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USE OF THERMAL ANALYSIS IN THE OPTIMIZATION OF POLYMERIC DIFFUSION BARRIERS IN CONTROLLED RELEASE DELIVERY SYSTEMS

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ABSTRACT

Increasingly a variety of polymers are being used as rate-controlling barriers in controlled release delivery systems. These diffusion barriers are usually in the form of thin films coated over the dosage form. The films are deposited from either solvent or water-based vehicles (latices or pseudolatices). Some recent applications involve placing the dosage form inside an injection molded polymeric barrier. Owing to the rigid nature and high glass transition temperatures (Tg) of most of the polymers being utilized pharmaceutically, plasticizers are used to soften (lower the Tg) the polymers. Sometimes a similar result can be accomplished by blending or modifying the polymers used. Thermal analysis is a very useful tool in the selection of the optimal type and use level of the plasticizer. The use of thermal analysis also aids in the proper selection of the application temperature for the barrier film and in the prevention of overplasticization. The latter may be particularly troublesome when the dosage form is required to pass an accelerated stability test (elevated temperature and/or humidity).

The study presented here will discuss the use of differential scanning calorimetry (DSC) and thermal mechanical analysis (TMA) in the selection of the optimal plasticizer type and use level to achieve the desired properties in the polymeric barrier. The polymers discussed in this study will include: ethyl cellulose, cellulose acetate, cellulose acetate butyrate and cellulose acetate phthalate. The plasticizer selection and the resulting Tg's will be discussed and the optimal plasticizer use levels will be presented. Some of the unique problems encountered in the use of DSC versus TMA methods also will be discussed.

INTRODUCTION

Polymeric materials have been used for some time in pharmaceutical coatings to provide protective barriers against environmental hazards such as abrasion, impact, high humidity, etc. They also have been used to hide poor appearance and mask poor taste of dosage forms. More recently polymeric film coatings are being increasingly used to provide controlled and/or enteric release barriers for medications. The films are deposited from either solvent or water-based vehicles (latices or pseudolatices). The water-based coatings are gaining preference in new drug delivery system development because of environmental and exposure concerns.

Most of the polymers being employed in such applications require modification owing to their rigidity (high glass transition temperature, Tg) at room temperature. Both the solvent

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and water-based coatings require plasticizers to lower the Tg. In addition, the water-based coatings require plasticization to achieve coalescence of the individual submicron polymer particles into a continuous barrier film.

The first consideration in choosing potential plasticizer candidates has to be given to the compatibility of the polymer and plasticizer. Thermodynamic solubility parameter tables are readily available and very useful in determining these theoretical compatibilities. Secondly, the regulatory status of the potential plasticizers has to be determined. The last problem to contend with is the availability of the pharmaceutically approved plasticizers in commercial quantities.

In the present study, when selecting the optimal test plasticizer type and use level only plasticizers that met the three initial requirements cited were considered. Samples of the polymers containing increasing amounts of plasticizer were prepared and the Tg's for each were determined. Empirical curves of plasticizer concentration versus temperature were plotted. The optimum use level for each particular plasticizer was determined by observing the major discontinuity in the slope of the curve. In cases where more than one plasticizer was evaluated the one that gave the greatest lowering in Tg at the lowest concentration was considered the most efficient (optimal) plasticizer.

EXPERIMENTAL

The plasticization studies on ethyl cellulose were performed on Aquacoat™ aqueous polymeric dispersion (FMC Corp.) All the cellulose esters were from Eastman Chemical Products, Inc. The plasticizers used were:

a) DBS (dibutyl sebacate): Union Camp Corp.
b) DEP (diethyl phthalate): Eastman Chemical Products, Inc.
c) TEC (triethyl citrate): Morflex Chemical Co., Inc.
d) Triacetin (glyceryl triacetate): Eastman Chemical Products, Inc.
e) Myvacet™ 9-40 distilled acetylated monoglycerides: Eastman Chemical Products, Inc.

Glass transition temperature measurements were carried out using Differential Scanning Calorimetry (DSC) at 5°C/min. and Thermal Mechanical Analysis (TMA, with penetration probe) at 10°C/min. The analyzers were models DSC-7 and TMA-7, Perkin-Elmer, Norwalk, Connecticut.

