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Influence of hydrophilic character of plasticizer and polymer on certain film properties

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Summary

Effect of plasticizer concentration on certain film properties: swelling, porosity and permeability, has been studied in films of two acrylate–methacrylate copolymers, A and B, differing only in hydrophilic quaternary ammonium content. It was found that the plasticizer (glycerol triacetate or glycerol tributyrate) content in both films cannot be varied beyond 16 ± 5% w/w of film weight if films suitable for handling and testing are to be produced. Mixing of the two analogous plasticizers offered a means of varying the content of individual plasticizer in the films whilst keeping the total amount and the general chemistry of it constant. Increase in the fraction of the more hydrophilic glycerol triacetate in the mixed plasticizer coupled with a decrease in the less hydrophilic glycerol tributyrate increased the urea permeability of the less hydrophilic films of polymer B; this was related to the leaching of glycerol triacetate which also resulted in enhancement of film porosity. In the more hydrophilic film of polymer A, urea permeability increased as the more hydrophilic glycerol triacetate fraction decreased and the less hydrophilic glycerol tributyrate fraction increased, a finding which was attributed to the potential of glycerol tributyrate for promoting film swelling and porosity. Permeability is therefore dependent on the hydrophilicity of both the plasticizer and polymer considered together.

Introduction

Polymer films find use as barriers in the design of controlled release devices. Whilst plasticizers are included in polymer films to prevent embrittlement they may cause modification of solute permeability, the extent of which is influenced by plasticizer concentration and its leaching from the film during permeation (Donbrow and Friedman, 1975). Thus plasticizer may be used to increase control of drug release from polymer films; Samuelov et al. (1979) have shown that drug release from ethyl cellulose films could be quantitatively related to the content of a water-leachable plasticizer, polyethylene glycol, in the film. Obviously, however, plasticizer concentration can only be varied within certain limits if serious impairment of necessary mechanical properties of the film, such as flexibility are to be avoided. Preliminary studies showed that cast films of certain cationic acrylate–methacrylate copolymers having suitable flexibility for handling may only be produced when the plasticizer (e.g. glycerol triacetate) concentration is 16 ± 5% w/w of the film. The problem of studying plasticizer effects at a wider concentration range in such a system was approached by using a mixture of two analogous plasticizers, glycerol triacetate (gta) and the less hydrophilic glycerol tributyrate (gtb) at varying proportions whilst keeping total plasticizer concentration constant at 16% w/w of the film. Gta is slightly soluble in water and is rapidly leached whilst gtb is water-insoluble and poorly leached from the films during permeation; varying the proportions of gta and gtb in the mixed plasticizer therefore offers a means of varying the hydrophilic character of the mixed plasticizer and its leachability from the films during permeation. Whereas a primary objective of this work was to procure enhancement of film permeability by the inclusion of the water leachable gta, a preliminary study has shown that the inclusion of the poorly leached gtb in film composition could also enhance permeability but of hydrophilic films only (Okor and Anderson, 1979); the permeability-enhancing effect of plasticizer leaching thus becomes important only in less hydrophilic polymer films. In this work the basis for these plasticizer effects were explored.

Materials and methods

Materials

Glycerol triacetate and glycerol tributyrate (both reagent grade, BDH) were used as plasticizers. Two acrylate–methacrylate copolymers, designated A and B, were received under the trade names Eudragit RL 100 and RS 100, respectively, from Rhom Pharma, Darmstadt; the polymers differ only in their content of quaternary ammonium (cation) groups in a ratio of 2:1, A having 66 moles cation per mole of polymer chain whilst B has 33 moles per mole of polymer chain. The presence of the polar cationic groups confer hydrophilic properties on the polymers including water uptake and swelling in aqueous medium. Urea (Analar grade and 10% w/v solution in water) was used as solute permeant, and acetone (Analar) was used as solvent in film casting.

Film preparation and evaluation

Films (thickness 19.8 ± 0.3 and 39.4 ± 0.7 μm (±S.E.)) were prepared by casting on a PTFE mold from an acetone solution containing the polymer, 2.5% w/w and plasticizer, 0.5% w/w using the method of Abdel-Aziz et al. (1975). Film thickness was determined at 10 random points on the film and the mean thickness calculated.

