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International Journal of Pharmaceutics 133 (1996) 161–170

international journal of pharmaceutics

Evaluation of physical properties of plasticized ethyl cellulose films cast from ethanol solution Part I

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Received 19 April 1995; revised 12 December 1995; accepted 17 December 1995

Abstract

Ethyl cellulose films plasticized with 0, 10 and 20% of five different plasticizers were prepared. The films were cast into teflon molds from ethanol solution. The plasticizers used were: dibutyl sebacate, triethyl citrate, triacetin, Myvacet® (acetylated monoglycerides) and diethyl phthalate. The physical properties of the films were evaluated using thermal analysis, tensile testing, porosimetry, scanning electron microscopy and hot stage microscopy. The results reported are glass transition temperature, tensile stress, percentage elongation at break, elastic modulus, total volume of pores, total surface area of pores and mean and median diameters of pores. On the basis of tensile tests and thermal analysis, dibutyl sebacate and Myvacet® were found to be the two most efficient plasticizers for ethyl cellulose films cast from ethanol solution.

Keywords: Ethyl cellulose; Plasticizers; Free films; Porosity; Mechanical testing; Thermal properties

1. Introduction

Polymers have been used in pharmaceutical formulations for several reasons including protection of the dosage form against environmental hazards and for hiding a bad taste, odour or appearance. The application widely studied today is sustained-release dosage forms.

Ethyl cellulose is the water-insoluble cellulose ether used most commonly in film coating for pharmaceutical purposes (Rowe, 1984; Porter, 1980). Because of its high glass transition temperature, it has to be plasticized to improve its thermal behaviour and tensile properties. Several studies show the importance of the type and amount of the plasticizer used (Entwistle and Rowe, 1979; Porter, 1980; Rowe et al., 1984a; Selinger and Brine, 1988; Lippold et al., 1990; Arwidsson et al., 1991; Hutchings et al., 1994; Guo, 1994). The amount of plasticizer affects the release rate of the film via structural changes it causes (Guo, 1994). Other important factors affecting the film properties are the coalescence temperature (Arwidsson et al., 1991; Parikh et al., 1993) and the type and amount of solvent used (Banker, 1966; Iyer et al., 1990; Kurz and Führer, 1993; Narisawa et al., 1993; Narisawa et al., 1994).

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PII S0378-5173(96)04436-5

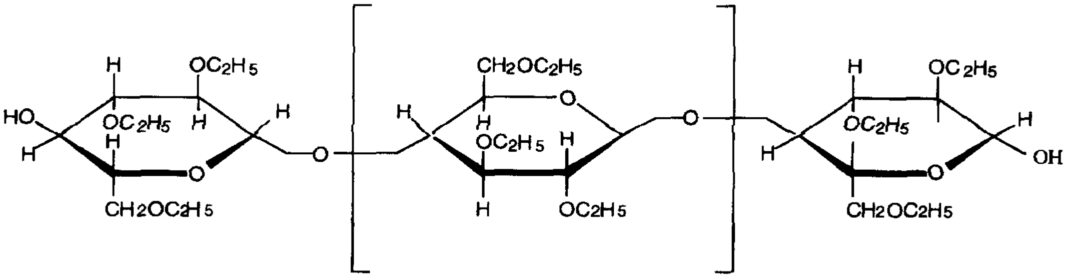

Fig. 1. Ethyl cellulose with complete ethoxyl substitution.

According to Aulton (1982), casting is a preferable method for producing films, when the aim is to study fundamental properties of the polymer formulation, although sprayed films would be more realistic when one thinks of real pharmaceutical coatings. Cast films are reproducible because environmental factors affect the film preparation less than with sprayed films. Isolated films are a good way to screen formulations (Porter, 1980) and to select the best ones for further studies. Correlation between mechanical properties of isolated and applied films has been reported (Rowe, 1983).

The primary aim of this work was to study the effects of various plasticizers on ethyl cellulose film properties in order to facilitate sustained-release film coating formulation. The secondary aim was to evaluate the methods used regarding the analysis of free films. The first part of this work, reported hereafter, concentrates on the physical characterization of the ethyl cellulose free films immediately after preparation. The second part will focus on the physical characterization of the best film compositions, selected on the basis of the results of the first part of this work, after a storage periods of differing conditions (+ 25°C with 60% relative humidity, + 25°C with 75% relative humidity and 35°C with 75% relative humidity).

