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Studies on the physical properties of mixed pectin/ethylcellulose films intended for colonic drug delivery

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Abstract

The mechanical and permeability properties of mixed ethylcellulose/pectin films cast from dibutyl sebacate (DBS) plasticised aqueous dispersions of Aquacoat® and Pectin USP have been investigated. The films were subjected to tensile testing and the tensile strength (σ), work of failure, elongation at break, elastic modulus (E) and the σ/E ratio have been determined. Increasing concentrations of pectin imparted increasing brittleness and decreasing toughness to the films. Despite the inclusion of increasing quantities of the hydrophilic pectin into the films, the permeability to moisture remained essentially the same. The results imply that there is a limit to the amount of pectin that can be included in the coating material to still produce a satisfactory film, but the protective nature of the ethylcellulose to moisture is not compromised. © 1997 Elsevier Science B.V.

Keywords: Colonic delivery; Pectin; Ethylcellulose; Film coating; Mechanical properties

1. Introduction

One approach for colon specific drug delivery is the utilisation of materials which are degraded by the bacterial enzymes present in the large intestine (Van den Mooter and Kinget, 1995). This approach has been extended to the synthesis of novel hydrogel copolymers containing azo bonds (Van den Mooter et al., 1992). Once in the gastrointestinal tract (GIT), if these polymers afford the correct permeability properties, they swell and will pass intact into the colon where they are broken down by bacterial enzymes. Although of scientific value, these polymers would require intensive toxicity testing before being approved for commercial use.

Pectin, a polysaccharide which forms an integral part of plant cell walls, is also susceptible to

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Table 1
The formulation details of the four different ethylcellulose/pectin films

	Formulation			
	1	2	3	4
Weight of Aquacoat® (g)	23.88	22.69	21.50	19.10
Equivalent weight of ethylcellulose (g)	6.40	6.08	5.76	5.12
Weight of DBS (g)	1.60	1.60	1.60	1.60
Conc. of DBS (%w/w)	20.0	20.0	20.0	20.0
Weight of 1% w/w pectin USP solution (g)	0	32.0	64.0	128.0
Equivalent weight of pectin USP (g)	0	0.32	0.64	1.28
Ethylcellulose/pectin ratio	100:0	95:5	90:10	80:20

colon specific bacterial enzyme degradation. It has further potential as a pharmaceutical excipient as it is available as a USP grade material and forms gels which retard drug release. The potential of pectin for colonic drug delivery has been shown by Rubinstein et al. (1993), Rubinstein and Radai (1995) who investigated calcium pectinate matrices and Ashford et al. (1993, 1994) who investigated compression coated pectin based systems.

The combination of a material which is degraded specifically by colonic bacterial enzymes with a film former has been investigated recently by Milojevic et al. (1996a,b) who looked at the combination of amylose with ethylcellulose and Eudragit®. Vervoort and Kinget (1996) also showed promising results combining an insoluble, highly polymerised, inulin with Eudragit RS®. Wakerley et al. (1996) combined Pectin USP with the commercially available ethylcellulose aqueous dispersion, Surelease®. The resultant coated tablets showed potential for colon specific delivery when tested in vitro.

The aim of this paper is to investigate the suitability, in terms of mechanical and permeability properties, of mixed pectin/ethylcellulose films intended as pharmaceutical coatings for colonic drug delivery. The influence of coalescence time and storage conditions on tensile properties was determined using load-time profiles of the films. Such an investigation will show whether pectin and ethylcellulose can be successfully combined in a pharmaceutical film of suitable elasticity, toughness, and permeability.

2. Materials and methods

2.1. Materials

The ethylcellulose aqueous dispersion used was Aquacoat® which was supplied as a gift from the F.M.C. Corporation, Newark, USA. Dibutyl Sebacate (DBS) was supplied by Acros Organics, New Jersey, USA. The sodium chloride was reagent grade and supplied by B.D.H., Poole, UK. The Pectin USP used was supplied as a gift from Citrus Colloids, Hereford, UK. For the permeability work, the Yellow Soft Paraffin was supplied by Hillcross Pharmaceuticals, Burnley, UK., the Beeswax B.P. by Evans, Speke, UK and the silica gel by B.D.H., Poole, UK.

