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An in vitro assessment of some mucosa-adhesive dosage forms

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Summary

An in vitro method was developed for the assessment of the adhesive force (i.e. the force required to break an adhesive bond) between a disc of test material and a model mucous membrane. This system showed reasonable reproducibility and produced data in agreement with previous studies. Some factors influencing the adhesive force were assessed and only increasing the rate of application of the tensile force was found to have a significant effect. Some putative mucosa-adhesive formulations were evaluated and some buccal tablets found to have minimal adhesive properties. It was concluded that only a small force is required to retain a dosage form within the buccal cavity. The stability of the adhesive bond was assessed for the two most adhesive materials (the poly(acrylic acids) Carbopol 934P and EX55) by subjecting to a continuous stress for 8 h prior to measuring the adhesive force. The Carbopol EX55 (polycarbophil) formed the most stable adhesive bond which remained intact for 8 h.

Introduction

The development of adhesive dosage forms for controlled drug delivery to or via mucous membranes is of interest with regard to local drug therapy, and the systemic administration of peptides and other drugs poorly absorbed from the gastrointestinal tract (GIT). Target sites for mucosa-adhesive drug delivery include the eye (Robinson, 1989), GIT (Ch'ng et al., 1985; Harris et al., 1989), cervix (Nagai, 1986), vagina (Gorsoy et al., 1989), oral cavity (Nagai and Konishi, 1987), and the nasal cavity (Nagai et al., 1984).

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Determination of the mucosa-adhesive bond strength is important in the development of adhesive dosage forms, and several methods have been developed to investigate this. Techniques that measure the tensile force required to break the adhesive bond between a model membrane and a test polymer have been reported (Ch'ng et al., 1985; Lejoyeux et al., 1989). Model membranes that have been used include rabbit gastric mucosa and mouse peritoneal membrane (Gu et al., 1988). On the assumption that materials that adhere to mucous membranes must first interact with the overlying layer of mucus, the force required to detach a test adhesive from a mucus or mucus glycoprotein gel has been investigated (Smart et al., 1984; Helliwell et al., 1990). Other techniques have involved the use of fluorescent probes (Park and Robinson, 1984), rheological investigations

(Hassan and Gallo, 1990), colloidal gold staining (Park, 1989) and in situ methods (Ranga Rao and Buri, 1989).

When formulating a mucosa-adhesive dosage form it is important to consider not only the strength, but also the duration of the adhesive bond. Mucosa-adhesive materials are hydrophilic macromolecules containing numerous hydrogen bond forming groups, particularly carboxyl groups (Smart et al., 1984). They have been described as 'wet' adhesives in that they become adhesive on hydration. However it is possible for them to over-hydrate to form a slippery mucilage (Chen and Cyr, 1970), and this may limit their use. This investigation forms part of a larger study on the development of a reliable in vitro technique to evaluate the strength and stability of mucosa-adhesion prior to in vivo assessment. In this investigation particular regard was paid to the development of dosage forms for drug delivery to the oral cavity.

Materials and Methods

Materials

Carbopol 934P and EX55 were obtained as a gift from BF Goodrich, Hounslow, U.K., polyethylene glycol 6000 (PEG), sodium chloride, sodium phosphate and sodium hydrogen phosphate from BDH, Poole, U.K., hydroxypropylmethylcellulose (HPMC) (Methocel K100M) from Colorcon Ltd, Orpington, U.K. and hydroxypropylcellulose (HPC) (average mol. wt. 1 000 000) from Aldrich Chemical Co., Gillingham, U.K.

Selection of model mucosal surface

In the evaluation of adhesion it is important to use uniform surfaces that allow the formation of reproducible adhesive bonds. It is difficult to obtain uniform surfaces when using biological materials. Mucus (or purified glycoprotein) gels and pig oral mucosa were considered in an initial study, but physical changes in the mucus gel over prolonged periods and the visibly non uniform nature of the pig oral mucosa precluded their use in this study. On examining rat GIT it was noted that the small intestine was relatively free of intestinal contents, and provided a macroscopically flat uniform surface (despite the presence of villi and microvilli observed on microscopic examination) that was suitable for use as a model membrane.