2. Materials and methods

2.1. Preparation of the free films

Ethyl cellulose type N-22 (EC) (Hercules Inc., USA) was dissolved in ethanol and after 3 h of mixing with a magnetic stirrer, the plasticizer was added. Thereafter, the stirring was continued for 30 min, which is the time that has been reported necessary for 95% of the DBS to mix properly (Iyer et al., 1990). The solution was then cast into round teflon molds of 7 cm in diameter. This method was chosen in order to produce large, unharmed pieces of film with no orientation of the molecules. Also Narisawa et al. (1993), Bodmeier and Paeratakul (1994) and Heinämäki et al. (1994) have used teflon surfaces to produce smooth free films.

The amount of solution needed to obtain a film with a thickness of 65 ± 5 μm varied from 2 to 2.3 g depending on the composition of the solution. The films were coalesced in 60°C overnight and peeled off the mold using a spatula and a surgeon's knife. The molecular structure of EC is presented in Fig. 1.

Eleven different types of films were prepared. In each solution, there was 10% (w/w) EC in ethanol. Plasticizers were added in ratios of 0, 10 or 20% (w/w) of EC. The plasticizers used were:DBS (dibutyl sebacate, Fluka Chemie AG, Switzerland)TEC (triethyl citrate, Eudraflex® Röhm Gmbh, Germany)Triacetin (glyceryl triacetate, Fluka Chemie AG, Switzerland)Myvacet® (9-45 distilled acetylated monoglycerides, Eastman Chemical Company, USA)DEP (diethyl phthalate, FTAL Chemical Sector, Belgium)

The molecular structures of the plasticizers are presented in Fig. 2.

2.2. Tensile testing

The apparatus used in tensile measurements

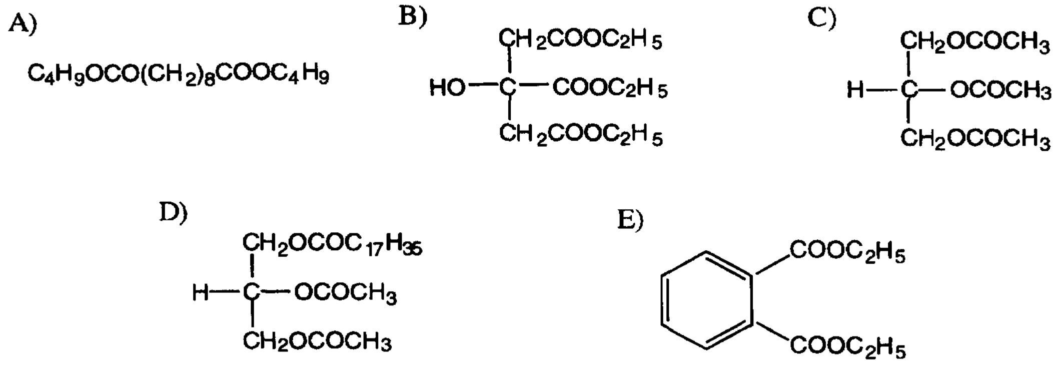

Fig. 2. Plasticizers used (A) DBS, (B) TEC, (C) Triacetin, (D) an example of Myvacet and (E) DEP.

was LR 30 tensile tester (Lloyd instruments Ltd., G.B.). Samples with a length of 60 mm and a width of 10 mm were cut with a sharp knife trying to avoid jagged edges. Each strip was measured at five points with a micrometer (Microstat, More and Wright Microsystems Ltd., G.B.) to ensure the thickness of 65 ± 5 μm.

The measuring speed used was 5 mm/min and the initial gauge length was 40 mm. Five parallel measurements were made for each type of films. The calculations are made as described by Odian (1981).

2.3. Porosimetry

The porosimetric measurements were carried out with Autoscan-33 mercury porosimeter (Quantachrome Corp., Syosset, NY, USA) and the apparatus used for the sample preparation was the Autoscan filling apparatus (Quantachrome Corp., Syosset, NY, USA). The method is based on the Washburn equation

$$r = \frac{-2\gamma \cos\theta}{P}$$

where r = the radius of the cylindrical pores; γ = the surface tension of mercury; θ = the contact angle; P = the applied pressure.

The method is described by Moscou and Lub (1981). The results were calculated by Poro 2PC, a data acquisition/reduction program for Autoscan porosimeters provided by Quantachrome Corp. The surface areas were calculated by integration of the mercury intrusion curves.