In the preparation of ethyl cellulose aqueous polymeric dispersion (Aquacoat™) and cellulose acetate phthalate latex (CAP) films, the latices were stirred with the selected plasticizer type and amount for 30 minutes and a pre-selected amount of the mixture sufficient to give a film of 0.8-1mm thickness was poured into an aluminium dish. The films were dried overnight at room temperature, followed by 8 hours at 60°C. These films then were analyzed by TMA after overnight equilibration at room temperature/humidity. In the preparation of cellulose acetate or butyrate films, the polymer was dissolved in an organic solvent (90% methylene chloride/10% methanol, w/) at 8% solids, mixed with the selected amount of plasticizer, cast and dried at room temperature to give a free film. These

resulting films were analyzed by DSC after overnight conditioning at room temperature/humidity.

RESULTS AND DISCUSSION

Since the present paper deals with the plasticization and the compatibility of selected polymers and plasticizers, it seems useful to introduce well known definitions of both. Plasticizers are materials which when incorporated into a polymer, assuming they are compatible, may lower the elastic modulus, second order transition temperature, melt temperature and viscosity. On the molecular level, plasticization is a weakening or breaking of selective bonds accompanied by the increase in intermolecular space (free volume)[1]. The compatibility of a specific polymer/plasticizer system is defined by the amount of plasticizer that can be added to the polymer without phase separation. Since the plasticizer behaves as a solvent for the polymer, the concept of solubility parameter can be applied[2]. An excellent review of the theories of plasticizer/polymer compatibility is presented in the publication by Sears & Darby[1] Table 1 shows the thermodynamic solubility parameter ranges (actual values depend on the method of calculation) for some of the plasticizers and polymers studied in this paper. These values are as reported in Sears and Darby.

TABLE 1
Solubility Parameter

Polymer/plasticizer	Solubility parameter (δ) ($cal^{1/2}\ cm^{-3/2}$)
Ethyl Cellulose	8.5-10.1
Cellulose Acetate*	9.23-9.33
Diethyl Phthalate(DEP)	8.9-9.92
Dibutyl Sebacate(DBS)	7.7-9.2
Triethyl Citrate	8.6-9.04
Glyceryl Triacetate(Triacetin)	8.84-9.93

* Range depends on degree of acetylation and hydrogen bonding

The glass transition temperatures (Tg) for Aquacoat™ aqueous polymeric dispersion (ethyl cellulose system) plasticized with

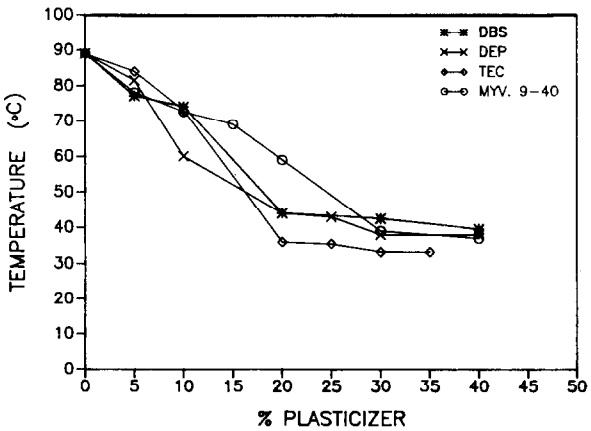

Fig.1. Tg of Aquacoat™ Dispersion (plasticized)

TABLE 2

Aquacoat™ Tg vs. % Plasticizer

% Plasticizer	DBS	DEP	TEC	MYVACET™ 9-40
0**	89	89	89	89
5	77	81.5	84	78
10	74	60	73	72.5
15	-	-	-	69
20	44	44	56	59
25	-	43	35.5	-
30	42.5	38	33.3	39
40	39.5	38	33.3*	37

* Done at 35%.

** Ethyl cellulose (neat) Tg = 129°C.

increasing (0->40% based on total solids) amounts of four selected plasticizers are shown in Table 2 and graphically in Fig.1.

Table 3 and Fig.2 represent the results for the glass transition temperature (Tg) of CAP latex films plasticized with increasing (0-30% based on total solids) amounts of two different plasticizers.