2.2. Methods

2.2.1. Film preparation

A quantity of Aquacoat® ECD30 (Table 1) was added to 1.60 g DBS and mixed using a magnetic flea and stirrer. The materials were stirred for 5 h. After 5 h, it was noted that there were no oily droplets present in the dispersion indicating that the plasticiser had partitioned into the polymer phase. The required quantity of 1% w/w pectin solution (Table 1) was then added and stirring continued for a further 30 min. The dispersions were added to rectangular Teflon moulds (26 × 16 cm) and placed in a levelled preheated oven set at 70°C. After the desired coalescence time (16 or 65 h) the films were removed from the moulds using a sharp knife. Strips of film were cut ensuring that

no nicks or tears, which may have caused premature failure in any subsequent tensile test, were introduced. Six initial strips, 80×10 mm in dimension, were cut followed by six further strips of equal dimensions cut perpendicularly to the initial six. The samples were checked to ensure freedom from air bubbles or other imperfections. The thickness of each sample was measured using a micrometer. If the S.D. of the five thickness measurements was greater than 10% of the mean thickness the samples were not included for testing. All samples had mean thicknesses in the range 100–200 μm. The samples were then stored at room temperature in desiccators containing either a saturated solution of sodium chloride (75% RH) or silica gel. Samples were maintained at these conditions for at least 1 week prior to testing.

2.2.2. Tensile testing

The mechanical properties of each test strip was evaluated using a Howden Universal Testing Machine fitted with a 500 N load cell. The technique used was based on the A.S.T.M. D638-89 (A.S.T.M., 1992) test method. Each test strip was clamped onto a metal flat faced grip after first attaching a small piece of fabric Elastoplast® to the metal grip via double-sided tape. The gauge distance was kept constant for each test at 50 mm. The cross-head speed for each test (strain rate) was set at 5 mm/min and the X–Y chart speed set at 2 mm/s. Results from samples which failed at and not between the metal grips were not included in any subsequent calculations. Tensile strength, elastic modulus, elongation at break and work of failure were calculated as below:

Tensile Strength (MPa)

$$= \frac{\text{Maximum force applied during the test (N)}}{\text{Initial cross} - \text{sectional area of the sample (mm}^2\text{)}}$$

Elastic Modulus (MPa)

$$= \frac{\text{Force at corresponding strain (N)}}{\text{Cross} - \text{sectional area (mm}^2\text{)}} \times \frac{1}{\text{Corresponding strain}}$$

Elongation at Break (%/mm^2)

$$= \frac{\text{Increase in length (mm)}}{\text{Original length (mm)}} \times \frac{100}{\text{Cross} - \text{sectional area (mm}^2\text{)}}$$

Work of Failure (kJ/m^2)

$$= \frac{\text{A.U.C. (N.s)} \times \text{cross} - \text{head speed (mm/s)}}{\text{Sample cross} - \text{sectional area (mm}^2\text{)}}$$

2.2.3. Permeability testing

Circular pieces of test film, 3.5 cm in diameter, free from air bubbles or other imperfections were cut from areas of each film sheet. The dimensions of each film sample were measured. Five thickness measurements were taken at evenly dispersed points on the samples. If the S.D. of the five thickness measurements was greater than 10% of the mean thickness the samples were not tested. All samples tested had thicknesses in the range 0.10–0.17 mm. The samples were stored in a sealed desiccator with a saturated solution of sodium chloride (to give an RH of 75%) for at least 1 week prior to testing.

