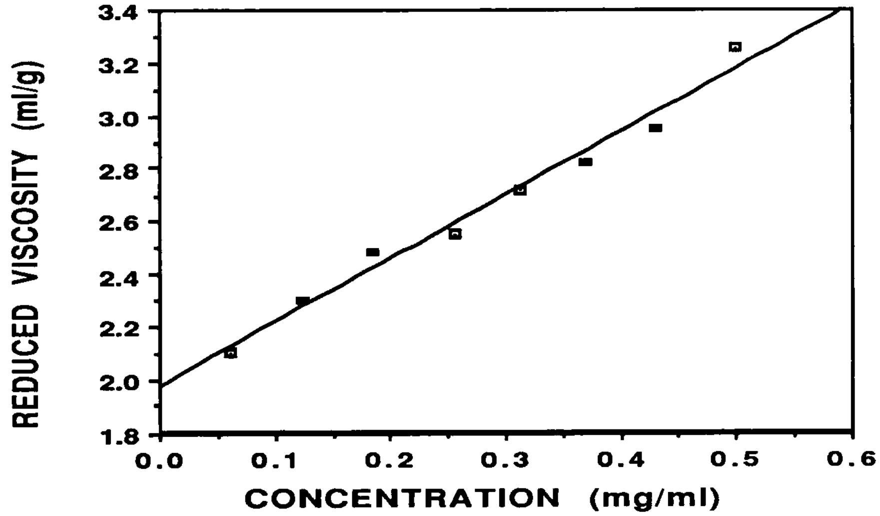

Figure 1. Determination of intrinsic viscosity for CA398-10 in glyceryl triacetate.

is polymer concentration, was plotted against C. Intrinsic viscosity was obtained by extrapolating to zero concentration. A typical plot is shown in Figure 1.

Mechanical Properties

Cast films were prepared from 10% w/w solution of polymer in methylene chloride/methanol; 90:10% w/w. Plasticizers were added at concentrations representing 10, 20, 30 and 40% of the solid polymer weight. Films were cast using an automatic film caster (Testing Machines, Amityville, NY). A 10 ml sample of the solution was poured onto a low-adhesion plastic sheet which was tightly clamped to a metal plate. As the solvent evaporated slowly, the film peeled off the plastic backing.

Strips of 1 cm width and at least 7 cm in length were cut perpendicular to the direction of casting with an Exacto knife for tensile testing. Films were stressed to failure at a constant speed (5 mm/60 sec) and load (500 N), using an MTS tensile tester (J and J Instruments, Minneapolis, MN). Thickness was measured using a micrometer gauge (L.S. Starrett, Boston, MA) which was sensitive to .001 inch. The tensile strength and modulus of elasticity were calculated as follows:

$$TS = \frac{LF}{h\ w} \qquad \text{Eq. 1}$$

$$ME = \frac{\tau}{\varepsilon} \qquad \text{Eq. 2}$$

where TS is tensile strength in mPa, LF is load at failure in N, h and w are film thickness and width, respectively, in mm, ME is the modulus of elasticity in Nm^{-2}, τ is stress in Nm^{-2}, and ε is strain. Tensile strength is a direct measure of film "hardness". The modulus of elasticity is high in hard films and low in soft films. Plasticization results in a decrease in both TS and ME.

RESULTS AND DISCUSSION

Intrinsic Viscosity

Values of intrinsic viscosity of the cellulose esters in a series of dialkyl phthalates and glyceryl triacetate are represented graphically in Figure 2. Viscosity data could not be obtained for CA 320S because this polymer was not soluble in any of the plasticizers. All of the remaining cellulose ester grades except

