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The permeability of enteric coatings and the dissolution rates of coated tablets

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The effect of an increasing concentration of plasticizer and pigment on the permeability to both water vapour and simulated gastric juice of cellulose acetate phthalate and polyvinyl acetate phthalate has been evaluated. There were significant differences between the permeability coefficients of each polymer, particularly with regard to water vapour. The presence of additives within the film coatings had a greater effect on the properties of cellulose acetate phthalate than those of polyvinyl acetate phthalate. Suitable formulations of each polymer were used to enteric coat 325 mg aspirin tablets, which were subsequently subjected to both the Disintegration Test for Enteric Coated Tablets B.P. and a dissolution procedure to monitor the release of drug in simulated gastric juice and simulated intestinal fluid. Both polymers demonstrated their suitability for producing enteric coatings. However, polyvinyl acetate phthalate yielded a faster release of aspirin in simulated intestinal fluid than did cellulose acetate phthalate.

Enteric coatings are applied to tablets to prevent the release of drugs in the stomach, either to reduce the risk of unpleasant side effects or to maintain the stability of the drug which might otherwise be subject to degradation if exposed to the gastric environment.

Most polymers that are used for this purpose are polyacids which function by virtue of the fact that their solubility in aqueous media is pH-dependent, and they require conditions with a pH higher than normally encountered in the stomach.

The basis for determining the efficacy of an enteric-coated tablet is a modified disintegration test, requiring that the product remain physically intact for a specified period when exposed to simulated gastric juice, and yet disintegrate readily when placed in simulated intestinal fluid. Even allowing for the divergence in test procedures of the various compendia, some question has been raised as to the suitability of such a test. Madan & Minisci (1976) showed that of 17 brands of enteric coated aspirin evaluated, although all passed the official U.S.P.XV test, 11 were unable to prevent the release of aspirin in simulated gastric juice. In addition, the availability of aspirin from some brands of enteric coated tablets was found to be unsatisfactory (Clark & Lasagna 1965; Levy & Hollister 1964).

Failure to prevent the release in gastric juice of drug from an otherwise intact enteric coated tablet could be permeability related. The permeability of cellulose acetate phthalate coatings to gastric juice and caffeine, a test drug substance, has been studied by Spitael & Kinget (1977a), while Spitael & Kinget (1977b) and Fites et al (1970) have discussed the effects of additives within the film.

A secondary benefit to be derived from the applied coating is the potential for increasing drug stability by limiting access to water vapour in the atmosphere. Lachman & Drubulis (1964) and Crawford & Esmerian (1971) have investigated the permeability to water vapour of cellulose acetate films, and the effect of additives thereon.

MATERIALS AND METHODS

The enteric properties of two polymers, cellulose acetate phthalate (Wako Pure Chemical Industries Ltd., Osaka, Japan) and polyvinyl acetate phthalate (Colorcon, Inc., West Point, PA, U.S.A.), were evaluated. The effect on these properties of two additives was also investigated; the first being a plasticizer, diethyl phthalate (Koch Light Laboratories, U.K.); and the second a pigment, red iron oxide (99·4–99·7% Fe_2O_3) (Cities Service Company, Columbian Div., Ohio, U.S.A.). All coating formulations were based on a 5% w/w polymer solution in a dichloromethane–methanol solvent mixture. Initially the solvent ratio chosen was 50 : 50 by weight. However, on evaporation this mixture resulted in precipitation of cellulose acetate phthalate. Subsequently, the azeotropic mixture (93% by weight of dichloromethane) was used for cellulose acetate

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phthalate while the original 50:50 mixture was retained for polyvinyl acetate phthalate.

The additive concentrations evaluated were 0, 10, 20, and 50% by weight of the polymer.

Placebo tablets (prepared by compressing a standard granulation consisting of lactose, starch, polyvinylpyrrolidone (PVP), and magnesium stearate) were coated in a conventional 16″ laboratory coating pan fitted with heated air supply and extraction using a Model 460 Binks air spray gun.

Free films of each formulation were prepared by spraying the coating solutions onto vinyl coated card cut and fitted inside the coating pan to form the inside surface of a frustum of a cone.

In order to evaluate the permeability of each film formulation to moisture, samples of film were sealed across the top (previously ground flat) of small ointment jars containing silica gel desiccant. Each jar was stored in a Patra humidity cabinet at 30 °C and 75% R.H. The permeability constant, P_T, for each formulation was calculated from the gain in weight of jar and contents utilizing equation (1)

$$Q = \frac{P_T A \Delta p t}{d} \quad .. \quad .. \quad (1)$$

where Q is the quantity of water vapour permeating the film in time t, A is the area of exposed film, d is the film thickness and Δp is the vapour pressure gradient across the film.

Weighed and marked placebo tablets, to which approximately 10% by weight of coating had been applied, were exposed to simulated gastric juice (0·06 M hydrochloric acid solution); in a disintegration tester. Periodically, each tablet was removed, surface dried with tissue, and reweighed.