The films were cut into 50-mm long and 6-mm wide strips. Ten strips were used in every measurement and three parallel measurements were performed.

2.4. Scanning electron microscopy (SEM)

The apparatus used was a JSM-840 A (Jeol Ltd, Japan) scanning microscope. Both surface and cross-section pictures were taken.

2.5. Differential scanning calorimeter (DSC)

The measurements were made with a Perkin Elmer 7 DSC (Perkin Elmer, USA) with an intracooler and nitrogen purge. Each sample consisted of 11–14 mg of small disks piled in the sample pans.

The samples were first cooled to −70°C, held there for 5 min and heated 10°/min upto 200°C to find the approximate Tg. Then the samples were heated just above Tg, cooled to −20°C and heated again 10°/min to 160°C. At least three parallel measurements were made with separate samples for each film type.

2.6. Microscopic studies

Samples of films were studied with an Olympus Highlight 2000 microscope (Olympus, Japan) equipped with a Mettler FP 82 HT Hot Stage attached to a Mettler FP 80 HT Central Processor (both Mettler, Switzerland) to clarify the cause of the signal obtained with DSC around 155–160°C.

3. Results and discussion

3.1. Tensile testing

As expected, the compositions with 20% plasticizer showed lower values of stress at break and elastic modulus compared to those with only 10% of plasticizer. The results are listed in Table 1. Fig. 3 shows that the results of elastic modulus were very reproducible.

In the two compositions containing 20% DBS or 20% Myvacet® there was a clear yield point to obtain. These were the plasticizers with a trend of growing elongation at break with increasing plasticizer concentration. These films also showed the lowest Tg values, hence, 20% of DBS and 20% of Myvacet® are the two most efficient plasticizer grades.

There are a number of problems, causing inaccuracy in the measurements, with the tensile testing of free films. Although the thickness of the films was measured very accurately, it was not possible to measure the width of the samples as accurately. Moreover, the cutting of the film may cause internal tensions and the edges of the samples may be uneven. This caused deviation in elongation and in stress at break, because the microscopic cracks in the edges of the films caused premature cracking of the whole film. Furthermore, the film is so light that it will not hang straight from the upper grip when attached to the lower, consequently the effective tension begins only after beginning the measuring of the elongation. This slight error was corrected by moving the stress-strain curves to start at the zero point of both stress and strain.

Also, the manufacturing of the mold may have caused some error as the method leaves a spiral shaped track, not more than a few microns deep, on the bottom of the mold. The track makes the

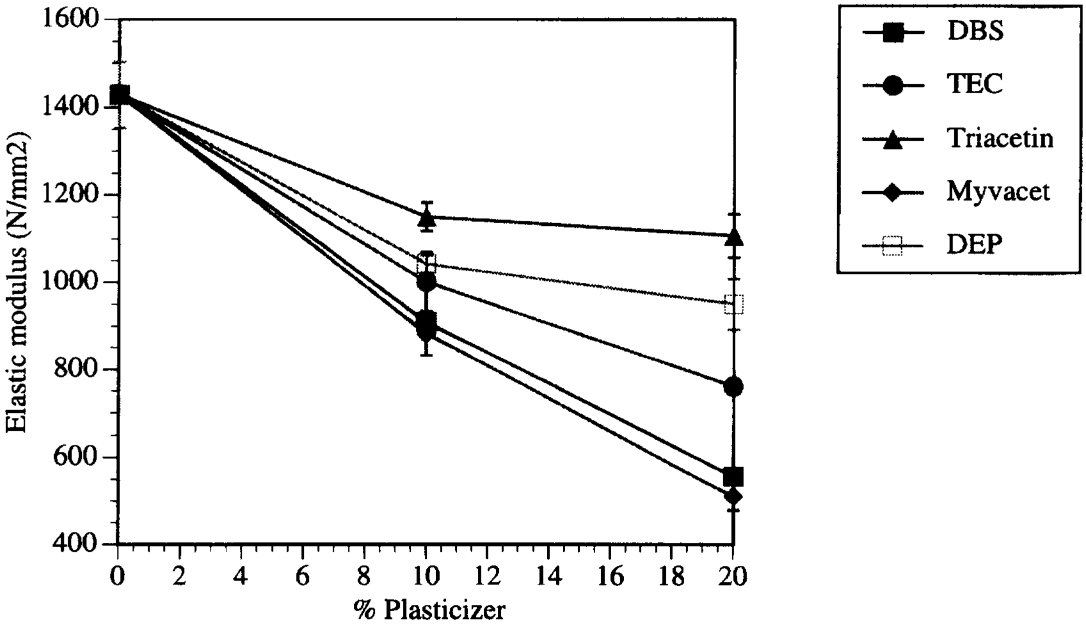

Fig. 3. Elastic modulus and its standard deviation vs. degree of plasticization.