Preparation of test formulations

10 g powder blends of the test materials were prepared in a pestle and mortar. These were compressed into 6.2 mm diameter 50 mg discs in a Specac infrared press using 1 tonne force for 5 s. An initial investigation revealed that convex tablets did not adhere to the flat mucosal surfaces used in this work, so these were ground into a fine powder and compressed into discs as described above.

Experiments

The middle section, discarding the first 40–50 mm at either end, of fresh intestine from male Wistar rats was frozen until required to inhibit muscle contraction. This was cut into 3 cm lengths, washed and mounted on a platform in isotonic phosphate buffer (pH 6.8) at 37 °C to expose a 1.1 cm diameter circle of tissue (Fig. 1). The test disc was attached to a 1.5 g weight using a cyanoacrylate adhesive (Loctite Supergluematic). This was suspended from a top pan balance (Oerturling HC22) (for the paste preparation, a thin layer was spread onto the lower surface of the weight) which was lowered onto the mucosal surface and left for 2 min. The platform was lowered at a rate of 1 mm/min until the disc pulled clear of the membrane and the force at which the adhesive bond

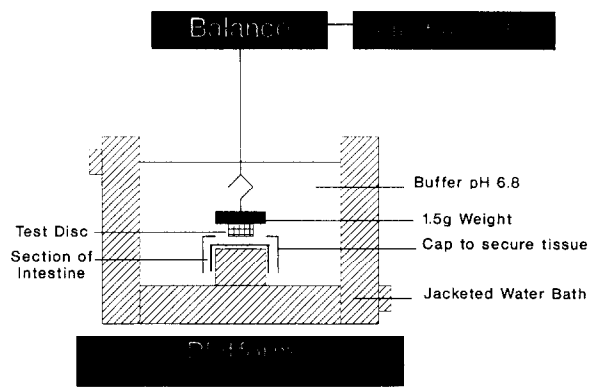

Fig. 1. Apparatus for assessing mucosa adhesion.

failed recorded. The results were calculated in terms of a standard 1 cm^2 disc. The work of adhesion (Ponchel et al., 1987) was not calculated in this study as it was considered that the area under the curve in these conditions was likely to provide information mainly related to the rheological behaviour of the hydrating and swelling test material.

An initial investigation examined the reproducibility of the test system using 15 discs of the known mucosa-adhesive Carbopol 934P. Tissues were obtained from three animals and five discs were tested on each.

A second study compared the results obtained using materials found to have varying adhesive properties in previous studies (Chen and Cyr, 1970; Smart et al., 1984).

Carbopol 934P discs were used to investigate some factors influencing the adhesive force obtained with this system, namely, the rate at which the platform is lowered (i.e. the rate at which the tensile force is applied), the initial contact time of the test disc and the mucous membrane, and the consolidation force applied (the load applied to the adhesive joint during the initial contact period).

Some commercially available mucosa-adhesive formulations Buccastem, Suscard Buccal, and Adcortyl in Orabase, were then tested, along with some formulations reported in previous studies.

The duration of adhesion of the most 'successful' formulations was evaluated by applying a tensile force of 1 N cm^{-2}, to the adhesive bond after the initial 2 min contact time and leaving for up to 8 h or until the bond had fractured. Every hour the tensile force acting on the adhesive joint was noted and if necessary adjusted back to 1 N cm^{-2}. After 8 h the force required to break the adhesive bond was evaluated.

Results

When 3×5 Carbopol 934P discs were tested the mean force required to break the adhesive bond was 2.94 with a standard deviation of 0.75. No significant difference was found between the forces obtained with tissues from different animals ($P > 0.05$, one-way analysis of variance).