Urea permeation rate through the films, (exposed film area, 23 cm^2 and thickness, 19.8 μm) was measured using the method of Abdel-Aziz et al. (1975). Films of polymers A and B containing pure gta, gtb and mixtures of gta and gtb in varying proportions were used for the study. With 10% urea solution (aq) in the donor compartment and water in the acceptor compartment, permeation experiment was conducted at 30 ± 0.05°C (films of polymer A) and at 37 ± 0.05°C (films of polymer B); no measurable permeation rate was obtained in films of polymer B at 30°C and films of polymer A swelled too rapidly and leaked at 37°C, hence the selection of the temperatures (30°C and 37°C) for the different studies. Film lower surface (in contact with substrate during film formation) was upstream in all experiments. The amount of urea transferred into the acceptor compartment was determined at time intervals for a maximum of 5 h using the spectrophotometric technique of Watt and Chrisp (1954). Each experiment was carried out in 4 replicates and the results were used to calculate the mean permeation rate; results were reproducible to ±6.5% of the mean.

The amount of water in the wet film (after contact with water, 30°C, 3 h) was obtained from the difference between the wet film weight and the film weight after drying at 70°C for 3 days to constant weight. The volume fraction of water, V, in the wet film was calculated using the formula:

$$V(\text{also the index of film porosity}) = \frac{1.0044(m - md)}{1.0044(m - md) + 0.8855md}$$

where m is the wet film weight, and md is the dried film weight, 1.0044 and 0.8855 are the specific volumes in $cm^3 \cdot g^{-1}$ of water and polymer, respectively, at 30°C determined by fluid displacement method in this laboratory.

Film swelling was expressed as the percentage increase in film volume after a film strip of dimensions: length 4.6 cm, width 1.3 cm and thickness 39.4×10^{-4} cm, had been in contact with water (30°C, 3 h) (time for maximal swelling). The percent increase in film volume was calculated from the observed increases in the film dimensions which were measured, the thickness with a digital micrometer, and the length and width with a pair of dividers.

The amount of plasticizer (gta or gtb) leached from the films under conditions of permeation experiments was determined by a method of gas-liquid chromatography (GLC). 1 μl of a solution or the plasticizer and internal standard, 0.02% glycerol diacetate (for gta determination), of 0.02% dibutyl phthalate (for gtb determination) was injected into a glass column (15.25 cm long and 0.625 cm o.d.) containing 1% silicone QF-1 (stationary phase) on chromosorb G, AW, DCMS, 80–100 mesh (supporting phase).

Gta determination was carried out at an oven temperature (200°C), detector (300°C), injection (290°C); gas flow rates, ($cm^3 \cdot s^{-1}$) were nitrogen (0.243), hydrogen (0.294), and air (2.660). Gtb was determined using the same conditions as for gta except that the detection temperature was increased to 350°C whilst the nitrogen flow rate was reduced to 0.141 $cm^3 \cdot s^{-1}$. The amounts of plasticizer in sample solutions were calculated from a calibration curve previously constructed using standard solutions of the plasticizer.

Results and discussion

The cumulative mass of urea transferred from donor to acceptor compartment fluid was plotted as a function of time for films containing various proportions of gta and gtb. Urea permeation rates, mg h^{-1} were calculated from the slopes of the linear (1–5 h) portions of the plots.

In the films of the more hydrophilic polymer A, urea permeation rate increased linearly as the fraction of the less hydrophilic gtb in the mixed plasticizer was increased, 0.2 to 1.0, and that of the more hydrophilic gta was decreased, 0.8 to 0 (Fig. 1). Assuming meanwhile, that the contribution of gta to the observed permeation rates was negligeable compared with the influence of gtb, permeability could be