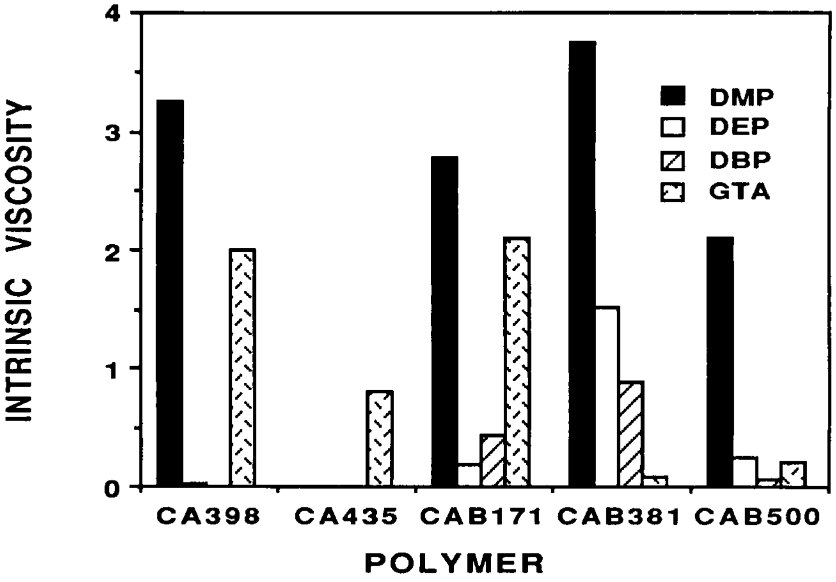

Figure 2. Intrinsic viscosity of polymers in various plasticizers. DMP = dimethyl phthalate; DEP = diethyl phthalate; DBP = dibutyl phthalate; GTA = glyceryl triacetate.

for CA 435-75S exhibit a maximum in the intrinsic viscosity for dimethyl phthalate. The intrinsic viscosity data reflect the tendency of a polymer to uncoil and associate with a plasticizer solvent. Therefore, high values of intrinsic viscosity imply a greater polymer-plasticizer interaction.

In general, intrinsic viscosity dropped as the phthalate hydrocarbon chain length increased (Fig. 2). Diethyl and dibutyl phthalate have minimum interaction with the acetates but are compatible to some degree with the acetate butyrates. Intrinsic viscosity values for glyceryl triacetate were relatively high in most cases but generally less than that of dimethyl phthalate.

Table 2. Tensile strength of various polymer-plasticizer combinations.

Polymer	**Plasticizer Conc. (%)**	**Tensile Strength (mPa)**			
		DMP	**DEP**	**DBP**	**GTA**
CA 320S	0	67	67	67	67
	10	12	19	47	41
	20	16	19	13	42
	30	13	36	10	29
	40	14	27	10	14
CA 398-10	0	68	68	68	68
	10	47	51	65	47
	20	33	36	35	39
	30	25	35	33	27
	40	19	33	34	24
CA435-75S	0	85	85	85	85
	10	81	66	78	51
	20	54	60	67	48
	30	47	49	65	48
	0	44	45	48	44
CAB 171-15S	0	47	47	47	47
	10	36	45	51	42
	20	28	32	29	33
	30	26	24	24	22
	40	18	21	22	20
CAB 381-2	0	33	33	33	33
	10	20	30	18	23
	20	11	16	9	16
	30	10	10	5	8
	40	7	7	7	7
CAB 500-1	0	-	-	-	-
	10	4.3	10	15	7
	20	4.5	11	10	8
	30	2.6	6	4	4
	40	2.6	7	3	2

Mechanical Properties

In mechanical testing the most efficient plasticizer is usually defined as the one that gives the best balance of end use properties for the amount incorporated. In this study the concentration of the plasticizer was varied from 10-40% of the

Table 3. Reciprocal of modulus of elasticity for various polymer-plasticizer combinations.

Polymer	**Plasticizer Conc. (%)**	**Reciprocal of modulus of elasticity (m^2/N)**			
		DMP	**DEP**	**DBP**	**GTA**
CA 320S	0	0.29	0.29	0.29	0.29
	10	0.67	0.50	0.32	0.31
	20	0.70	0.55	0.61	0.38
	30	0.95	0.42	0.80	0.45
	40	0.76	0.54	0.94	0.61
CA 398-10	0	2.4	2.4	2.4	2.4
	10	4.0	3.0	2.7	3.8
	20	4.9	4.4	4.0	4.7
	30	6.2	5.7	5.0	5.7
	40	8.3	5.9	5.5	6.6
CA435-75S	0	2.2	2.2	2.2	2.2
	10	2.7	3.1	2.5	3.5
	20	3.4	3.1	3.3	4.0
	30	4.0	4.0	3.6	3.7
	0	4.8	4.2	4.8	4.4
CAB 171-15S	0	0.33	0.33	0.33	0.33
	10	0.48	0.41	0.39	0.44
	20	0.64	0.51	0.59	0.57
	30	0.60	0.65	0.73	0.95
	40	0.96	0.76	0.80	1.11
CAB 381-2	0	0.58	0.58	0.58	0.58
	10	0.87	0.60	0.80	0.85
	20	1.4	0.90	0.97	0.94
	30	1.9	1.7	1.67	1.9
	40	8.2	2.6	2.75	2.2
CAB 500-1	0	-	-	-	-
	10	3.8	1.1	1.1	2.2
	20	3.5	1.2	1.6	2.4
	30	11	3.0	6.1	7.3
	40	12	1.9	8.3	9.7