TABLE 1

The detachment forces obtained with materials of known adhesive properties

Material	*n*	Mean force (N cm^{-2})	S.D.
Carbopol 934P	5	2.75	0.99
HPMC	5	1.14	0.5
Gelatin	5	0.07	0.02
PEG	5	0	0

Clear differences were seen between materials of known adhesive properties ($P < 0.05$, one-way analysis of variance) (Table 1).

Only the effect of increasing the rate of application of the tensile force was found to have a significant effect ($P < 0.05$, Student's *t*-test) on the adhesive forces (Table 2).

When comparing a variety of putative mucosa-adhesive formulations Carbopol EX55 and Carbopol 934P demonstrated the greatest adhesive force (Fig. 2), while the inclusion of HPC into a Carbopol 934P formulation produced an insignificant reduction in the adhesive force ($P > 0.05$, Student's *t*-test). Suscard Buccal and Buccastem appear to be only moderate adhesives in this study. Cohesive failure of the Adcortyl in Orabase paste was observed to be the cause of the adhesive failure.

The two most successful adhesive formulations were evaluated to find the duration of the adhesive bond under stress (Table 3). It was observed that the applied tensile force did not re-

TABLE 2

Some factors that influence the adhesive force of Carbopol 934P conpacts (n = 5)

Contact time (min)	Consolidation weight (g)	Rate platform lowered (mm/min)	Mean force (N cm^{-2})	S.D.
0	1.5	1	2.82	1.08
2	1.5	1	2.75	0.99
5	1.5	1	4.21	1.22
2	1.5	2	3.17	1.28
2	1.5	4	5.01	1.21
2	3.2	1	3.21	0.69

TABLE 3

The duration of adhesion of mucosa-adhesive formulations under an applied stress

Formulation	*n*	Duration of adhesion (h)	Mean force ($N\ cm^{-2}$) after 8 h	S.D.
Carbopol 934P	4	8	0.88	0.09
Carbopol EX55	4	> 8	2.01	0.25

main constant but reduced slowly over each hour. Carbopol EX55 was adhesive for 8 h, while adhesive failure with the Carbopol 934P discs was seen to result from cohesive failure of the formed gel layer.

Discussion

The initial investigation using discs of Carbopol 934P revealed that this apparatus was able to detect mucosa-adhesion, although the variation in the results suggested that smaller changes in adhesive properties may go undetected.

The rank order of adhesive force agrees with previous investigations (Table 1). Carbopol 934 is known to be a good mucosa adhesive while HPMC is less so, gelatin is a fair adhesive and PEG is not adhesive (Smart et al., 1984; Chen and Cyr, 1970). This technique may therefore be seen to give data in agreement with previous investigations.

The increased adhesive force obtained when increasing the rate at which the tensile force is applied (Table 2) would suggest that the adhesive

