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In vitro assessment of the adhesiveness of film-coated tablets

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Summary

A method has been developed to assess the adhesivity of capsules and film-coated tablets. The adhesiveness of tablets, a property important during aqueous film-coating processes and oesophageal transit, has been studied using a strain gauge device to measure the force required to detach the dosage form from a planar moist surface. The results obtained by this method correlate well with those obtained using an ex vivo method involving strips of porcine oesophageal mucosa. Non-disintegrating tablets were coated with hydroxypropyl cellulose (HPC), hydroxypropylmethyl cellulose (HPMC) and the polymethacrylate copolymers Eudragit E100 and L100. The influence of film-coat thickness, and added poly(oxyethylene) glycol (PEG) of varying molecular weight was studied. While Eudragit polymers had little adhesive potential, HPC and HPMC film-coats became more adhesive with increase in film thickness, but the presence of PEG of molecular weight > 1000 markedly reduced adhesiveness.

Introduction

The assumption that pharmaceutical dosage forms reach the appropriate region of the gastrointestinal tract rapidly and without hindrance is not always borne out in practice. With the appearance, in the last decade, of several reports of oesophageal injury following the oral administration of solid dosage forms (Kikendall et al., 1983), it is now clear that oesophageal transit cannot be taken for granted and injury at this site is accepted as another iatrogenic disease. While it has been recognised that various 'inactive' components of formulations can elicit adverse reactions (Smith and Dodd, 1982), relatively little attention has been paid to the role that the physical nature of a dosage form can play in this aspect of drug therapy. There is now evidence that the physical characteristics of a dosage form can influence its passage down the oesophagus, thus indirectly modifying the incidence of oesophagitis induced by irritant drugs (Al-Dujaili et al., 1983). Attention has been focussed on the adhesive characteristics of tablet and capsule surfaces; Chopra and Tawashi (1982, 1984, 1985) considered adhesiveness of film-coating materials from the point of view of tablet processing, and isolated oesophageal preparations have been developed to assess the tendency of dosage forms to adhere to mucosa (Marvola et al., 1982; Swisher et al., 1984). In a previous report the adhesiveness of proprietary formulations was assessed using an ex vivo technique involving strips of porcine oesophagus (Al-Dujaili et al., 1986). This paper reports on the adhesiveness of tablets film-coated with some

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commonly used polymers, using an in vitro method which provides a more reproducible measurement system than those employing tissue surfaces, but which also correlates with the earlier ex vivo techniques (Al-Dujaili et al., 1986).

Materials and Methods

Tablet preparation

Tablets (slightly biconvex, 10.4 mm diameter and 450 mg mean weight) were made by direct compression to the formula: heavy magnesium carbonate (BDH, U.K.) 50%, Emcompress (Forum Chemicals, U.K.) 49% and magnesium stearate (BDH) 1%. These cores were film-coated by dipping into solutions of polymethacrylate copolymers (Eudragit E100 and L100, Rohm Pharma, F.R.G.) and hydroxypropyl cellulose (Klucel-L F, Hercules, U.K.) in ethanol : acetone 1 : 2 w/w, and two grades of hydroxypropylmethyl cellulose (Pharmacoat 606 and 615, Shin-Etsu Chemical, Japan) in ethanol : dichloromethane 1 : 1 w/w. The tablets were dried with a hot-air drier followed by 30–45 min at 50–60°C in a vacuum oven. Poly(oxyethylene) glycols (m. wt. 600 to 6000, BDH) were added to the coating solutions to produce mixed films. The thicknesses of film-coats were measured by examining cross-sections of tablets with an epi-fluorescence microscope fitted with an eye-piece scale.

Some of the proprietary tablet formulations examined in the previous paper (Al-Dujaili et al., 1986) were used to compare adhesivity measured by the ex vivo and in vitro test methods.

