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Permeability and mechanical properties of a new polymer: cellulose hydrogen phthalate

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Summary

Films prepared from a new pH-dependent polymer, cellulose hydrogen phthalate (CHP), containing different proportions of plasticizers, were studied to evaluate their possible application to produce retard coated dosage forms. Neat CHP films were brittle and broke easily upon handling, therefore plasticizers were needed to improve the mechanical properties. Dibutyl phthalate, a hydrophobic plasticizer, was found to be an ineffective plasticizer since it did not improve the mechanical properties. However, glycerol, a hydrophilic plasticizer, was shown to be effective. These results were confirmed by differential scanning calorimetry analysis of the various plasticized CHP films. Permeability studies using theophylline as a model drug revealed that increasing the concentration of the hydrophilic plasticizer in the film enhanced the permeation rate and reduced the time lag, whereas the concentration of the hydrophobic plasticizer did not affect significantly either the permeation rate or the time lag. CHP films plasticized with glycerol could therefore be used in coating processes for the design of gastro-resistant delivery dosage forms.

Introduction

The importance and pharmaceutical applicability of polymer films are well established in providing protective coatings and controlling drug release from dosage forms. The main polymers used for film formation have been classified into 3 categories: gastrosoluble, enteric or gastro-resistant, and insoluble (Brossard, 1982). The characterization of these films is carried out using various experiments which enable the evaluation of the mechanical properties (Lefort des Ylouses, 1974), dissolution properties (Boisrame et al., 1979), and permeability to humidity, gas or various drugs (Rona and Le Perdriel, 1974; Gurny, 1976). Under specific experimental conditions the rate of molecular transport of drugs through a polymer film may be affected by the nature of the coating or casting solvent (Spitael and Kinget, 1977), and by inclusion of additives (plasticizers) in the film composition (Donbrow and Friedman, 1975).

Donbrow and Friedman (1974) have shown that the main factor in determining the suitability

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of a film for development of a sustained release preparation of the drug is the permeability of the the film to the drug. The release rate of medicinal substances from insoluble polymers depends mainly on the ability of the drug to permeate through the polymer. If the polymers are soluble in the digestive system, drug release rate is determined both by the permeability of the film and the rate of dissolution of the polymer in the gastro-intestinal tract, at different pH conditions (Stempel, 1966). Thus, the determination of the permeation rates through polymeric films and the resulting values of the permeability coefficient appears to be a simple method of providing predictable and controllable release rates of drugs in the design of a controlled release delivery system like microspheres or microcapsules (Fites et al., 1970; Alhaiquet et al., 1981).

For these reasons, films prepared from a new polymer, cellulose hydrogen phthalate (CHP), have been studied to evaluate their possible applications to produce coated forms (Dor et al., 1986). The solubility properties of CHP are similar to those of acetophthalate cellulose (a gastro-resistant polymer). The possible influence of plasticizer as a film component and the mechanical properties of the films were also examined.

CHP has been synthesized and kindly supplied by Prof. G. Levesque, U.A., C.N.R.S. 480, Laboratoires des composés Thioorganiques, I.S.M.R. de Caen, France.

Theophylline was selected as a model substance because of its wide use in controlled release dosage forms already marketed by various pharmaceutical companies.

Experimental

Materials

Solvents (acetone and ethanol) and glycerol (GLY) were purchased from Frutarom Laboratory Chemicals, Haifa, Israel. Dibutyl phthalate (DBP) was supplied by British Drug Houses Ltd., Laboratory Chemicals Division, Poole, U.K. Theophylline conformed to USP.

Film preparation

The films containing different proportions of plasticizers (either glycerol or DBP) were cast from an acetone-ethanol (7 : 3 v/v) solution comprising 25% (w/v) film-forming agent on glass plates, using the technique of Kanig and Goodman (1962). The plasticizers were added at the following concentrations: 10, 15, 20, 30, 50 and 70% (w/w of the total solids) in the casting solution. After allowing the solvent to evaporate for 24 h, the film was removed from the plate without difficulty by immersion in distilled water and subsequently air dried for an additional 24 h.