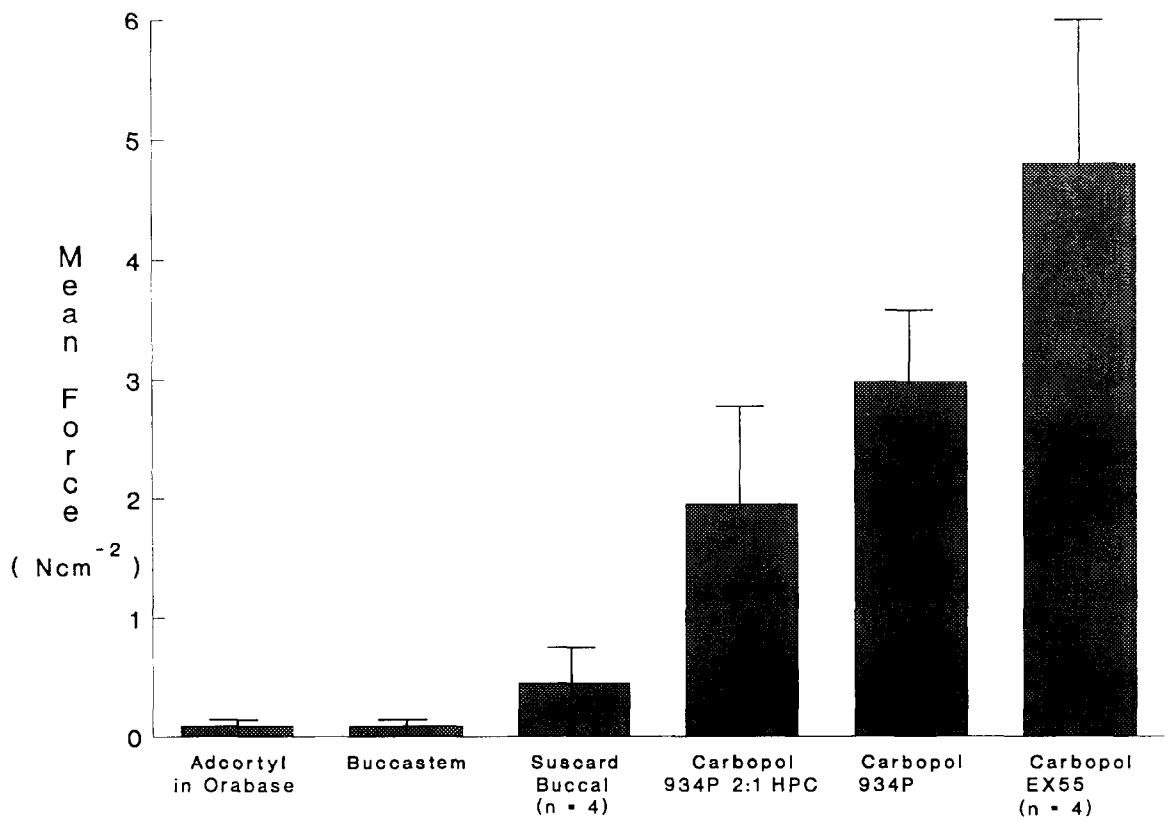

Fig. 2. A comparison of some mucosa-adhesive formulations ($n = 5$ except where stated otherwise).

bond is viscoelastic in nature, i.e. at faster rates of stress application the adhesive bond has less time to deform and flow. Varying the contact time did not have a significant effect on the adhesive force and it may be concluded that adhesive bond formation is fairly rapid. Doubling the consolidation force prior to testing did not have a significant effect in this study.

The poly(acrylic acid)-containing formulations (Carbopol 934P and Carbopol EX55) demonstrated the greatest adhesive force (Fig. 2). Formulations containing Carbopol 934P and HPC have been developed (Nagai, 1986). The presence of HPC reduced, but not significantly ($P > 0.05$, Student's t-test) the adhesive force, thus confirming that it is possible when formulating to 'dilute' the Carbopol 934P in a mucosa-adhesive preparation. Both Suscard Buccal, containing modified HPMC and Buccastem, containing ceratonia and xanthan gum, would be predicted to be less adhesive than the poly(acrylic acids) (Smart et al., 1984), and this is confirmed in this study. As both are established buccal delivery systems it may be concluded that only a small adhesive force is required to retain a dosage form within the buccal cavity. This would be an important consideration when formulating an adhesive dosage form for buccal delivery as stronger adhesives, which may cause mucosal damage, may not be necessary for this route.

When subjected to a constant stress, the gradual reduction in the tensile force over 1 h may be explained by the deformation and swelling of the hydrating test disc. Carbopol 934P remained adhesive for up to 8 h (Table 3), but was observed to have swollen to form a clear gel. Adhesive joint failure was seen to be a cohesive failure of the gel. Carbopol EX55 remained adhesive for 8 h, and a significantly larger ($P < 0.05$, Student's t-test detachment force was required to dislodge it. Thus it may be concluded that the more heavily cross-linked Carbopol EX55 would be a better candidate for stable long term mucosa-adhesion.

This test system provided information on both the strength and stability of the adhesive bond and will be used in the further development of bioadhesive controlled drug delivery systems. In future work this in vitro system will be developed to further investigate the stresses likely to be experienced by a dosage form within a body cavity, i.e. tangential and peeling stresses.

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