polymer weight. Tensile strength and modulus of elasticity and were measured with change in concentration (Tables 2,3). Typical results are shown in Figures 3 and 4 for the CA 398-10 polymer. Tensile strength decreases gradually as the concentration of placticizer is increased (Fig. 3) with dimethyl

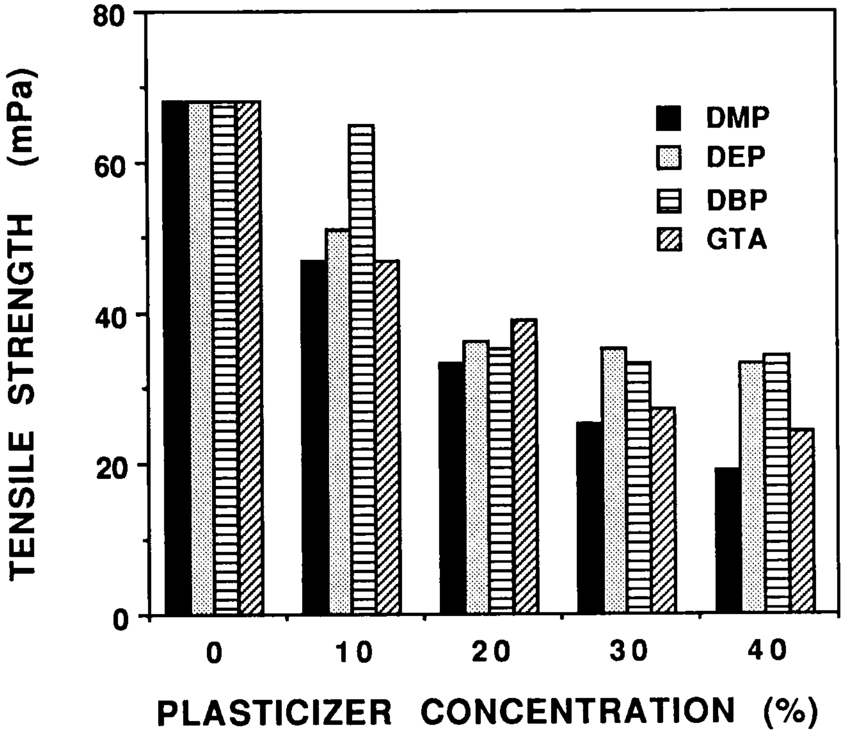

Figure 3. Effect of plasticizer concentration on tensile strength of CA398-10. Plasticizers same as in Fig. 2.

phthalate and glyceryl triacetate showing the largest effect. In figure 4, the reciprocal of the modulus of elasticity is plotted against film composition. An increase in the reciprocal indicates an increase in film elasticity and flexibility. Dimethyl phthalate has the greatest influence in increasing the reciprocal of ME in these films. Glyceryl triacetate is next, followed by diethyl and then dibutyl phthalate.

For CA 320S, dimethyl phthalate is again the most efficient of this group of plasticizers (Tables 2, 3). Large changes in