The permeability test was based on the A.S.T.M. standard test method for water vapour transmission of materials (Dry Cup Method). (A.S.T.M., 1993). Recently dried silica gel was used as the desiccant and a 50:50 mixture of Yellow Soft Paraffin/Beeswax B.P. as the sealant. The containers were stored in sealed desiccators maintained at a constant temperature of 23.8 ± 1.0°C and a humidity of 75% RH. The sample containers were weighed at 24-h intervals and plots of weight gain against time constructed. Once steady state conditions had been achieved for four consecutive weighings, the experiment was stopped. The permeability constant (P) for the films was calculated as below:

$$P = R_{wvt} \times t$$

where P is the permeability constant (mg/h/mm per kPa) and t is the film thickness (cm) and

$$R_{wvt} = W/A.\Delta P$$

where R_{wvt} = water vapour transmission rate (mg/h/mm^2 per kPa); W = amount of moisture transmitted through the film (mg/h), i.e. the slope of the weight gain versus time plot. A = area of exposed film (mm^2); and ΔP = the water vapour pressure difference across the film (kPa).

3. Results and discussion

The formulation and processing conditions for the preparation of the films was chosen to optimise film properties. Arwidsson et al. (1991) and Parikh et al. (1993) have both shown that 70°C was the optimum temperature for the production of ethylcellulose films with maximum tensile strength, elastic modulus and work of failure. Bodmeier and Paeratakul (1994) found water insoluble plasticisers such as DBS gave more ductile films due to better partitioning into the polymer phase and that concentrations above 20% gave little increase in the plasticiser concentration in the polymer phase regardless of the mixing time. The mixing time of the plasticiser required to obtain sufficient partitioning and suitably ductile films, i.e. 5 h, is similar to that of Lippold et al. (1990).

In terms of mechanical properties, an ideal film for coating should have a high tensile strength, a large elongation at break and a high elastic modulus. Such films will be hard and tough without being brittle (Aulton, 1995). Fig. 1 shows the influence of pectin concentration, coalescence time and storage relative humidity on the tensile strength of the films. Pectin concentration and coalescence time has little effect, whereas the tensile strength of the films is higher when stored at low humidity. It is difficult to compare tensile strength results between different groups of workers because of differences in both film preparation and testing methods. Hutchings et al. (1994) obtained similar values of tensile strength for sprayed films of ethylcellulose plasticised with DBS whereas Obara and McGinity (1994, 1995) obtained considerably higher values.

Fig. 2 shows the influence of pectin concentration on the elastic modulus. Film coalescence is clearly complete at 16 h. Increasing the pectin concentration increases the elastic modulus which is further increased by storage at low humidity. This is consistent with further plasticisation of the films by water in a similar manner to the H.P.M.C. films examined by Aulton et al. (1981).

Rowe (1983) hypothesised that data from tensile testing of free films could be used not only comparatively during film formulation development but also to predict the incidence of coating defects during processing. In particular, the ratio of tensile strength to elastic modulus (σ/E) was a valuable tool with high values preferable for film formulations as these were indicative of fewer process related problems. Fig. 3 shows that increasing pectin concentration is associated with a decrease in the σ/E ratio. Thus the inclusion of pectin may lead to processing becoming more problematic as the pectin concentration is increased although actual process data would be required to establish whether this was indeed the case.

Fig. 4 shows that the work of failure to break the films decreases as the concentration of pectin in the films increases. Work of failure is representative of film toughness, hence this decreases with the inclusion of pectin, although it is largely unaffected by storage humidity. This is similar to the findings of Aulton et al. (1984) examining films containing solid inclusions. They found that al-