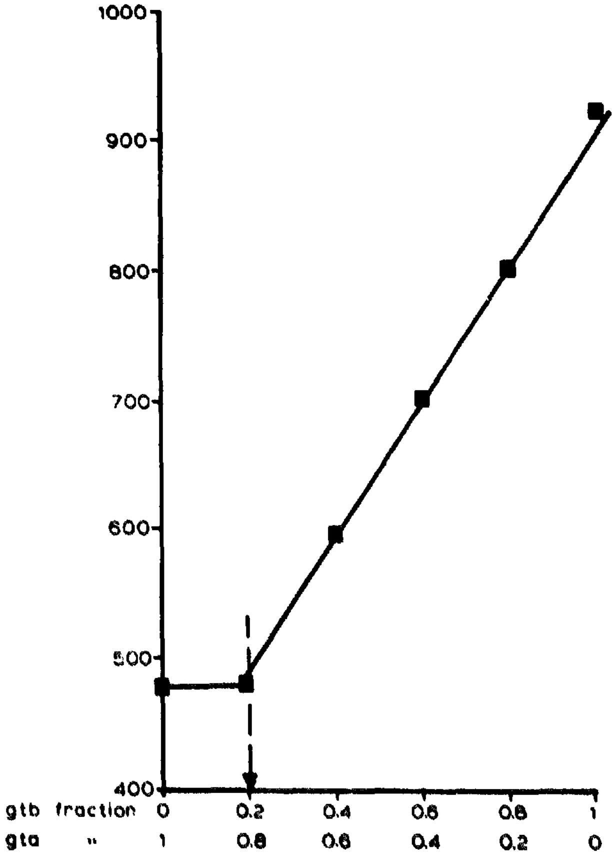

Fig. 1. Dependence of urea permeation rate (ordinate, $mg \cdot h^{-1}$) on plasticizer composition (abscissa: glycerol triacetate, gta and glycerol tributyrate, gtb fractions in mixed plasticizers consisting of gta and gtb) in films of polymer A.

correlated with gtb content in the film by the expression:

$$Ju = 480 + 500(f_{gtb} - 0.2) \tag{1}$$

where Ju is the urea permeation rate, $\mathrm{mg \cdot h^{-1}}$, and f_{gtb} is the fraction of gtb in the mixed plasticizer. The constants 480 $\mathrm{mg \cdot h^{-1}}$, and 500 $\mathrm{mg \cdot h^{-1}}$ were obtained from the y-intercept and slope, respectively, of the plot in Fig. 1.

The change in film permeability as plasticizer composition was varied depended on the hydrophilic character of the film-forming polymer; thus in the films of the less hydrophilic polymer B, urea permeation rate decreased exponentially as the fraction of gtb was increased and that of gta was decreased (Fig. 2). Film permeability now seems to depend mainly on gta content in the film, according to the relationship in Eqn. 4 as follows. From Fig. 2 the semi-logarithmic relationship between permeation rate and gta fraction is:

$$\log Ju = \log 0.159 + 2.0\,(f_{gta} - 0.17) \tag{2}$$

in the limits of f_{gta} (0.17–1.0); f_{gta} is the gta fraction in the mixed plasticizer. 0.159 and 2.0 were calculated from the y-intercept and the slope, respectively, of the graph

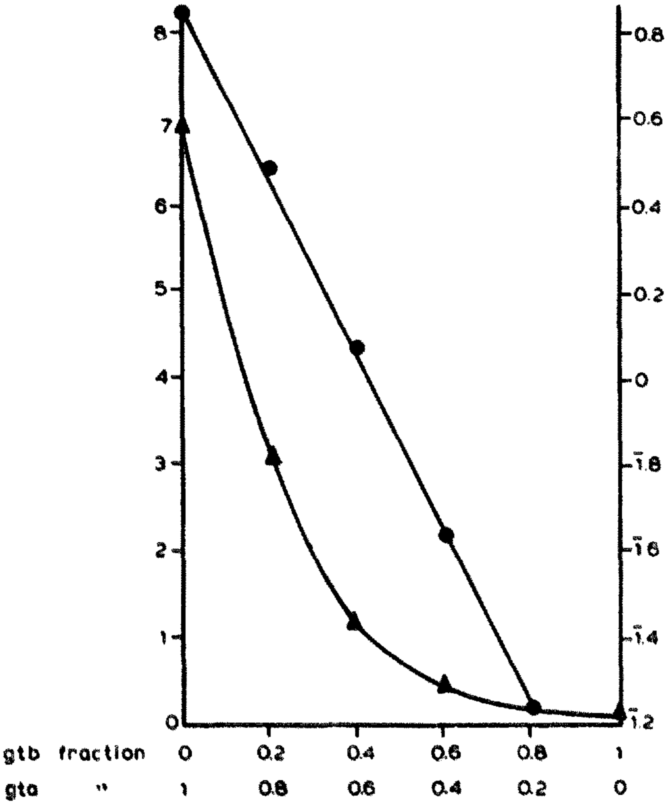

Fig. 2. Dependence of urea permeation rate, ▲ (left ordinate, $\mathrm{mg \cdot h^{-1}}$) and the logarithm of the rate, ● (right ordinate, log $\mathrm{mg \cdot h^{-1}}$) on plasticizer composition (abscissa) in films of polymer B.