The permeability constant, Pg, for each formulation was calculated using equation (2). In this case the permeant was assumed to be water since it constitutes 99·9% of the test solution where M is the

$$M = \frac{Pg\ A\ C_1\ t}{d} \quad .. \quad .. \quad (2)$$

number of moles of liquid permeating the film in time t, A is the area of exposed film (calculated from the original tablet geometry), C_1 is the concentration of permeant in the external liquid, and d is the film thickness.

Finally, two coating formulations for each polymer at a 5% w/w concentration, and containing in addition either (i) 0·5% w/w diethyl phthalate or (ii) 0·5% w/w diethyl phthalate and 1·0% red iron oxide were applied to 325 mg aspirin tablets, sufficient to give a 10% weight gain.

Tablet samples from each formulation were subjected to the B.P. Disintegration Test for Enteric Coated Tablets to ensure compliance.

Subsequently, the dissolution characteristics of both uncoated and coated tablets were evaluated using the U.S.P. basket method, and using either the simulated gastric juice or intestinal fluid specified in the B.P. enteric test as the dissolution medium.

RESULTS AND DISCUSSION

A comparison of the permeability of each polymer to water vapour indicates that there are some significant differences between the two materials (see Fig. 1).

Chemically there are obvious differences between the two polymers. Polyvinyl acetate phthalate has a vinyl backbone into which various groups, namely phthalate, acetate and hydroxyl, have been substituted. Any hydrophilicity will be attributable to the substituent groups. Cellulose acetate phthalate has the typical cellulosic structure with similar substituent groups to polyvinyl acetate phthalate. It is conceivable that because of this cellulose backbone, cellulose acetate phthalate may be the more hydrophilic polymer of the two.

According to Swarbrick et al (1972), any affinity of water vapour for the polymer leads to significant sorption of water molecules, resulting in plasticization of the film and subsequently increased permeability, as postulated by Kumins et al (1957).

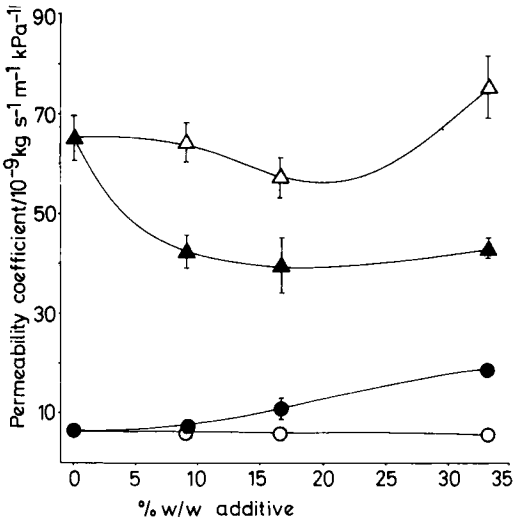

FIG. 1. Effect of additives on the permeability to water vapour of polyvinyl acetate phthalate (P.V.A.P.) and cellulose acetate phthalate (C.A.P.) films (points represent a mean of 5 replicates) ● P.V.A.P. + plasticizer. ▲ C.A.P. + plasticizer. ○ P.V.A.P. + pigment. △ C.A.P. + pigment.

In addition to chemical differences being responsible for the observed differences in moisture permeability, there is a possibility that physical differences in film structure could also be implicated. Although the initial intention was to utilize the same solvent blends for each polymer, precipitation of cellulose acetate phthalate occurred on solvent evaporation unless the azeotropic solvent mixture was used. Unfortunately the azeotropic mixture was not a suitable solvent for polyvinyl acetate phthalate. Since cellulose acetate phthalate was sprayed using a more volatile solvent, this could potentially create a more porous film, resulting in a higher permeability to water vapour.

The addition of a plasticizer to a polymer generally decreases the cohesive forces between chains, resulting in an increase in segmental mobility. Consequently this should reduce the activation energy for diffusion and thus increase the diffusion coefficient. Support for this is given by Kumins et al (1957) who found that an addition of up to 25% w/w dioctyl phthalate to a vinyl acetate-chloride copolymer resulted in a five-fold increase in the permeability to water vapour at 32 °C, with a corresponding reduction in activation energy for diffusion from 31 to 8·4 kJ mol^{-1}. Although this would explain the behaviour of the polyvinyl acetate phthalate films, it would seem to contradict that shown by cellulose acetate phthalate, which is typical of that already documented (Delporte & Jaminet 1978). If the potential exists, as already discussed, for the cellulose acetate phthalate films in this study being more porous, then the presence of a suitable plasticizer, in essence a solvent for the polymer, could result in a reduction of that porosity owing to a solvation effect, and consequently reducing permeability of the coating to moisture.