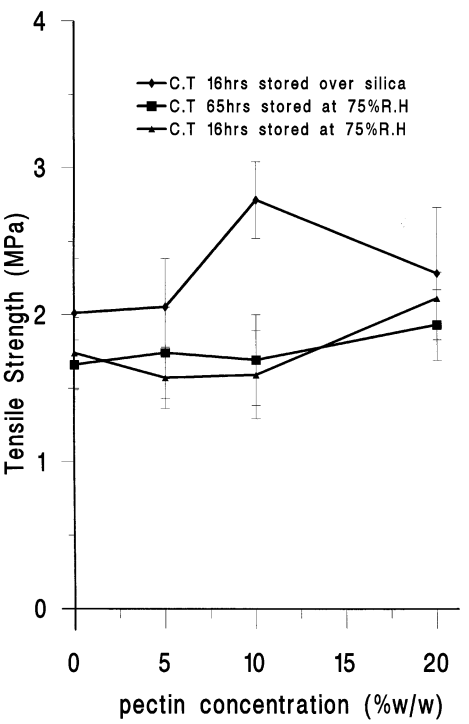

Fig. 1. The influence of pectin concentration on the tensile strength of mixed films. CT, coalescence time ($n = 6$).

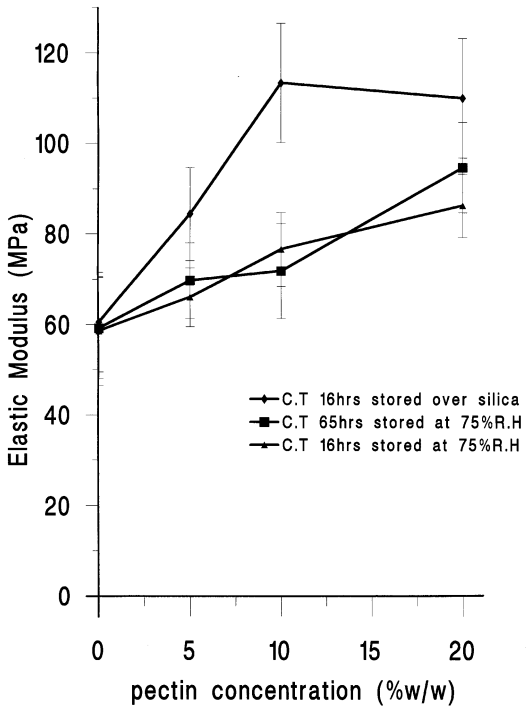

Fig. 2. The influence of pectin concentration on the elastic modulus of mixed films. CT, coalescence time ($n = 6$).

though the shape of the stress, strain curve changed on storage at different humidities, the toughness was largely unaffected.

Elongation at break (corrected for varying film thickness) decreases with increasing pectin concentration for these mixed ethylcellulose/pectin films (Fig. 5). Elongation at break is a measure of the ductility of a film and elongation can be regarded as a characteristic which defines the ability of a film to deform before failure occurs. Low values for elongation at break imply brittleness in the film. So, as the percentage of pectin in the film increases it is less capable of deforming to allow elongation. Okhamafe and York (1984) hypothesised that for films including fillers, failure was brought about in one of two ways. Either solid particles, such as titanium dioxide, caused excessive stress concentration, or a filler–polymer interaction caused a reduction in the mobility of the polymer chains (this was shown by increased values for Elastic Modulus). Since pectin is not present as a solid in the mixed films it is unlikely to cause excessive stress concentrations in a manner similar to titanium dioxide. Therefore it may be that pectin acts by reducing polymer chain deformation capacity by affecting polymer chain mobility.

The passage of water vapour through free films is described by Fick's Law (Kanig and Goodman, 1962). However for many films Fick's law may not apply. Kanig and Goodman (1962) and Patel et al. (1964) showed that for many cellulosic films, water vapour permeation varied according to film thickness. It was only with more lipophilic systems such as the butyl methacrylate films tested by Banker et al. (1966) that Fick's law was applicable. Deviations from Fick's law are caused by water sorption into the film via the formation of hydrogen bonding between the water and the hydrophilic region of the polymer. Hence in thicker films it is more likely that sorption will occur and therefore Fick's law will not apply.