Table 1
Results of tensile testing, five parallel measurements made ($n = 5$)

Plasticizer	Stress at break ± S.D. (N/mm^2)	Maximum stress ± S.D. (N/mm^2)	Elongation at break ± S.D. (%)	Elongation at Max.stress ± S.D. (%)	Elastic modulus ± S.D. (N/mm^2)
—	9.86 ± 1.88		0.77 ± 0.15		1428.1 ± 74.5
10% DBS	10.55 ± 1.93		1.40 ± 0.31		908.2 ± 21.0
20% DBS	7.49 ± 0.32	8.05 ± 0.49	2.19 ± 0.23	2.14 ± 0.23	556.2 ± 13.9
10% TEC	13.26 ± 1.34		1.59 ± 0.24		999.9 ± 68.0
20% TEC	8.70 ± 1.13		1.39 ± 0.22		760.4 ± 10.8
10% Triacetin	11.62 ± 1.77		1.08 ± 0.18		1149.4 ± 32.5
20% Triacetin	9.18 ± 3.72		0.90 ± 0.41		1105.4 ± 50.2
10% Myvacet	13.16 ± 1.11		2.03 ± 0.20		881.9 ± 50.4
20% Myvacet	7.34 ± 0.31	7.54 ± 0.37	2.78 ± 0.37	2.68 ± 0.31	508.6 ± 30.1
10% DEP	12.54 ± 2.81		1.94 ± 0.36		1041.5 ± 19.9
20% DEP	11.41 ± 0.84		1.35 ± 0.11		948.9 ± 58.2

bottom of the film uneven, as can be seen in the SEM pictures.

3.2. Porosity

Because of the smoothness of the surface of the films studied, the only way for the mercury to penetrate into the film are the edges of the sample strips. This can be seen in the SEM pictures of the films and is why the smoothness and regularity of the cutting is very important in porosity measurements.

Another fact to be considered is the compressibility of the film. The more elastic the film, the more it deforms under pressure, and this decrease in volume is reported by the equipment as an increase in the volume of mercury, which normally corresponds to the volume of pores. It is impossible to correct this error because it is different with each material, depending on its elasticity.

The results of measurements are shown in Table 2. Due to the quite large standard deviations and the facts described above, it is impossible to say how significant the effect of elasticity is and, hence, the only fully reliable result of these measurements is that the porosity of EC films plasticized with DEP decreases with increasing plasticizer concentration.

3.3. Scanning electron microscopy (SEM)

Preparing the samples for the SEM pictures may have caused some damage to the films. The only way to obtain cross sections which do not alter the porous structure is to freeze a strip of film in liquid nitrogen and break it while frozen. If there is any water in the pores, it will crystallize and expand and possibly break the structure of the pores.

The micrographs show that the pores of all the films are very small and surfaces very smooth, so the pictures confirm the results of the mercury porosimeter: the porosity of these films is very low. Figs. 4 and 5 show the cross sections of films plasticized with 20% of DBS and Triacetin, respectively.