(Fig. 2). Eqn. 2 may be re-written as:

$$0.43 \ln Ju = 0.43 \ln 0.159 + 2.0\left(f_{gta} - 0.17\right) \qquad (3)$$

a plot of ln Ju vs f_{gta} which therefore gives a slope of $2.0/0.43 = 4.7$ nearly, and hence the exponential dependence of permeation rate on gta fraction is given by:

$$Ju = 0.159 \cdot e^{4.7}\left(f_{gta} - 0.17\right) \qquad (4)$$

Thus the change in permeation rate in films of polymer B, as plasticizer composition was varied, occurred in a direction opposite to the corresponding change in films of polymer A. These effects of plasticizer on film permeability could be associated with plasticizer depletion or its retention and film-swelling during permeation, both leading to an increase in film porosity.

Plasticizer leaching and permeability

Rapid leaching of gta from the films occurs during permeation; for instance, about 97% of its initial amount, 0.016 g in the film was recovered in compartment fluids within the first 30 min of a 5 h permeation experiment (Table 1). Gta leaching might be expected to increase film porosity and fluid uptake during permeation and affect film permeability, since permeation through these films occurs mainly through fluid-filled channels or pores in the film structure (Abdel-Aziz et al., 1975). However, increase in porosity resulting from gta leaching was only seen in films of the

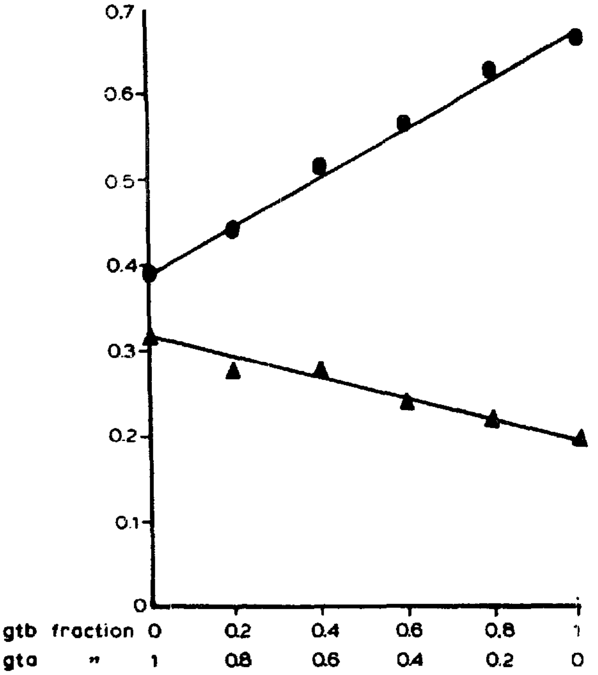

Fig. 3. Dependence of film porosity, i.e. volume fraction of water in the films after contact with water, 30°C, 3 h, (ordinate) on plasticizer composition (abscissa) in films of polymers A, ●; and B, ▲.

TABLE I

LEACHING OF GLYCEROL TRIACETATE (gta) AND GLYCEROL TRIBUTYRATE (gtb) FROM FILMS OF POLYMER A (39.4 μm THICK)

Sampling time (min)	Fraction of plasticizer leached	
	gta	gtb
10	0.81	0
30	0.97	0
60	0.97	0.31
120	-	0.31
180	-	0.36

The initial amount of plasticizer, gta or gtb, in this film (mean weight, 0.10 g) was 0.016 g.

less hydrophilic polymer B. In Fig. 3 it can be seen that the porosity of films of polymer B increased linearly as the gta fraction in the mixed plasticizer increased and gtb fraction decreased; thus the change in film porosity depended on gta fraction mainly.