Determination of film thickness

The thickness of each disk-shaped dry film was measured in 5 places by means of a Tesa master micrometer (Tesa, Switzerland). The measured thickness did not vary by more than 0.5% over the film surface.

Mechanical and thermal properties

The mechanical properties studied were:

(a) tensile strength, σ, which is a measure of the stress required to break the film;
(b) tensile modulus, E, which is a measure of the stiffness of the film; and
(c) fracture energy, γ, determined by the tear test, which is a measure of the resistance of the film to tearing (this test was applied only to the glycerol films).

For the mechanical property measurements, two film thicknesses for each plasticizer were studied. The plasticizers were used at 50% concentrations. Due to the brittleness of the films, sample preparation was difficult. Cutting the films to the proper size introduced defects in the edges of the specimens. This problem was effectively solved by cutting the films while they were still wet with solvent.

In principle, the fracture energy is a true material property, independent of the specimen geometry and test configuration, and is therefore a more fundamental measure of strength than the tensile strength (Marom et al., 1977).

The mechanical properties were measured on an Instron tensile testing machine. The specimens were conditioned for about one day at ambient conditions. For the tensile strength and tensile modulus, the test conditions are given in Table 1.

TABLE 1

TEST CONDITIONS FOR MECHANICAL CHARACTERIZATION OF THE CHP PLASTICIZED FILMS

For explanation, see text in the Experimental section.

Plasticizer	Thickness (μm)	Gauge length (cm)	CHS (cm/min)	Nominal strain rate (min^{-1})
Gly	23	5	0.5	0.1
Gly	59	5(10)	0.5(1)	0.1(0.1)
DBP	25	5(10)	0.05(0.1)	0.01(0.01)
DBP	62	5(10)	0.05(0.1)	0.01(0.01)

The numbers in parentheses in Table 1 are alternate gauge lengths, cross-head speeds (CHS) and nominal strain rates that were used in preliminary tests to investigate the effect of gauge length on the results. Approximately 15–20 specimens were used for each film, for the primary gauge length (5 cm).

For the tear test (glycerol specimens only), the "trouser leg" specimen configuration was used (Marom et al., 1977; Peppas, 1977; Ahagon and Gent, 1975). (The DBP films were too brittle to perform a tear test on.) The specimen dimensions were 7 cm × 2 cm × t, where t is the film thickness. A slit 5 cm long was inserted along the center line of the specimen. The CHS was 5 cm/min. The fracture energy, γ, was calculated from $\gamma = f/t$, where f is the average force required to propagate the tear.

The glass transition temperatures (T_g) of the polymer films were determined by differential scanning calorimetry (DSC). A Mettler TA3000 system, equipped with a TC10A microprocessor and DSC30 attachment, was used. Approximately 2 mg of material were placed in an aluminum pan, which was then sealed. A hole had been previously punched in the pan lid. A nitrogen flow of 60 cm^3/min was maintained during the measurements. A scanning rate of 10°K/min was used for all the experiments. The materials with glycerol were scanned from −110 to 100°C, and the specimens with DBP were scanned from −150 to 100°C. The neat film was scanned from −110 to 100°C. The T_g was taken as the midpoint of the transition.

Sorption studies

Solutions of theophylline were used at 3 concentrations: 0.05, 0.01 and 0.005 M. Samples of CHP powder and plasticized CHP films weighing 30 mg (±0.05 mg) were added to 20 ml of the test solution and placed in a thermostatically controlled room at 37°C. The experiments were continued until equilibrium, i.e., until sorption by the film was complete, as shown by the absence of any further decrease in the drug concentration in solution.

Determination of diffusion rate through the film

Disk-shaped specimens 12.56 cm^2 in area were cut from the larger films, but only 11.34 cm^2 was in contact with the drug solution. The membrane was placed between two halves of a diffusion cell holding a volume of 56.6 ml of liquid (tubes and half-cell). One compartment of the cell contained the drug solution and was in contact with the air face surface of the film, and the other compartment contained distilled water. Both compartments were previously warmed to 37°C. Circulation of the solutions in the cells was performed with a peristaltic pump (Watson–Marlow) operated at a flow rate of 31 ml/min. Temperature was controlled at 37°C. At suitable intervals, the concentration of theophylline which had diffused into the water through the film was measured spectrophotometrically at 272 nm. The spectrophotometer (LKB Biochrom 4073-200 serial interface) was coupled with an Apple II computer using LKB Biochrom Ltd., DOS 3.3 program which read and stored the optical density readings. Measurements were continued for 10 h and experiments were at least duplicated; reproducibility was within 3–6% of the mean. For the diffusion experiments the theophylline concentration used in the donor compartment was 0.05 M.