The presence of a pigment in the formulation had little effect on the permeability of the polyvinyl acetate phthalate films. The initial reduction, followed by an ultimate increase, in permeability of the cellulose acetate phthalate formulations is typical of the behaviour predicted by the Chatfield theory, whereby the permeability is reduced by the presence of the pigment particles, which cause an increase in tortuosity of the diffusion pathway. Ultimately the binding capacity of the polymer is exceeded, a point often termed the critical pigment volume concentration, so that further increases in pigment concentration cause a corresponding increase in permeability.

Fig. 2 indicates that in examining the behaviour of the various film formulations when exposed to

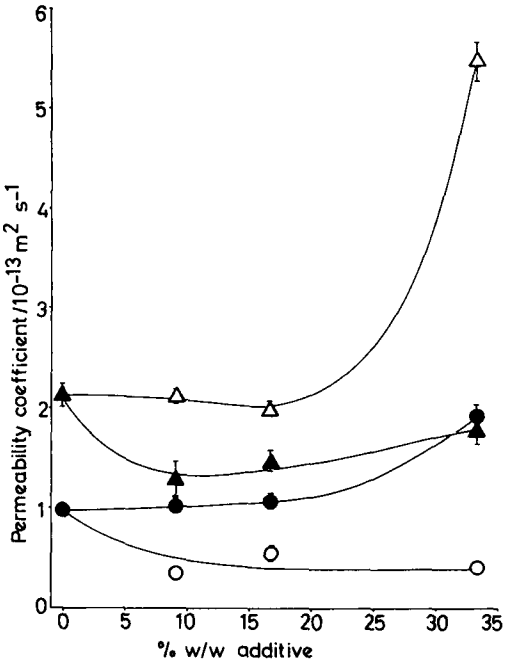

FIG. 2. Effect of additives on the permeability to simulated gastric juice of polyvinyl acetate phthalate (P.V.A.P.) and cellulose acetate phthalate (C.A.P.) films applied to placebo tablets (points represent a mean of 5 replicates). ● P.V.A.P. + plasticizer. ▲ C.A.P. + plasticizer. ○ P.V.A.P. + pigment. △ C.A.P. + pigment.

simulated gastric juice, although the magnitude of the differences between the two polymers has been reduced relative to that seen for water vapour permeability, the quantitative effects of the various additives are similar to those already discussed. The apparent reduction in permeability of cellulose acetate phthalate films compared to those of polyvinyl acetate phthalate may be associated with a concentration effect of the diffusant (previously water vapour, now liquid water). A negative concentration effect, as described by Rouse (1947), results in a clustering of water molecules at certain polar sites (potentially more numerous in a polymer with a cellulosic backbone such as cellulose acetate phthalate) in the polymer network. This effectively causes some immobilization of the diffusant.

All samples of the coated aspirin tablets were found to comply with the requirements of the B.P. Disintegration Test for Enteris-coated Tablets. In addition, when subjected to a dissolution test, although the uncoated aspirin tablets yielded 100% drug dissolved in simulated gastric juice after approximately 30 min, no trace of aspirin could be

detected over a 3 h period in the same dissolution medium when the enteric coated tablets were evaluated.

The results for the evaluation of the dissolution characteristics of both the uncoated and enteric coated aspirin tablets in simulated intestinal fluid are highlighted in Table 1. Although the release characteristics for all the coated tablets are more than adequate for this type of formulation, it can be seen that the aspirin is more rapidly available from the polyvinyl acetate phthalate formulations than from those based on cellulose acetate phthalate.

Table 1. Dissolution of uncoated and enteric coated aspirin 325 mg tablets in simulated intestinal fluid (buffer solution pH = 6·8) at 37 °C.

Formulation	T50 (min)*	T90 (min)*
Aspirin cores	5 (±1½)	12 (±3)
Enteric coated aspirin		
(a) P.V.A.P./D.E.P. 10 : 1	25 (±2½)	35 (±6½)
(b) P.V.A.P./D.E.P./Pig. 10 : 1 : 2	23 (±7½)	35 (±8)
(c) C.A.P./D.E.P. 10 : 1	30 (±4)	45 (±11½)
(d) C.A.P./D.E.P./Pig. 10 : 1 : 2	27 (±6)	52 (±8½)

Key: P.V.A.P.—polyvinyl acetate phthalate
C.A.P. —cellulose acetate phthalate
D.E.P. —diethyl phthalate
Pig. —pigment
* Mean of 3 replicates.

In conclusion, although there are some observable differences between the relative permeabilities of the two polymers evaluated, differences which could ultimately have an effect not only on their performance as enteric coatings, but also on the ultimate stability of the product, their ability to form coatings which comply with the requirements of the official enteric test has been confirmed. In addition, in spite of the adverse reports (Levy & Hollister 1964; Clark & Lasagna 1965; Day et al 1976; Madan & Minisci 1976) often associated with enteric coatings, the efficacy of the coated aspirin tablets has been established by a suitable dissolution test.

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