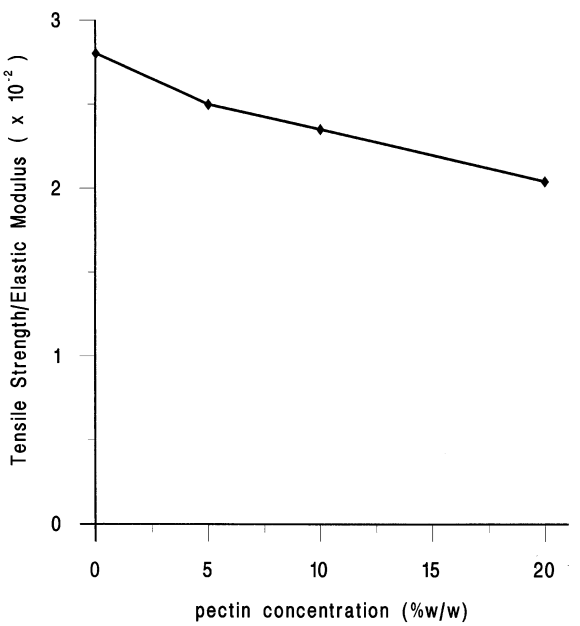

Fig. 3. The influence of pectin concentration on tensile strength to elastic modulus ratio (σ/E) for films stored at 75% RH ($n = 6$).

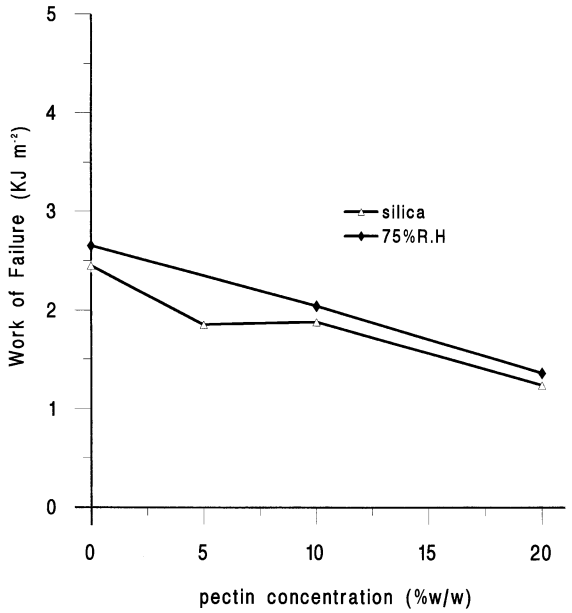

Fig. 4. The influence of pectin concentration on the work of failure of mixed films ($n = 6$).

Fig. 6 shows that for a mixed 95:5 ethylcellulose/pectin film in the thickness range 100–170 μm, Fick's law is applicable. Similar results were

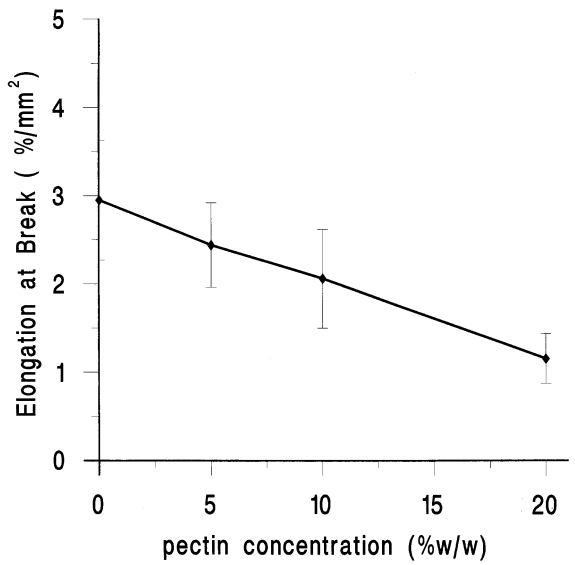

Fig. 5. The influence of pectin concentration on the elongation at break for mixed films stored over silica gel ($n = 6$).