Theory of permeation

Drug transport through a polymeric film may be characterized under steady-state conditions by means of Fick's first law which can be expressed as:

$$\frac{dQ}{dt} = P \cdot A \cdot \frac{C_2 - C_1}{l} \qquad (1)$$

where Q is the cumulative amount of drug that has penetrated in time t through a surface of area A, C_2 and C_1 are the concentrations of the drug in the permeating and sink solutions respectively, l is the thickness of the membrane and P is the permeability constant. P is a measure of the transfer rate of a specific drug from bulk solution on one side of the membrane to bulk solution on the other side, through unit thickness and area of a specific membrane. This equation has been verified in numerous investigations by various authors (Fites et al., 1970; Donbrow and Friedman, 1974 and 1975).

Under the experimental conditions used, C_2 is in excess, and thus integrating Eqn. 1 yields:

$$Q = \frac{P \cdot A \cdot C_2}{l} \cdot t \qquad (2)$$

The plot of the drug concentration transferred against time produces a straight line, the slope of which gives the permeation rate according to:

$$\frac{dC}{dt} = \frac{P \cdot A \cdot C_2}{l \cdot V} \qquad (3)$$

where V is the sink solution volume, and dC/dt is the slope of the linear relationship. Slopes were calculated by the least squares method from the results of the permeability experiments.
The relation,

$$P = D \cdot S \qquad (4)$$

where D is the diffusion coefficient of the drug within the membrane and S is the membrane–solution partition coefficient or the solubility coefficient was originally developed by Barrer (1939). Henry's law for gas permeation of polymer membranes was also found to be applicable to diffusion processes of some drugs through polymers (Donbrow and Friedman, 1975; Gurny, 1976; Donbrow and Benita, 1982). Although these authors reported that it was difficult in practice to apply Eqn. 4 to complex systems owing to deviations from ideal conditions, it was decided in the present study to make an attempt to calculate D using Eqn. 4 and to compare the values obtained to those calculated from the time lag measurements according to the following equation:

$$D = l^2/6L \qquad (5)$$

where D is the diffusion coefficient in the film, l is the thickness of the film and L is the time lag intercept obtained by extrapolation of the steady-state slope to the time axis of the permeation plot. The permeation data were then used to calculate the diffusion coefficient in the membrane according to Eqns. 3 and 4 (Tanquary and Lacey, 1974).

Results and Discussion

Permeability results

For evaluation of diffusion coefficients of theophylline in CHP films, the solubility of the drug in the film was required. It was measured by sorption using the technique previously reported by Donbrow and Friedman (1975) and the solubility coefficient of theophylline for CHP-water was calculated according to the equation:

$$S = C_s/C_1 \qquad (6)$$

where S is the solubility coefficient, C_s is the equilibrium concentration of the drug in the CHP phase and C_1 is the equilibrium concentration of the drug in the aqueous phase. The results of sorption studies indicated that the variation in plasticizer content from 10 to 70% had practically no influence on the solubility coefficient, which remained constant at 37 ± 3 and 12 ± 3 for DBP and glycerol, respectively. These results indicate that the solubility of theophylline is very low and unfortunately cannot be exploited for comparison purposes between Eqns. 4 and 5, because of a lack of sensitivity of the experimental methods used.

The initial attempts to prepare films based on pure polymer failed. The cast films were brittle and broke easily upon handling. It was then decided to use various plasticizers. Two categories of plasticizers were tested, differentiated mainly by their aqueous solubility (hydrophilic and hydrophobic plasticizers). It should be pointed out that the diffusion of theophylline through various films obeys Fick's first law according to Eqn. 3

since an apparent zero-order equation was observed; for example, the linear relationship between Q and t resulted from diffusion experiments using films containing various glycerol concentrations, as shown in Fig. 1.