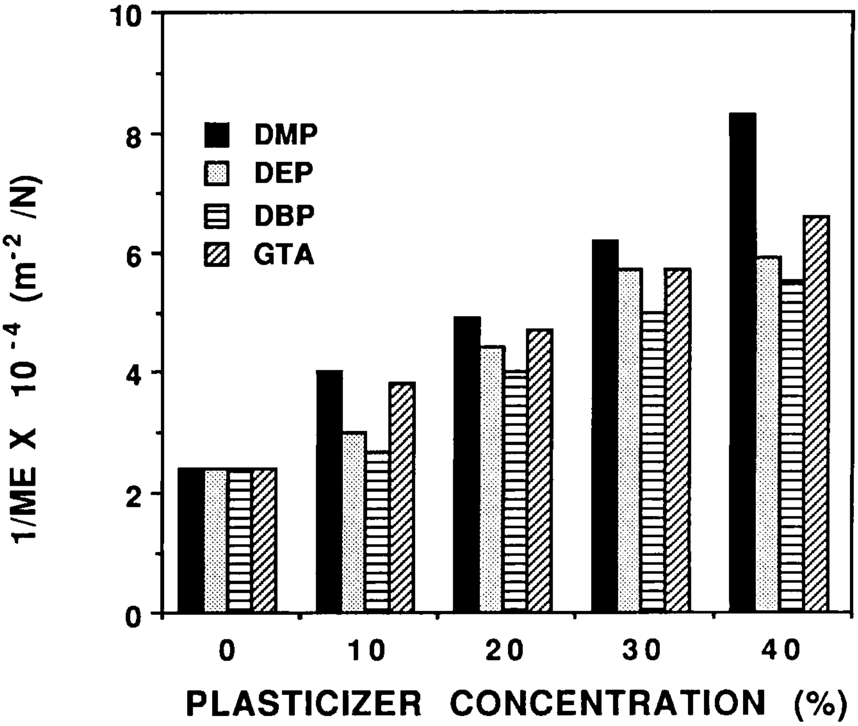

Figure 4. Effect of plasticizer concentration on reciprocal of modulus of elasticity of CA398-10. Plasticizers same as in Fig. 2.

mechanical properties are obtained at only 10% concentration of this plasticizer. The second best plasticizer is dibutyl phthalate, although 20% of it is required for a substantial effect.

The properties of CA 435-75S are modified to a lesser extent by the plasticizers as compared to the other cellulose acetate grades. Glyceryl triacetate works well at low concentrations (10-20%) and then at 30% its effects level off. Dimethyl and diethyl phthalate are similar in their effects .

Dimethyl phthalate and glyceryl triacetate appear to be less efficient at 10 and 20% levels when combined with the cellulose acetate butyrates as compared to their effects on the cellulose acetates. Elasticity of CAB 171-15S is affected to about the same degree by all of the plasticizers. Glyceryl triacetate is the most effective in raising the elasticity at higher concentrations.

The films of CAB 381-2 containing 40% plasticizer were hazy, indicating separation of excess plasticizer. There are some incongruities in the modulus of elasticity for CAB 381-2 (Tables 2, 3). Disregarding a couple of suspect "spikes", all of the plasticizers behaved similarly, producing modest increases in elasticity at high concentrations. Dimethyl and dibutyl phthalate were most effective in lowering tensile strength of these films at concentrations up to 30%.

It was not possible to prepare free films of CAB 500-1 because of the brittleness of this material. Also, films containing high plasticizer content (30% and higher) were not clear. The limited data obtained are summarized in Tables 2 and 3. At the concentrations employed, dimethyl phthalate was the most effective plasticizer of those investigated.

Relation between intrinsic viscosity and mechanical properties

Dimethyl phthalate and glyceryl triacetate exhibit a maximum in the intrinsic viscosity. They also are the most effective in lowering tensile strength and raising modulus of elasticity. However, there is not a perfect correspondence between the intrinsic viscosity and mechanical properties. One reason is that not all polymers could be dissolved in all of the plasticizers. Secondly, as has been mentioned above, intrinsic viscosity measurements utilize the plasticizer as solvent and contain low polymer concentrations while the opposite ratio is found in polymer films.

CONCLUSIONS

The mechanical test results indicate the dimethyl member is the most efficient plasticizer for cellulose acetates and acetate butyrates in a group of phthalates. Glyceryl triacetate's effectiveness is comparable to dimethyl phthalate. Their intrinsic viscosity values are also the largest of the plasticizers studied. Therefore, maximum interaction (high intrinsic viscosity) is related to optimum efficiency.

These results also illustrate the potential capability of such a relatively simple technique as intrinsic viscosity measurements in the screening of plasticizers. A disadvantage of the technique is that the plasticizer is in much higher concentration than the polymer, whereas the opposite is true in a film.

ACKNOWLEDGEMENT

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