The plot of porosity, V against gta fraction, f_{gta} (Fig. 3) gives the relationship

$$V = 0.20 + 0.12\,f_{gta} \qquad (5)$$

Inspection of Eqns. 4 and 5 show that the change in porosity and permeability with gta content were not parallel. The rapid increase in permeability with increasing gta

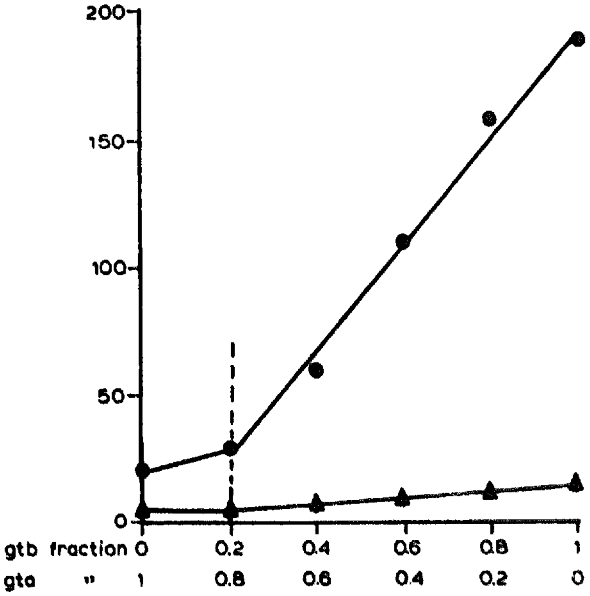

Fig. 4. Dependence of film swelling, i.e. percentage increase in film volume after contact with water, 30°C, 3 h (ordinate) on plasticizer composition (abscissa) in films of polymers A, ●; and B, ▲.

after a certain gta content, 0.6 has been reached (Fig. 2) suggests that enhancement of permeability following plasticizer depletion occurs only after a critial porosity of 0.25 (corresponding to 0.6 gta fraction) has been attained.

Film swelling and permeability

In films of polymer A the change in porosity as plasticizer composition varied was more closely associated with the gtb fraction, f_{gtb} (Fig. 3). The plot of V against f_{gtb} yields the relationship:

$$V = 0.39 + 0.30\, f_{gtb} \tag{6}$$

Now gtb is water-insoluble and therefore poorly leached from the film during permeation (Table 1); only 36% of its initial content in the film could be recovered in compartment fluids after 3 h. Thus the increase in porosity cannot be associated with gtb leaching. Now water has a plasticizing effect on polymer structures resulting in polymer film flexibility and swelling as water is imbided. The extent of film swelling will therefore depend on the polymer capacity for water uptake and the retention of plasticizer, e.g. gtb which contributes to the plasticizing effect of water.

Polymer B has only half the content of the hydrophilic cationic groups in polymer A, resulting in a lower water uptake potential in polymer B in comparison with polymer A. Experiments in this laboratory showed that polymer A potential for water uptake was 4 times greater than that of polymer B. Fewer cationic centres in polymer B also lead to greater polymer cohesiveness in the resulting films since the mutual repulsiveness of the cationic centres will tend to discourage polymer cohesion during film formation. Consequently the films of polymer A were generally more swellable than those of polymer B (Fig. 4). Gta undergoes rapid leaching and it will not contribute to film swelling which depended mainly on gtb content in the films; thus from Fig. 4 (films of polymer A):

$$S\% = 25 + 210\,(f_{gtb} - 0.2) \tag{7}$$

and for films of polymer B:

$$S\% = 5 + 13\,(f_{gtb} - 0.2) \tag{8}$$

where S% is the film swelling percent and f_{gtb} is the fraction of gtb in the mixed plasticizer. Eqns. 7 and 8 clearly indicate that the dependence of film swelling on gtb content (in the limits of f_{gtb}, 0.2–1.0) was about 16 times greater in films of polymer A than in the films of polymer B; hence the film swelling contributed significantly to the porosity and permeability of films of polymer A only. Thus each 0.1 in gtb fraction in the range 0.2–1.0 caused an increase in film swelling of 21%, film porosity of 0.03, and urea permeation rate of 50 $\text{mg} \cdot \text{h}^{-1}$. Further work is, however, required before a general correlation between film swelling, porosity and permeability can be established.

Previous studies (Donbrow and Friedmann, 1975) have demonstrated the linear dependence of permeability on the film content of a water-leachable plasticizer; in this study, however, an exponential relationship (Eqn. 4) was obtained for a similar polymer–plasticizer system suggesting that any relationship between permeability and content of a leachable plasticizer in a film will depend on concentration levels of plasticizer selected for study and the mechanism of permeation which are the basic differences in the previous and present studies. The results permit a conclusion that whilst the inclusion of a hydrophilic water-leachable plasticizer in a hydrophobic polymer film may be used to enhance permeability, similar enhancement may be achieved by the inclusion of a hydrophobic, poorly leached plasticizer in a hydrophilic porous polymer film, thus providing further means of obtaining control of drug release through polymer films.

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