Increasing the concentration of the hydrophilic plasticizer (glycerol) in the film enhanced the permeation rate (Table 2) and reduced the time lag whereas the concentrations of the hydrophobic plasticizer (DBP) did not significantly affect either the time lag or the permeation rate (Figs. 2 and 3). It was also interesting to note that at lower plasticizer concentrations (less than 20%), the permeability constant values were higher for DBP than for glycerol. This could be attributed to the structure as detected by scanning electron microscope (SEM) observations (Figs. 4 and 5) which indicate that the film containing 15% DBP is probably less glassy than the film containing glycerol prepared under identical experimental conditions. However, glycerol appeared to be a more effective plasticizer as reflected by the higher permeability constant values obtained in the diffusion experiments while the concentration variation of DBP did not affect significantly the structure of the film as suggested by the lack of influence on the kinetic parameter values (Fig. 3). This was also supported by the results yielded in the differential scanning calorimetry experiments (see later). This would, therefore, explain the difference in the permeability behavior between the DBP and glycerol plasticized films. In spite of the fact that glycerol was water soluble no difference in the morphological aspect of the film was observed after immersion for 24 h in water (Fig. 5A). However, at high concentration (50%), several large pores were detected, probably formed after leaching out of the dissolved glycerol (Fig. 5B). With an increase in porosity, the void volume would be expected to be occupied by external solvent diffusing into the film. This would promote rapid diffusion of the drug molecule through the film and would reduce the time lag as observed in Fig. 3. Another reasonable explanation for the elevation of the release rates with increasing hydrophilic plasticizer concentration could be the swelling of this type of membrane in water as a function of the nature and concentration of plasticizer which might also influence the permeability of the membrane to the drug.

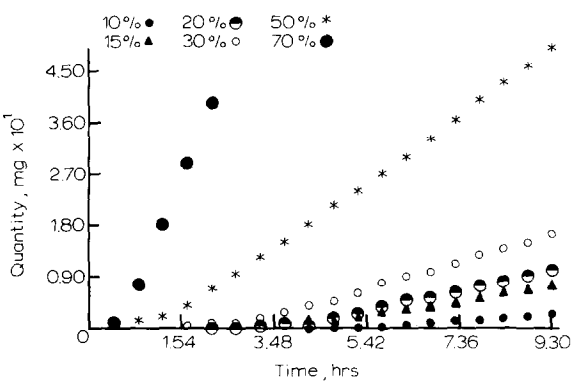


Fig. 1. Influence of the glycerol concentration on theophylline diffusion through CHP films.

TABLE 2

CELLULOSE HYDROGEN PHTHALATE FILM COMPOSITIONS [a] AND PERMEATION CONSTANTS

Plasticizer	% Plasticizer in film (w/w)	Thickness [b] (μm)	Permeation constant ($cm^2/s \times 10^{10}$)
Dibutyl phthalate	10	25.20	1.93
	15	27.00	1.61
	20	28.40	1.59
	30	30.80	1.43
	50	32.20	1.74
	70	33.00	1.97
Glycerol	10	23.00	0.40
	15	23.40	0.89
	20	24.60	1.18
	30	25.60	1.16
	50	26.20	4.14
	70	29.20	14.94

[a] For all films, the CHP concentration was 25% (w/w) in acetone-ethanol (7:3, v/v).

[b] The thickness for each plasticizer concentration is determined by the average of 5 measurements per film sample on a minimum of 4 samples.

Mechanical characterization

The average results (including the standard deviations) of the mechanical property measurements are shown in Table 3. The tensile modulus values must be viewed with caution because they