Measurement of adherence

The apparatus (Fig. 1) consisted of a stainless steel blade (25 × 2 × 0.06 cm) to the upper and lower surfaces of which were bonded strain gauges, 3 cm from the fixed end (E). The four electrical resistance strain gauges were connected in Wheatstone bridge circuit to a stabilised power supply (1.0 V) and digital multimeter; the voltage response was sensitive to, and linear against, applied load (1 mV = 0.0365 g). At the free end of the blade a thin glass stub (3 × 2 × 0.2 cm, D) was attached. Above the stub a piston rod (B) could be

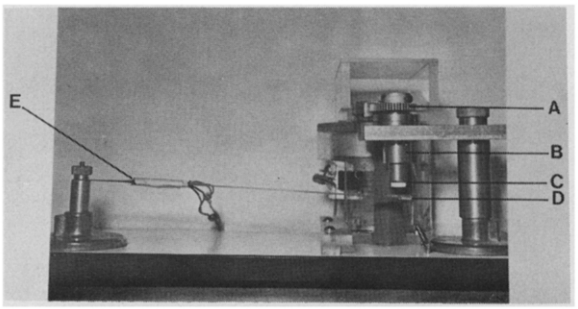


Fig. 1. Apparatus for measurement of tablet adhesiveness: (A) motor-driven gear, (B) piston-support bush, (C) piston rod with tablet attached, (D) glass stub, (E) strain gauges bonded to steel blade.

steadily raised at 4.2 mm · min^{-1} by a motor-driven gear (A). The tablet to be tested was fixed with double-sided adhesive tape to the piston rod (C). Ten μl of distilled water (or citric acid–phosphate buffer solutions) were placed on the glass stub, the piston rod screwed down to allow the tablet surface to be wetted without pressing on the blade, contact maintained for 1 min, then the piston was raised. The multimeter reading when separation occurred was used to calculate the force

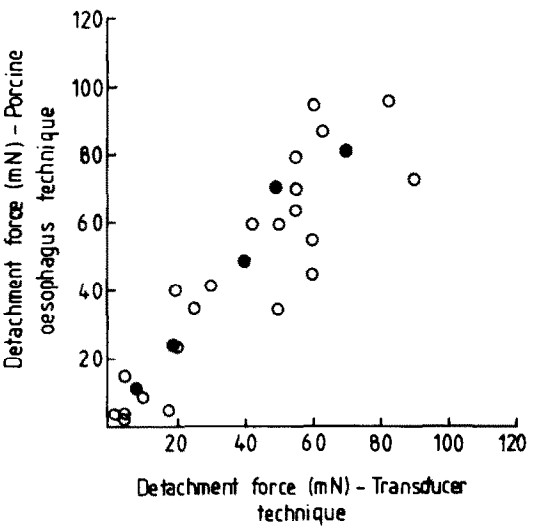
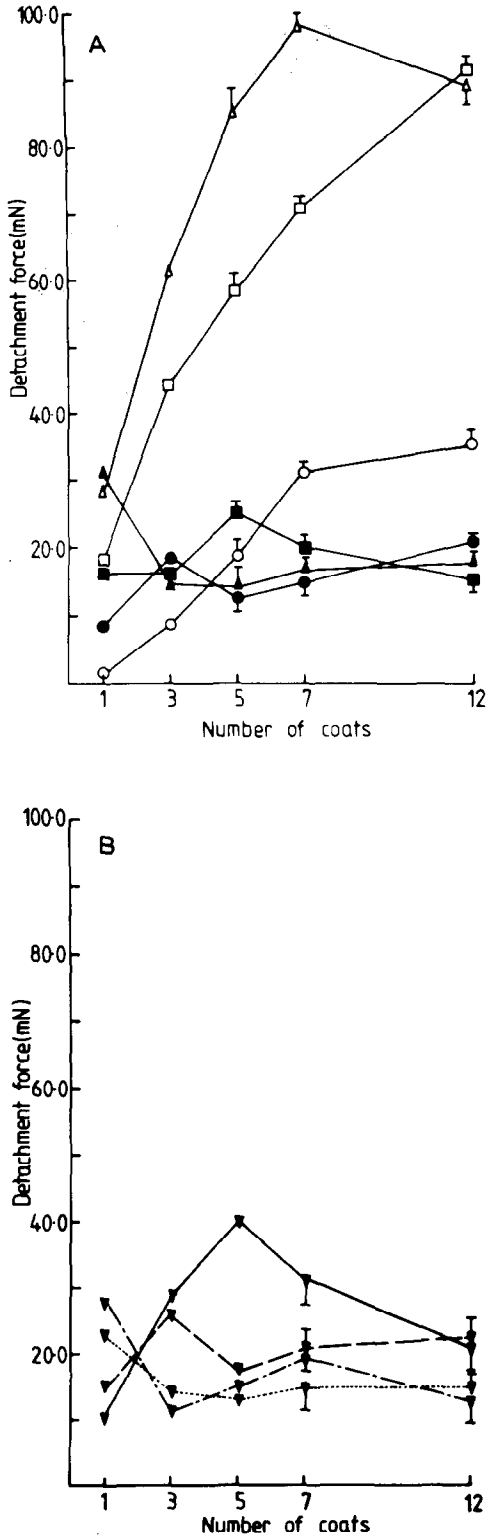