The cellulose acetate and butyrate films were cast from solvent and plasticized with two selected plasticizers based on their compatibility with the esters (Table 4)[1]. Three cellulose acetates (CA) and three cellulose acetate butyrates (CAB) were evaluated, the differences being in the degree of acetyl and butyryl substitution. Structures of the polymers used in this study are presented in Figure 3. Table 5 and Figs. 4 and 5 represent the results of glass transition temperatures (Tg) for a number of cellulose acetates and cellulose acetate butyrates plasticized with two selected plasticizers at use levels ranging from 0->40%.

For Aquacoat™ aqueous polymeric dispersion (ethyl cellulose) the results indicated that for three out of the four plasticizers

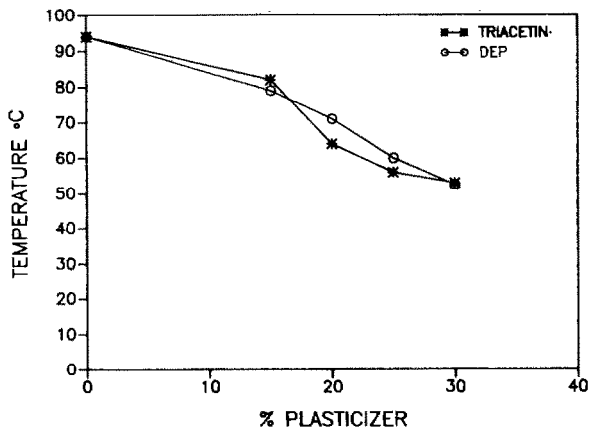

Fig.2. Tg of Plasticized CAP Latex

TABLE 3

CAP Latex Tg vs. % Plasticizer

Plasticizer/Amount %		Glass Transition Temp. (Tg) °C
Triacetin	0	94
Triacetin	15	82
Triacetin	20	64
Triacetin	25	56
Triacetin	30	53
DEP	0	94
DEP	15	79
DEP	20	71
DEP	25	60
DEP	30	52.5

studied (DBS, DEP, TEC) the optimal use level is around 20% where for Myvacet™ 9-40 is at around 30%. The results have also indicated that the TEC is the most efficient plasticizer followed closely by the other three. In the case of CAP latex two plasticizers were evaluated. Of the two, Triacetin seemed to be slightly more efficient, with both plasticizers optimal use level being at around 25%.

The results for the cellulose esters indicated very minor differences between the efficiencies of the two plasticizers used in the study. They showed, however, much greater variability in the effectiveness of either of the plasticizers with the six different cellulose ester grades. In the course of this study it was observed that the use of DSC resulted in reproducible data

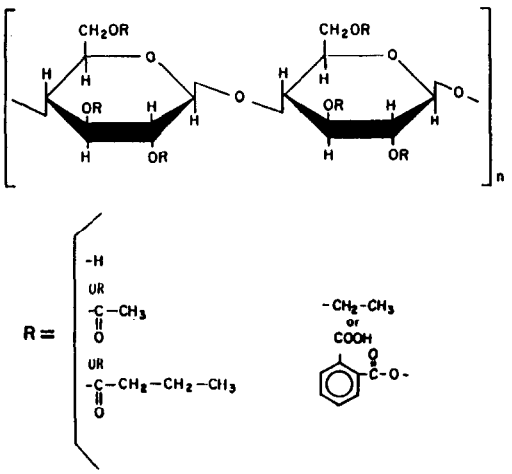

Fig.3. Cellulose Ester Structure

TABLE 4

Cellulose Ester - Plasticizer Compatibility[1]

Grade	Triethyl Citrate	Acetyl Triethyl Citrate	Tributyl Citrate	Glyceryl Triacetate	Glyceryl Tributyrate	Polyethylene Glycol 400
CA 320-S	C	C	P	C	P	-
CA 398-10	C	C	P	C	P	-
CA 435-75S	C	C	P	C	C	-
CAB 171-15S	C	C	P	C	C	I
CAB 381-2	C	C	P	C	C	I
CAB 500-1	C	C	P	C	C	I

C - Compatible
I - Incompatible
P - Partially Compatible

for the cellulose esters which were prepared from solvent. However, in the case of aqueous polymeric dispersions (Aquacoat™, cellulose acetate phthalate latex) no clear Tg's were observed by DSC. Most likely this is caused by the presence of other, interfering additives in the latex systems. The use of TMA proved very useful in these cases giving clear softening points which are directly related to the Tg's.