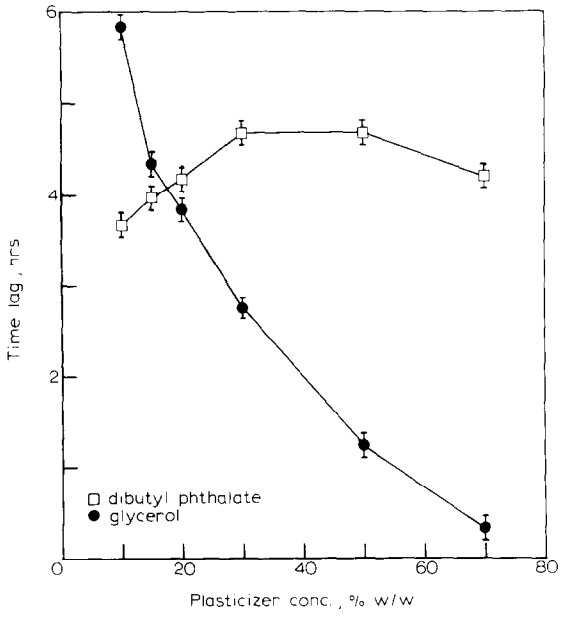


Fig. 2. Influence of the plasticizer concentration in CHP films on the time lag in theophylline diffusion experiments.

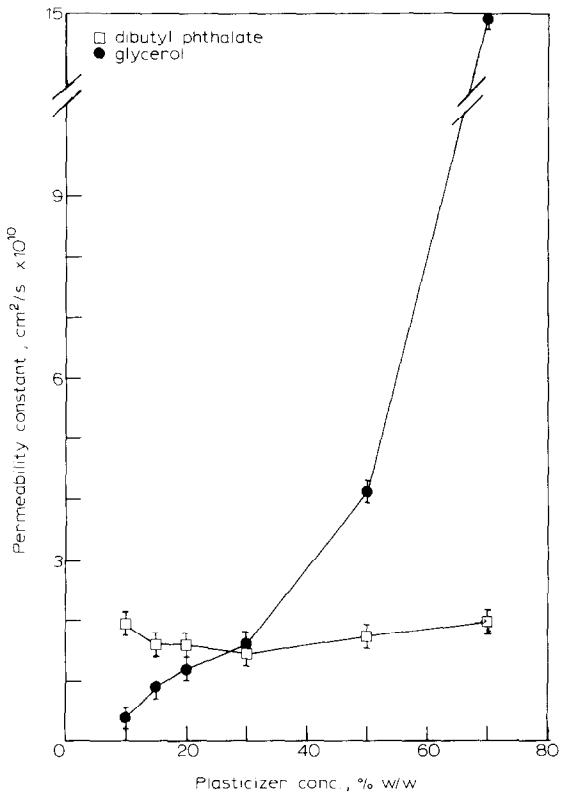


Fig. 3. Influence of the plasticizer concentration in CHP films on the permeability constant of theophylline.