Fig. 2. Correlation between detachment force data obtained for commercial film-coated tablets using the ex vivo porcine oesophageal strip and in vitro methods: closed symbols represent experimental tablets coated with HPMC-606 from 2.5% w/w solution.



required to detach the tablet from the moist surface. For each reading 6–8 tablet samples were used.

The adhesivity of proprietary film-coated tablets and some experimental tablets were also determined using the ex vivo porcine oesophageal strip test system described in the previous paper (Al-Dujaili et al., 1986).

Results and Discussion

Fig. 2 shows the correlation between the measurements of adhesion of some commercial and

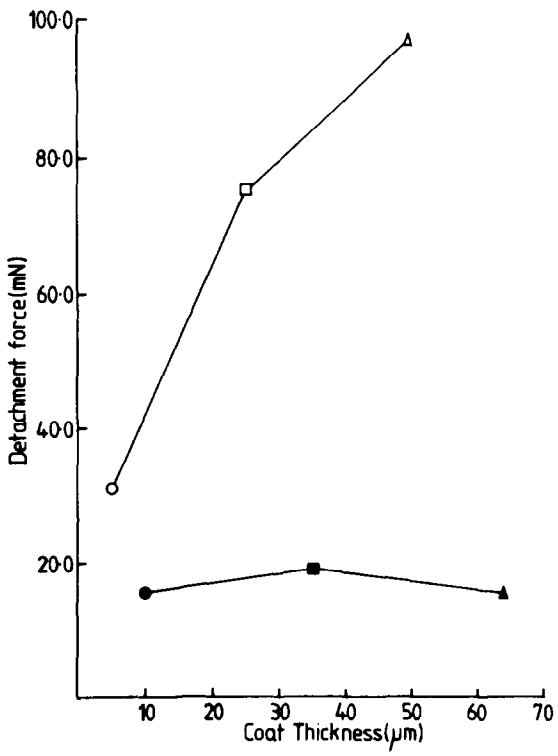


Fig. 4. Effect of film thickness on adhesiveness of tablets given 7 coats of HPC from (○) 1%, (□) 2.5% and (△) 4.5% w/w solutions; closed symbols represent solutions containing 4.5% w/w PEG 6000.

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Fig. 3. Adhesiveness of tablets coated with HPC: (A) from (○) 1%, (□) 2.5% and (△) 4.5% w/w solutions, closed symbols represent solutions containing 4.5% w/w PEG 6000; (B) from 3% w/w solutions containing (———) 1%, (– – – –) 2.5%, (– · – · –) 4% and (· · · · · ·) 5.5% w/w PEG 6000. (Error bars = ± S.D.)

experimental formulations using the ex vivo method described in the previous paper (Al-Dujaili et al., 1986) and those obtained with the transducer technique described here; regression analysis showed the gradient of the line to be 1.06, with a correlation coefficient of 0.88. These results indicate that the in vitro technique described here is a useful predictive method.

Low detachment forces were required when the film-coat comprised either Eudragit E100 (5.5–8 mN) or L100 (7–11 mN), the latter being slightly more adhesive. The number of applied coats had little influence on adhesivity, neither did the presence of poly(oxyethylene) glycol (PEG) 6000. The results agree with those obtained by Marvola et al. (1983) and Kannikoski et al. (1984) using isolated oesophageal preparations, who also suggested that the low adhesivity may be due to the hydrophobicity of these polymers.