3.4. Differential scanning calorimetry (DSC)

Measuring of the glass transition points of EC

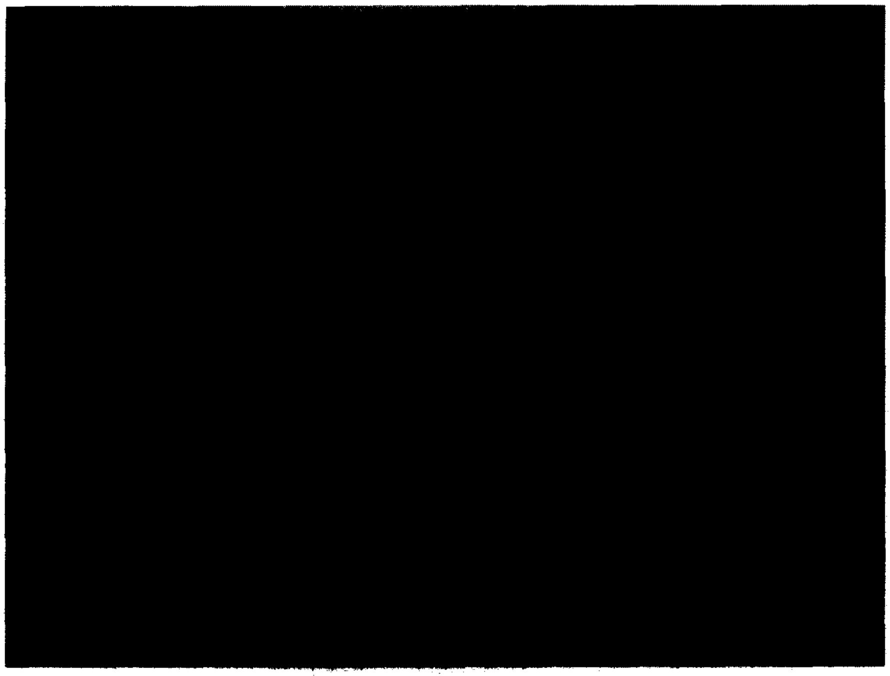

Fig. 4. Cross section of film plasticized with 20% DBS.

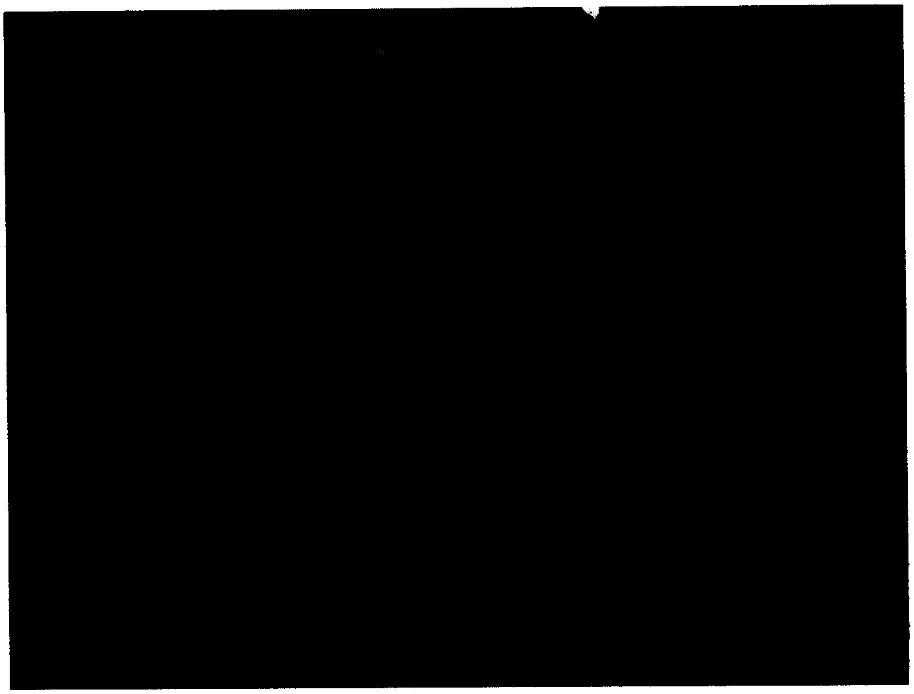

Fig. 5. Cross section of film plasticized with 20% Triacetin.