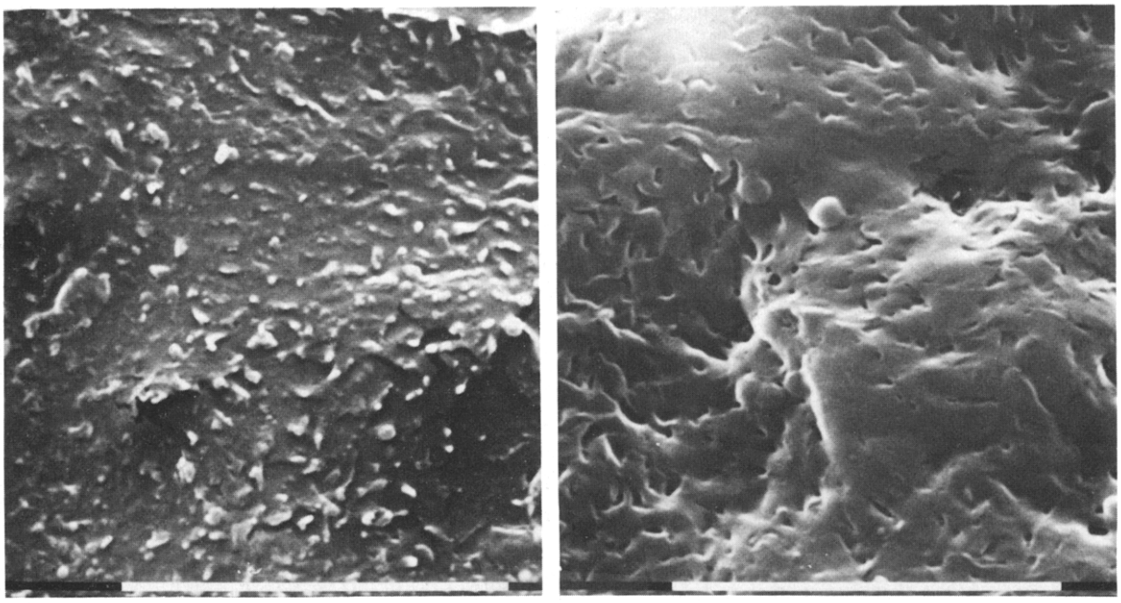


Fig. 4. Scanning electron photomicrographs of films. A, 15% DBP in dry CHP film; B, after 24 h water immersion.

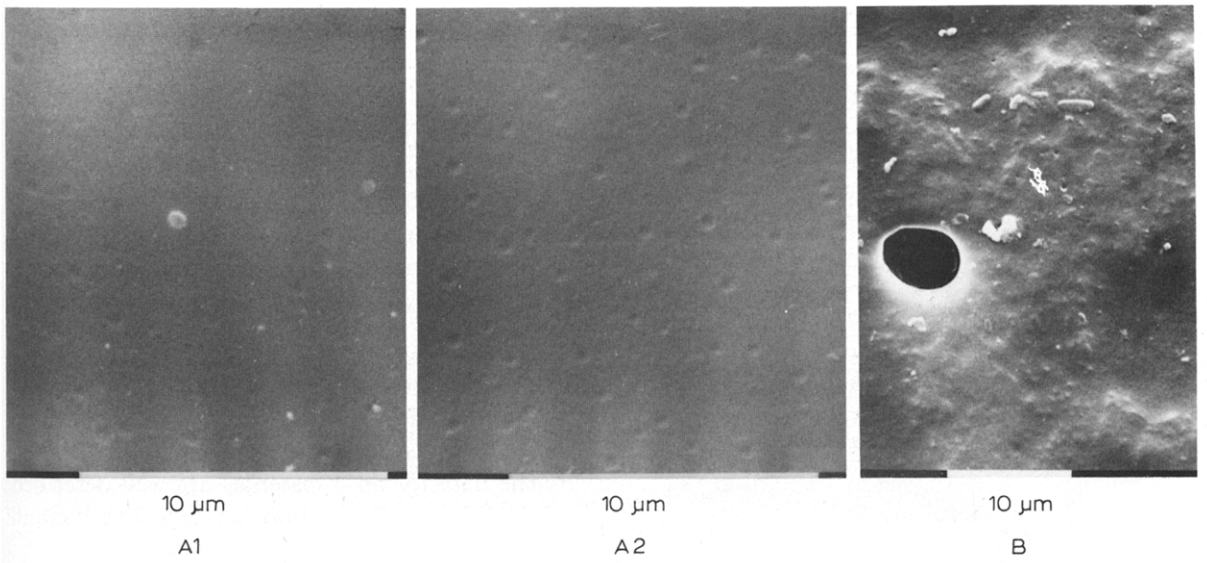


Fig. 5. Scanning electron photomicrographs of films. A1, 15% glycerol in dry CHP film; A2, after 24 h water immersion; B, 50% glycerol after leaching out of the hydrophilic component.

were determined from the load–time curve of the tensile testing machine. The numbers in parentheses represent values from the longer gauge lengths, and are the average of only a few specimens and hence the standard deviations are omitted. Several points should be noted. The mechanical properties are functions of film thickness and plasticizer and appear to be functions of gauge length. The DBP specimens have higher tensile strengths and moduli. The thinner specimens, for both materials, have higher tensile strengths and moduli, but, at least for glycerol, the thicker specimen is tougher, as measured by a higher value of γ. The 50% DBP, 25 μm material appears to be particularly sensitive to flaws, as noted by the high scatter in σ and the large difference in σ between the 5 and 10 cm gauge lengths. The extensibilities of all the films were very low, and are consistent with the general trend that the thicker films are more tough, less brittle than the thinner films and the glycerol films are tougher than the DBP films.