In contrast to Eudragit, films of the water-soluble polymer, hydroxypropyl cellulose (HPC), were found to be highly adhesive, the forces required for detachment increasing with both polymer concentration and the number of coats applied. Fig. 3 shows the results for HPC with and without PEG 6000; clearly PEG reduces the adhesive nature of HPC. These results are plotted as a function of the number of applied coats, but Fig. 4, however, shows the results for HPC films as a function of the initial thickness of the applied coat; the effect of addition of PEG 6000 on both thickness and adhesion is clearly shown. These HPC–PEG mix-

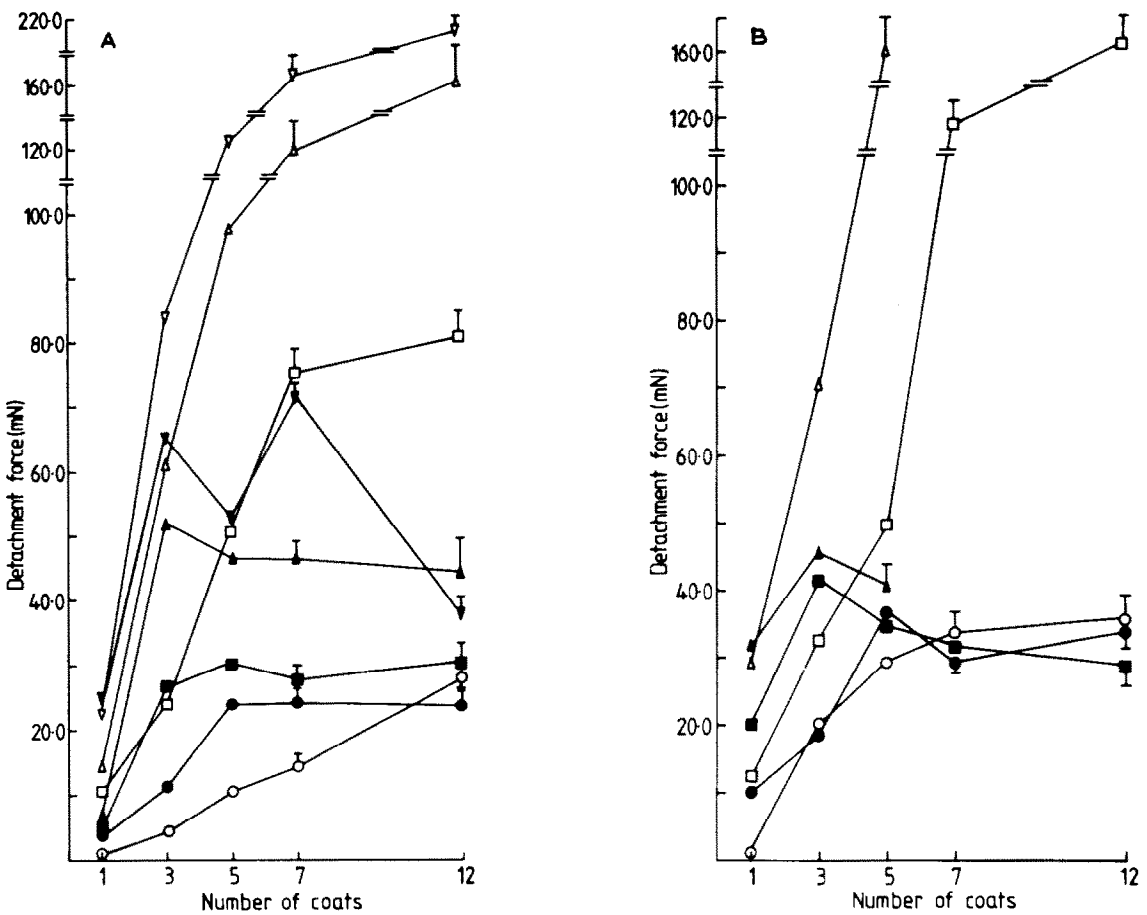

Fig. 5. Adhesiveness of tablets coated with HPMC (A) 606 and (B) 615 grades from (○) 1%, (□) 2.5%, (△) 4% and (▽) 5.5% w/w solutions; closed symbols represent solutions containing 4% w/w PEG 6000. (Error bars = ± S.D.)