CONCLUSION

A number of polymers and plasticizers useful in producing controlled release diffusion barriers were studied and the use of thermal analysis to optimize the type and use level of selected plasticizers was discussed. It should be understood, however, that the selection of the optimal type and use level of a plasticizer based on thermal analytical results does not necessarily lead to optimum controlled release dosage forms. The optimal plasticizer type and use level for a particular pclymer

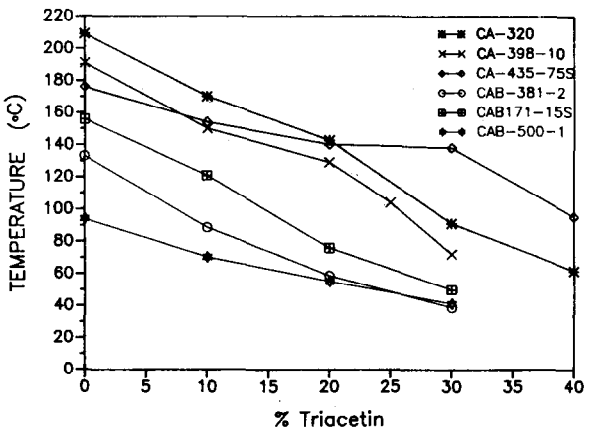

Fig.4. Tg of Plasticized Cellulose Esters

TABLE 5

Thermal Analyses Results for Plasticized Cellulose Esters

Cellulose Ester	Plasticizer	Tg (°C) at % Plasticization 0	10	15	20	25	30	40
CA-320S	Triacetin	209	170	-	142.6	-	91	61.5
	Triethyl citrate	209	170	-	149.6	123	81	71.7
CA-398-10	Triacetin	191	150	-	129	104	72	W
	Triethyl citrate	191	164	-	120	-	86	W
CA-435-75S	Triacetin	176	154	-	140	-	138	95.2
	Triethyl citrate	176	151	-	143	-	138	
CAB-381-2	Triacetin	133	88.5	-	58.5	-	38.5	W
	Triethyl citrate	133	106	76	58.2	-	40	W
CAB-171-15S	Triacetin	156	121	-	76	-	50	W
	Triethyl citrate	156	124	107	88	-	57	W
CAB-500-1	Triacetin	94	70	-	55	-	41	W
	Triethyl citrate	94	70	61	54	-	-	W

W - "Wash out" (Tg not observed, too much plasticizer present).

is often not the one which will achieve the most desired controlled release rate for a specific drug through that polymeric diffusion barrier. The desired release rates through the barrier depend on many factors such as coating thickness, plasticizer concentration, drug polymer solubility, drug polymer interaction and film coalescence (the effects of drying temperature and duration)[8]. The usefulness of thermal analysis lies with the ability imparted to screen experimentally a number of potential plasticizers and to choose initially the most efficient ones.

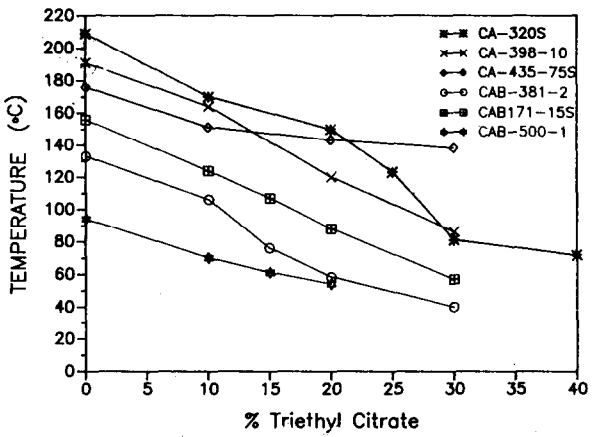

Fig.5. Tg of Plasticized Cellulose Esters

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Aquacoat - FMC Corporation Trademark
Myvacet - Eastman Kodak Co. Trademark