TABLE 3

MECHANICAL PROPERTIES OF THE CHP PLASTICIZED FILMS

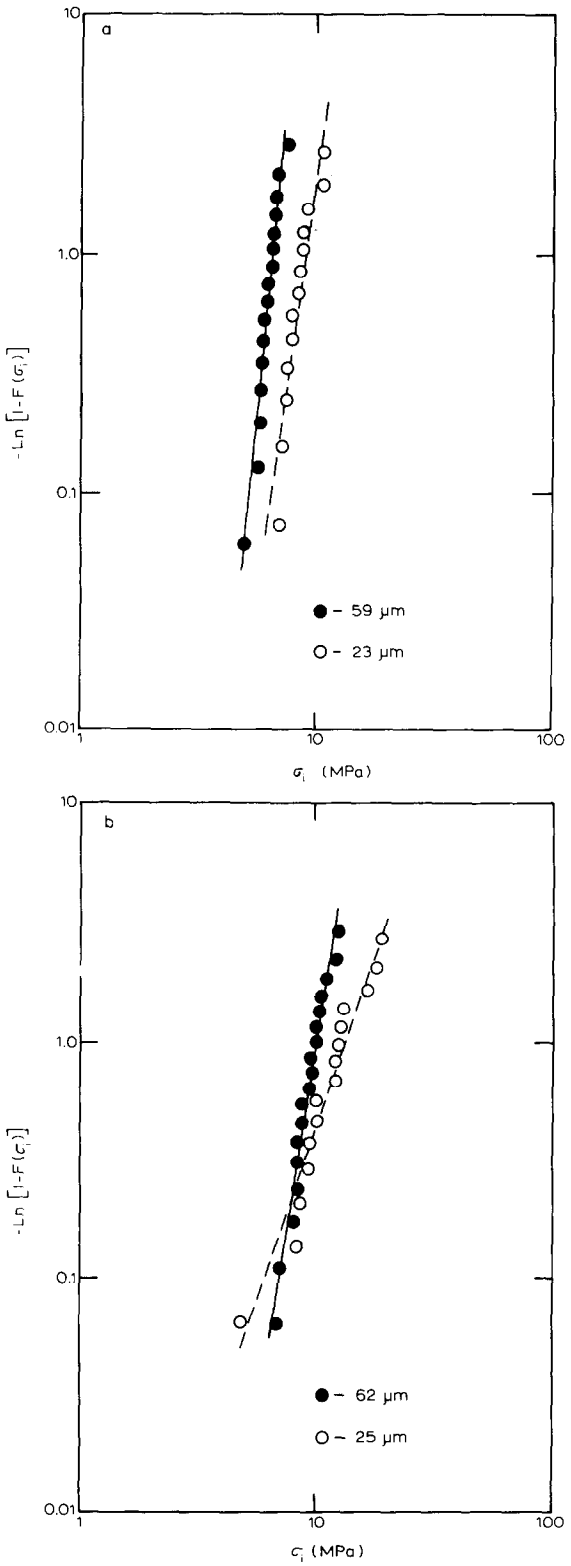
Plasticizer	Thickness (μm)	Tensile strength (MPa)	Tensile modulus (GPa)	Fracture energy (J/m^2)	Ultimate extension
Gly	23	8.5 ± 1.2	0.43 ± 0.07	310 ± 45	5%
Gly	59	6.2 ± 0.61 (5.9)	0.26 ± 0.02 (0.32)	850 ± 110	10%
DBP	25	11.9 ± 3.9 (5.0)	1.2 ± 0.1 (1.41)	–	1%
DBP	62	9.6 ± 1.6 (8.2)	1.05 (1.26)	–	1–2%