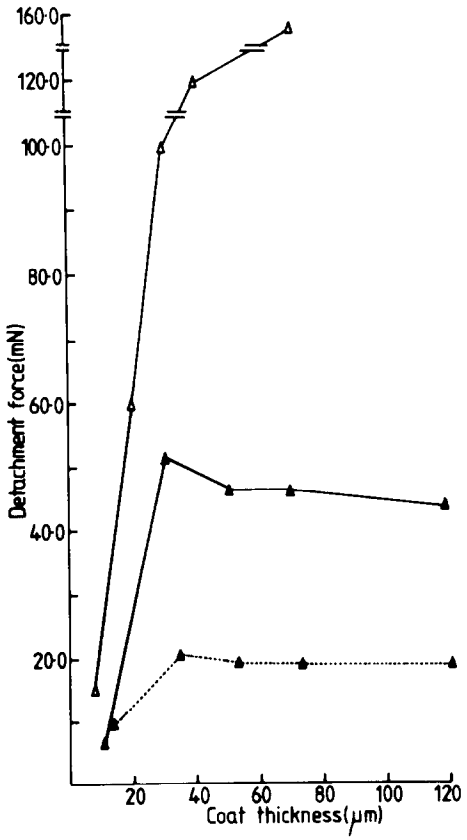

Fig. 6. Effect of film thickness on adhesiveness of tablets coated with HPMC-606 from 4% w/w solutions; closed symbols represent solutions containing (———) 4% and (·····) 6% w/w PEG 6000.

tures contain more PEG than HPC and the overriding effect of the glycol is seen.

As with HPC, film-coats of water-soluble hydroxypropylmethyl cellulose (HPMC) were found to be highly adhesive, their adherence increasing with the concentration of coating solution, the polymer grade, the number of coats applied and the overall film thickness. Fig. 5 shows the results for the two grades of HPMC studied. Again, the overall effect of adding PEG was to reduce sub-

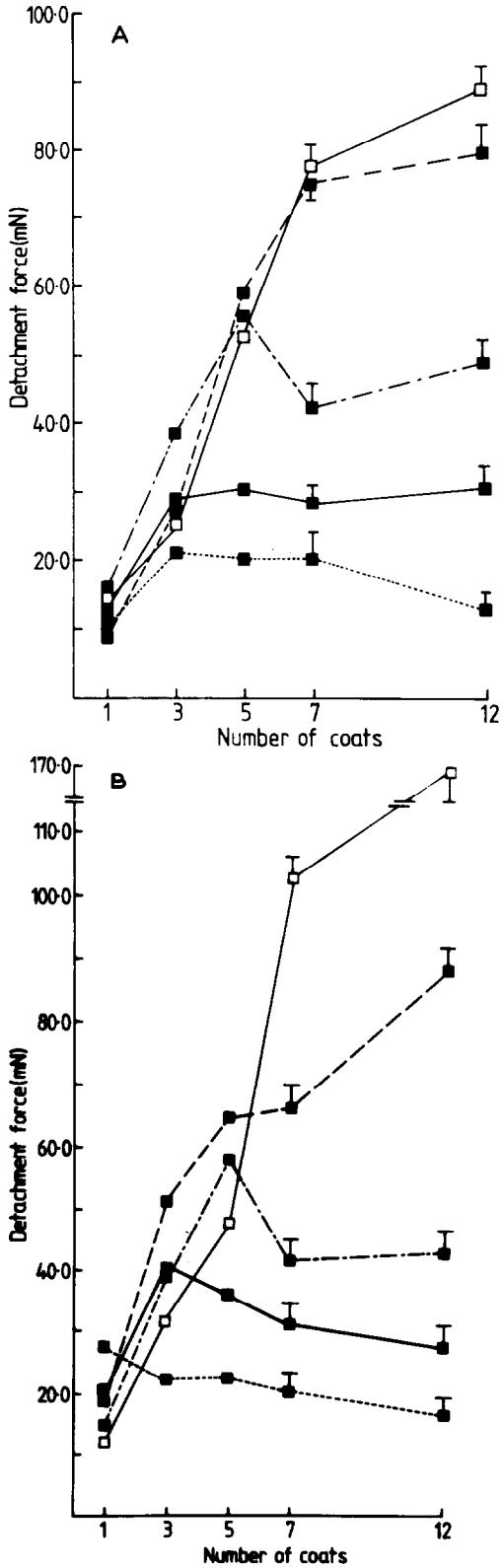

Fig. 7. Adhesiveness of tablets coated with HPMC (A) 606 and (B) 615 grades from 2.5% w/w solutions containing (– – – –) 1%, (–·–·–) 2.5%, (———) 4% and (·····) 6% w/w PEG 6000 (closed symbols). (Error bars = ± S.D.)