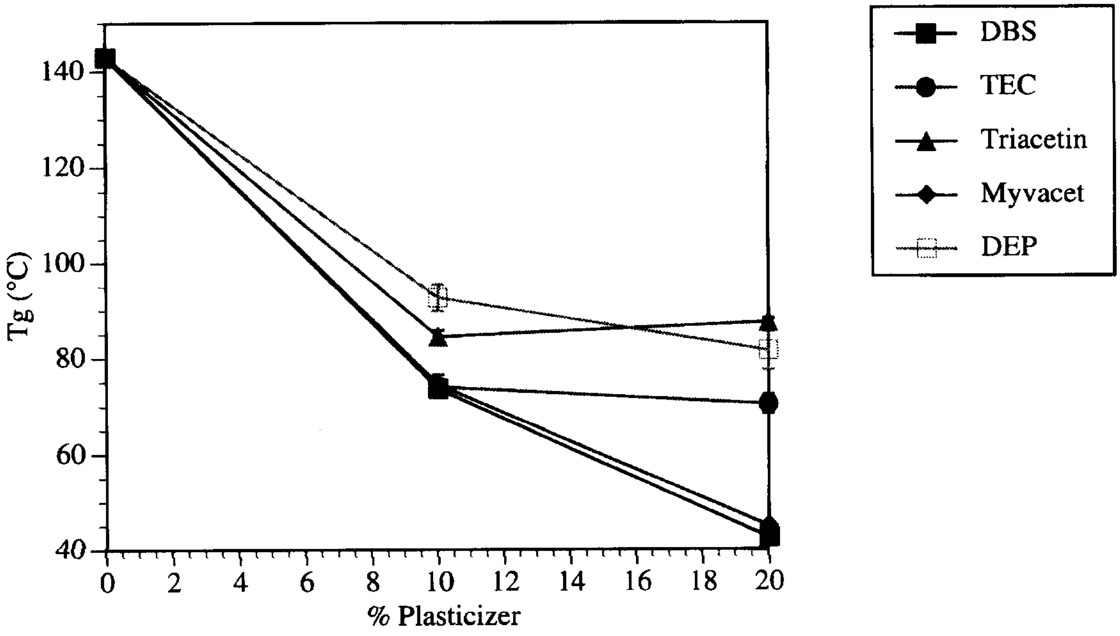

Fig. 6. T_g and its standard deviation as a function of plasticization grade.

Table 2
Results of porosity measurements, three parallel measurements made (n = 3)

Plasticizer	Total intruded volume ± S.D. (cc/g)	Total surface area ± S.D. (m^2/g)	Diameter: Mean ± S.D. (μm)	Diameter: Median ± S.D (μm)
—	0.096 ± 0.010	26.09 ± 1.11	14.71 ± 1.45	15.53 ± 2.08
10% DBS	0.084 ± 0.012	24.76 ± 0.39	13.60 ± 1.76	14.46 ± 1.89
20% DBS	0.093 ± 0.003	26.09 ± 2.59	14.33 ± 1.32	15.21 ± 1.74
10% TEC	0.096 ± 0.013	28.92 ± 2.84	13.27 ± 0.56	14.65 ± 0.69
20% TEC	0.091 ± 0.010	27.54 ± 5.80	13.46 ± 1.84	14.18 ± 2.32
10% Triacetin	0.088 ± 0.006	24.87 ± 2.31	13.92 ± 0.17	15.29 ± 0.38
20% Triacetin	0.087 ± 0.016	23.89 ± 3.65	14.39 ± 0.90	16.07 ± 1.25
10% Myvacet	0.087 ± 0.006	23.97 ± 3.65	14.25 ± 0.96	15.60 ± 1.49
20% Myvacet	0.094 ± 0.001	26.22 ± 3.15	14.53 ± 1.68	15.04 ± 2.15
10% DEP	0.089 ± 0.017	25.32 ± 0.95	14.07 ± 2.08	15.11 + 1.95
20% DEP	0.070 ± 0.001	22.40 ± 0.97	12.59 ± 0.82	13.27 ± 1.37

films with DSC is very difficult because the signal is very weak. In the second heating, there was either no Tg to obtain, or the signal was too weak to be observed. The probable reason for this is the slow recovery of the rigid ethyl cellulose chains. In a test where the sample was held for 1 h in −20°C after heating and then heated again, there was a little change in Cp on the second heating. Because of the extremely long waiting time for the second heating, the transitions were determined from measurements including only one heating. Because of the calculating method, the ΔCp val-