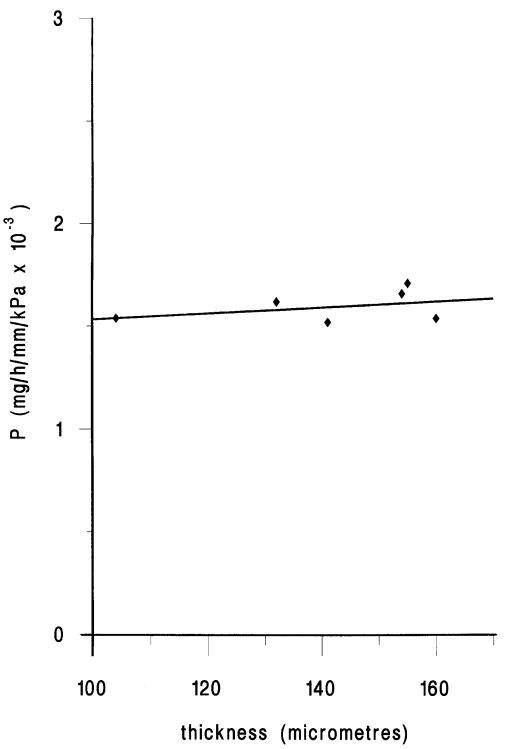

Fig. 6. The relation between the permeability coefficient and film thickness for 95:5 ethylcellulose/pectin films ($n = 5$).

obtained for other compositions of the mixed films. Therefore it is reasonable to compare results obtained for the permeability constant (P) of the different film compositions even though they varied somewhat in thickness.

Fig. 7 shows the relationship between the permeability constant and pectin concentration.

The addition of pectin does not greatly affect the permeability constant of the ethylcellulose films. It may have been expected that the addition of the more hydrophilic pectin to ethylcellulose would result in an increased permeability through the films. However, from the earlier tensile testing results, it would appear that the combination of ethylcellulose with pectin has a marked influence on the mobility/nature of the ethylcellulose chains. The addition of pectin, which has the ability to hydrogen bond, may interact with the ethylcellulose, and hence decrease the sites avail-

able for an ethylcellulose–water interaction. Thus, the expected increase in permeability constant does not occur.

4. Conclusions

The results from the tensile and permeability testing of mixed ethylcellulose/pectin films suggest that an interaction between the two materials is occurring. Pectin in some way reduces ethylcellulose chain mobility and causes the mixed films to change from soft, tough films to hard, strong or even brittle ones. Hence the amount of pectin that can be incorporated into the ethylcellulose and still produce a viable film coat may be limited. The lack of change in the permeability of the films with the incorporation of pectin is a valuable asset, the protective effect of ethylcellulose in the upper GI tract not being compromised by the inclusion of pectin.

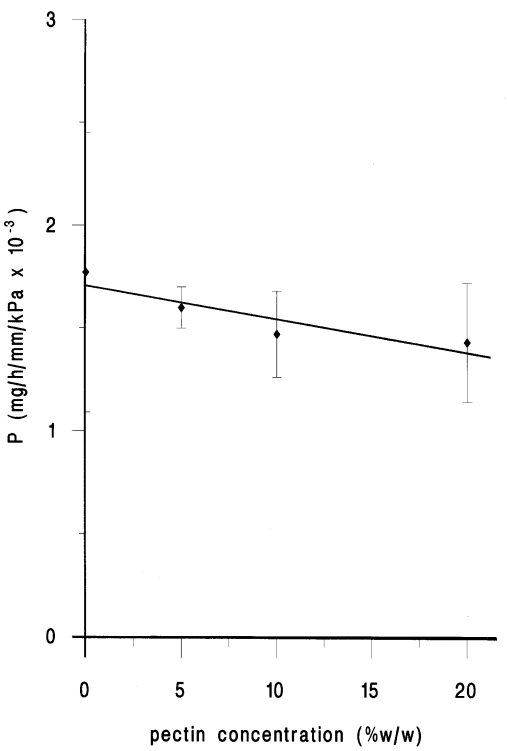

Fig. 7. The influence of pectin concentration on the permeability coefficient of mixed films ($n = 5$).

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