stantially the adhesiveness of the film and to diminish its relationship with HPMC concentration and applied film thickness (Fig. 6). The tackiness of HPMC–PEG mixed films varied with PEG 6000 content (Fig. 7). It also appeared that the adherent properties of mixed films depended upon the molecular weight of the added PEG (Fig. 8).

To examine the effect of pH on the adhesiveness of HPMC, buffer solutions (pH 2, 5 and 7) were substituted for water to moisten the film-coat. At each coating thickness it was evident that the substitution of buffer for water reduced the overall adhesivity (Fig. 9) possibly because of the effect of ionic strength on polymer solubilility and rate of solution.

Generally, these results support the data obtained by Marvola and colleagues using an isolated porcine oesophagus model (Marvola et al., 1983; Kannikoski et al., 1984). They suggest, by analogy with hard gelatin capsules, that the relatively high adhesiveness of HPMC may be due to the formation of a viscous gel on dissolution at the mucosal interface. Indeed it was noted that in the short time-scale of an experiment the amount of HPMC in the thin aqueous film between tablet and glass stub could rise to about 30% w/w, at which concentration the viscosity of HPMC is well in excess of 5 Pa. However, although viscous solutions are not necessarily adhesive (as for adhesion to occur there must be bonding interactions between the two surfaces involved), experiments preliminary to the studies reported here showed that the HPMC coat on a proprietary tablet formulation visibly dissolved on immersion in water to form a viscous, and highly adhesive, mass between the tablet and underlying surface (Florence et al., 1984).

Poly(oxyethylene) glycols lower the intrinsic viscosity of HPMC solutions (Entwistle and Rowe, 1979; Okhamafe and York, 1985), suggesting a

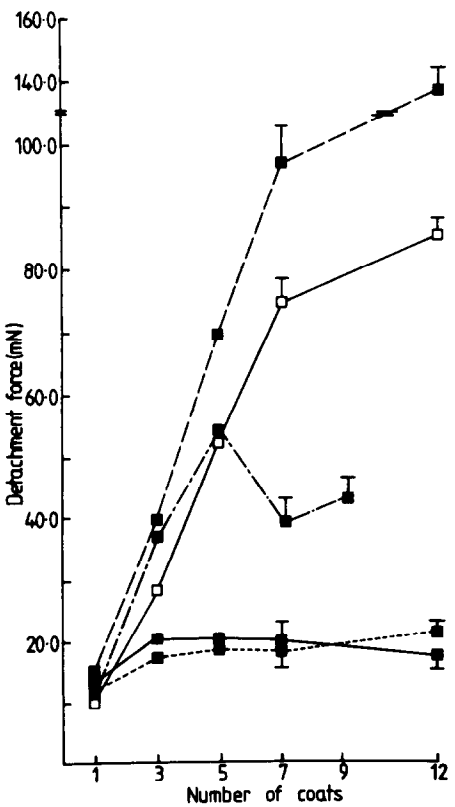

Fig. 8. Effect of PEG molecular weight on adhesiveness of tablets coated with HPMC-606 from 2.5% w/w solutions containing 6% w/w plasticiser (closed symbols): (– – – –) PEG 600, (– · – · –) PEG 1000, (———) PEG 4000 and (· · · · · ·) PEG 6000. (Error bars = ± S.D.)