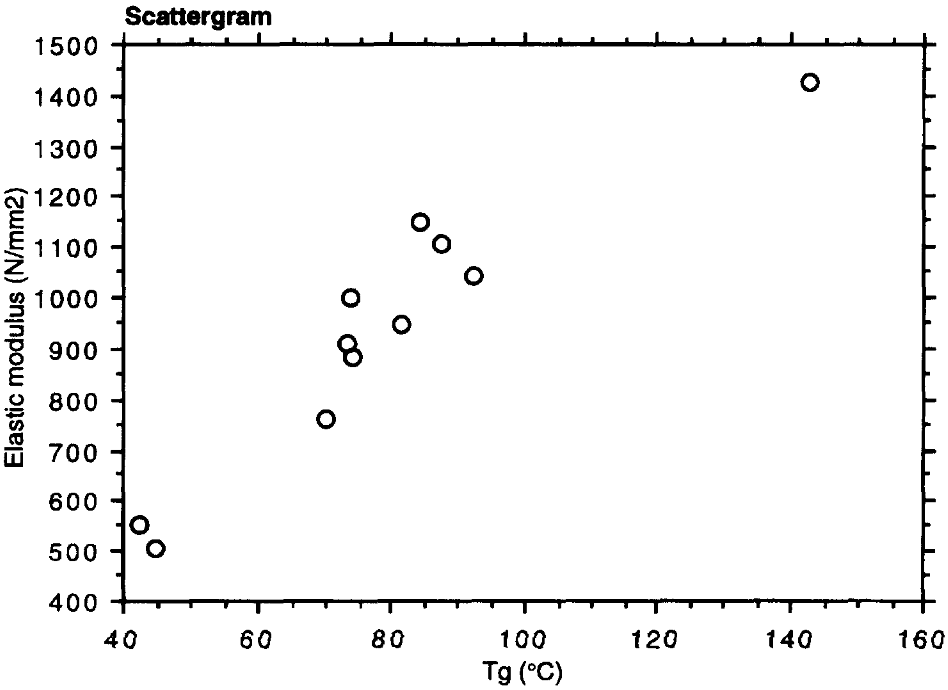

Fig. 7. Correlation of T_g and elastic modulus.

ues were not determined.

The Tg of pure ethyl cellulose has been measured using the torsional braid pendulum (Rowe et al., 1984a) and a Dupont 990 DSC apparatus (Entwistle and Rowe, 1979). The results of these two methods were very similar, 135°C and 129°C, respectively. In this study the measured result was a little higher. The cause of this discrepancy may be the size of the sample and, especially, its heterogeneity. A potential source for error is the heat transition in the sample. Porosity and the number of the sample disks in the pile affect the density of the sample and the glass transition point. Also, the relative humidity that has possibly been absorbed by the sample can affect the Tg. With thinner films, even the film thickness causes variation in Tg (Keddie et al., 1994).

In some of the samples, two glass transitions were observed: one at the right temperature and another one at the temperature corresponding to the Tg of ethyl cellulose. This was the case with 10% of TEC, DEP and Triacetin. It seems that some of the polymer is probably not plasticized, that is, the system is biphasic.

Fig. 6 shows the change in Tg when the amount of plasticizer is changed.

The results of the DSC measurements give very similar information to the tensile tests about the efficiency of the different plasticizers.

3.5. Microscopic studies

In the thermographs of some of the samples, a signal was obtained around 155-160°C. This transition was shaped like a combination of melting and glass transition signals and was identified as softening and the macro structure collapsing by means of a hot-stage microscope technique. Kurz and Führer (1993) reported the glass transition of ethyl cellulose films at about 450 K (≈ 177°C), this softening transition is possibly what he saw. The temperature he reported is a little higher, probably because of the faster heating rate he used. The cause of the glass transition-like behaviour, i.e. a change in heat capacity, may be due to the homogenization of the sample.

4. Conclusions

Although there were many possible artefacts disturbing the measurements, the results of both DSC measurements and tensile tests show clearly that DBS and Myvacet® are the two most efficient plasticizers for ethyl cellulose films produced by casting from ethanol solution. Only 10% of these plasticizers affected the physical properties of the film, approximately as much as 20% of either of the two second-best plasticizers, TEC and DEP. The effect of concentration was drastic with DBS and Myvacet®, whereas it had hardly any effect with Triacetin, the worst plasticizer, and DEP. It was also found that 30 min is not a sufficient mixing time for all the plasticizers. DSC measurements revealed a biphasic system in films plasticized with TEC, DEP or Triacetin. Obviously, the long chained DBS and acetylated monoglyceride molecules penetrate the polymer chains better than the more spherical TEC, DEP and Triacetin molecules.

The secondary aim of this study was to acquire some basic knowledge about the physical characterization of thin polymer films and to try to correlate the results of different measurements with each other. The low porosity results obtained by mercury porosimetry were qualitatively confirmed by SEM micrographs. The correlation of the results of DSC and tensile measurements was 0.939, and disregarding the three poorly mixed formulations, 0.972. This indicates that the two methods give very similar information about the materials tested, though tensile testing does not show the poor mixing of the plasticizer. The correlation is presented in Fig. 7.

Because of the problems discussed above, the results presented are not the absolute truth about the physical properties of the films studied; nevertheless, they permit to rank the five plasticizers according to their applicability in ethyl cellulose-based pharmaceutical coatings.

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