The measured tensile strengths of brittle solids are subject to large amounts of scatter which can be described by the Weibull distribution function (Hull, 1981; Chatfield, 1970). This distribution can be represented by,

$$F(\sigma) = 1 - \exp\left[-(\sigma/b)^a\right] \tag{7}$$

where $F(\sigma)$ is the cumulative failure probability, a is the Weibull shape parameter and b is the Weibull scale parameter; a is a measure of the scatter and b is a measure of the mean of the results. The smaller the value of a, the broader the distribution. From Eqn. 7,

$$1 - F(\sigma) = \exp\left[-\sigma/b)^a\right] \tag{8a}$$



$$-\ln[1 - F(\sigma)] = (\sigma/b)^a \tag{8b}$$

$$\ln(-\ln[1 - F(\sigma)]) = a \ln \sigma - a \ln b \tag{8c}$$

Thus, if the data can be represented by the Weibull distribution function, a plot of $\ln(-\ln[1 - F(\sigma)])$ vs $\ln \sigma$ should yield a straight line with slope a and intercept $-a \ln b$. The values of $F(\sigma)$ can be computed from (Chatfield, 1970)

$$F(\sigma_i) = i/(N + 1) \tag{9}$$

where N is the total number of experiment observations and σ_i is the ith tensile strength.

The results of the analysis are shown in Fig. 6a, b. The data for all 4 materials are well described by the Weibull distribution function. The Weibull parameters are summarized in Table 4.

The parameters a and b show clearly the larger scatter in the data for the DBP films (smaller a values) and the higher values of tensile strength for the DBP films (larger b values).

Differential scanning calorimetry

The results of the glass transition temperature (T_g) measurements are summarized in Fig. 7. Glycerol is a more effective plasticizer than DBP, as reflected in the lower transition temperatures of the glycerol-plasticized films. The permeability studies were conducted at 37°C, which is indicated by the horizontal dashed line in Fig. 7. Thus, the DBP films, which have T_gs above 37°C, are in the glassy state during the permeability experiments. The glycerol films, at the higher concentrations of plasticizer, have T_gs below 37°C; they are in the rubbery state during the tests. Since rubbery polymers are far more permeable than glassy polymers (Brydson, 1972), this may help explain the difference in the permeability behavior between the glycerol- and DBP-plasticized films. Also, at the lowest concentrations of plasticizer, where the glycerol and DBP films are in the glassy state, the difference in permeability may be explained by the difference in polarities

←

Fig. 6. Weibull distribution log–log plots of plasticized CHP films. a, 50% glycerol, 23 μm thick and 59 μm thick; b, 50% DBP, 25 μm thick and 62 μm thick.

TABLE 4

WEIBULL PARAMETERS OF THE CHP PLASTICIZED FILMS

a and b calculated according to Eqn. 8c.

Plasticizer	Thickness (μm)	a	b
Gly	23	7.21	9.03
Gly	59	10.30	6.51
DBP	25	2.95	13.46
DBP	62	6.63	10.19

between glycerol and DBP; permeability generally decreases with increasing polarity (Billmeyer, 1971).

In summary, the neat CHP films have low mechanical properties, and plasticizers are needed to improve these mechanical properties. DBP was found to be an ineffective plasticizer since it did not improve the mechanical or permeability properties of the CHP films. In view of the overall results reported in the present study, it appears that glycerol (above 20%) is an effective plasticizer in CHP film formulations. These plasticized films can be used in coating processes for the design of gastro-resistant delivery dosage forms.

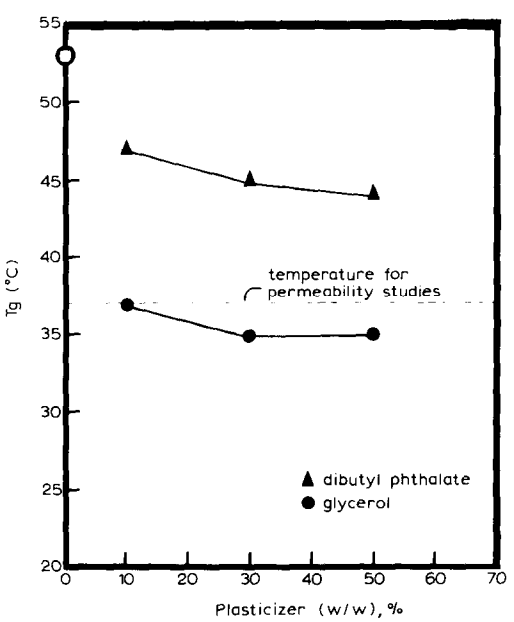


Fig. 7. Glass transition temperatures of plasticized CHP films as a function of plasticizer content.

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