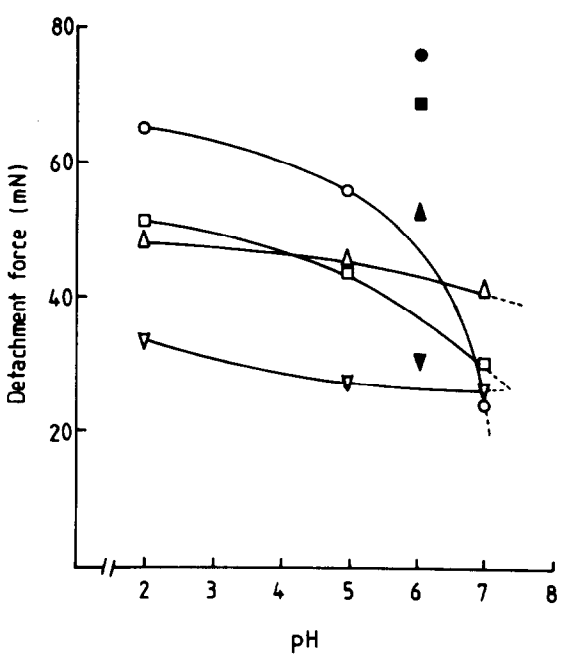

Fig. 9. Effect of pH of the aqueous phase on adhesiveness of tablets coated with HPMC-606 from 2.5% w/w solution: (▽) 3, (△) 5, (□) 7 and (○) 9 coats; closed symbols represent distilled water.

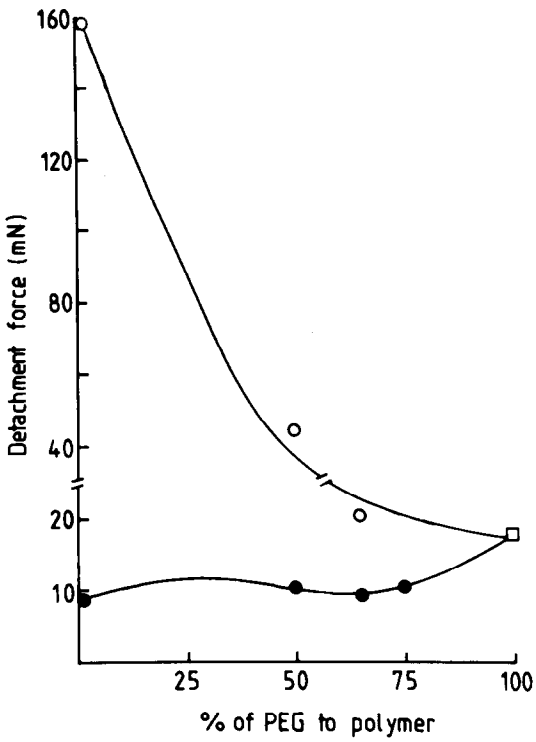

Fig. 10. Effect of PEG 6000 on adhesiveness of film-coating polymers: experimental tablets with 12 coats of (○) HPMC-606 and (●) Eudragit L100.

degree of incompatibility and change in the conformation of the cellulose polymer. In our experiments relatively high concentrations of PEG were used. PEG solutions are obviously less adhesive than the celluloses studied; Fig. 10 summarises the results showing the progressive reduction in adhesivity in systems containing up to 100% PEG 6000 in both HPMC and Eudragit systems. The adhesivity is not additive, confirming the non-ideality of the mixtures. Adhesion must be due to attractive interactions between the polymer molecules in solution working against the 'elongation' of the solution between two separating surfaces. Reduction in such interactions would lead to lower adhesivity.

It is clear that the mechanical characteristics of films should not be the exclusive consideration in the formulation of coating mixtures, and that cognisance should be taken of their potential to become adhesive in vivo, particularly when the dosage form does not disintegrate rapidly. Additives can profoundly affect the tackiness of films (Marvola et al., 1983; Chopra and Tawashi, 1985) and, as has been shown here with HPMC and the commonly used plasticizer PEG; those excipients which optimise the end-use properties of tablet coatings (Aulton et al., 1981) may also reduce product adhesiveness.

The development and further application of in vitro tests such as the method described here, which do not suffer from the disadvantages inherent in biological systems, should serve to identify potentially hazardous formulations and help clarify the factors associated with adhesiveness and the problems of dysphagia and oesophageal injury, and perhaps also aid in the design of systems in which muco-adhesion is deliberate (Park and Robinson, 1984).

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