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The adhesiveness of proprietary tablets and capsules to porcine oesophageal tissue

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Summary

A direct method of measuring the adhesion of tablets and hard-shell capsules to moist oesophageal tissue ex vivo is described and used to assess the adhesivity of some commercial formulations. Uncoated and sugar-coated tablets exhibited low adhesion, the forces required for detachment varying between 0.5 and 2.5 mN, while capsules were more adhesive with detachment forces between 25 and 88 mN. Film-coated tablets showed considerable variation, some exhibiting low adhesivity while others displayed detachment forces between 45 and 90 mN. Although there is some correlation between adhesivity of experimental dosage forms and oesophageal transit, the relatively rapid loss of film coats by dissolution reduces the significance of these measurements to adhesion in more distant parts of the gastrointestinal tract.

Introduction

The adhesiveness of oral dosage forms during their passage down the oesophagus has been suggested to be a cause or preliminary step in the oesophagitis and dysphagia following ingestion of solid medication (Kikendall et al., 1983). It is known that gelatin becomes adhesive on hydration and that some film-coating materials display a degree of tackiness which may be problematic during film-coating procedures (Chopra and Tawashi, 1985), but little is known about the mechanisms of adhesion to tissue. Marvola and coworkers (1982) developed a technique to assess the tendency of tablets and capsules to adhere to mucosal surfaces which involved pulling the dosage form through an intact oesophagus and measuring the forces required to separate the tablet or capsule from the isolated preparation. We have developed (Florence et al., 1984) an alternative technique in which the forces of separation are measured without frictional stress, thereby allowing a more direct analysis of adhesion.

Here we describe the technique and report on the adhesivity of a series of commercial dosage forms to porcine oesophageal tissue ex vivo. The products studied were chosen because of their reported implication in adverse reactions (Al-Dujaili et al., 1983) or their unusual physical characteristics such as size or shape.

Materials and Methods

The proprietary formulations of tablets and capsules examined and their characteristics are listed in Tables 1–3.

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TABLE 1

COMMERCIAL UNCOATED AND SUGAR-COATED TABLETS EXAMINED FOR ADHESIVITY

Brand name (Manufacturer)	Form	Drug	Diam./Length (mm)
Brontina (Brocades)	Uncoated	Deptropine citrate	6.1
Isoket Retard (Schwarz)	Uncoated	Isosorbide dinitrate	9.0
Midamor, 5 mg (Morson)	Uncoated	Amiloride hydrochloride	9.6
Nu-Seals Aspirin (Lilly)	Sugar-coated	Aspirin	14.8
Rinurel (Warner)	Uncoated	Paracetamol, phenylpropanolamine, phenyltoloxamine citrate	10.5
Sorbitrate, 20 mg (Stuart)	Uncoated	Isosorbide dinitrate	10.0
Tedral SA (Warner)	Uncoated	Theophylline, ephedrine hydrochloride	9.6
Terramycin, 100 mg (Pfizer)	Sugar-coated	Oxytetracycline	10.5
Terramycin, 250 mg (Pfizer)	Sugar-coated	Oxytetracycline	10.5

TABLE 2

COMMERCIAL FILM-COATED TABLETS EXAMINED FOR ADHESIVITY

Brand name (Manufacturer)	Drug	Diam./Length (mm)
Achromycin (Lederle)	Tetracycline hydrochloride	9.8
Aldomet, 500 mg (Merck Sharp and Dohme)	Methyldopa	12.9
Berkolol, 40 mg (Berk)	Propranolol hydrochloride	8.1
Ceporex, 500 mg (Glaxo)	Cephalexin	11.7
Cetiprin, 200 mg (old formulation, KabiVitrum)	Emepronium bromide	11.2
Cetiprin, 200 mg (new formulation, KabiVitrum)	Emepronium bromide	11.2
Crystapen V (Glaxo)	Penicillin V	10.2
Deteclo (Lederle)	Tetracycline, chlortetracycline and demeclocycline hydrochlorides	11.2
Erycen, 250 mg (Berk)	Erythromycin	10.7
Erythromic, 250 mg (Abbott)	Erythromycin	10.8
Ferrograd C (Abbott)	Ferrous sulphate, sodium ascorbate	18.3
Fortral (Winthrop)	Pentazocine hydrochloride	9.7
Glucophage, 850 mg (Rona)	Metformin hydrochloride	12.9
Imperacin (ICI)	Oxytetracycline	10.5
Inderal, 40 mg (ICI)	Propranolol hydrochloride	8.2
Inderal, 160 mg (ICI)	Propranolol hydrochloride	11.1
Irofol C (Abbott)	Ferrous sulphate, sodium ascorbate, folic acid	18.3
Lopresor, 100 mg (Geigy)	Metoprolol tartrate	11.2
Napsalgesic (Dista)	Dextropropoxyphene napsylate, aspirin	15.5
Osmosin (Merck Sharp and Dohme)	Sodium indomethacin	8.3
Ponstan Forte (Parke Davis)	Mefenamic acid	19.2
Tetrachel (Berk)	Tetracycline	10.2

TABLE 3

COMMERCIAL CAPSULE FORMULATIONS EXAMINED FOR ADHESIVITY

Brand name (Manufacturer)	Drug	Length (mm)
Anafranil, 10 mg (Geigy)	Clomipramine hydrochloride	14.0
Anafranil, 25 mg (Geigy)	Clomipramine hydrochloride	14.1
Dalacin C (Upjohn)	Clindamycin hydrochloride	16.0
Epanutin, 100 mg (Parke Davis)	Phenytoin sodium	15.8
Epanutin with phenobarbitone (Parke Davis)	Phenytoin sodium, phenobarbitone	15.0
Expansyl Spansule (Smith Kline and French)	Ephedrine sulphate, diphenylpyraline hydrochloride, trifluoperazine hydrochloride	17.8
Gevral (Lederle)	Multivitamins, minerals	24.8

Measurement of adhesion to oesophageal tissue

The technique was developed after consideration of the method of Marvola and colleagues (1982), with the intention of quantifying adhesion by measuring the forces required to separate two parallel surfaces without both adhesional and frictional forces coming into play. The apparatus developed is shown in Fig. 1; it comprised a modified electronic balance with which the force required to separate moist oesophageal tissue from one surface of a dosage form could be determined. The balance (Oertling Model R20) was modified by affixing to the balance pan a plastic stub (D), on to which a 3×2 cm strip of fresh porcine oesophagus (preserved in cold Krebs' solution) was fixed by the serosal surface with Histoacryl adhesive. The dosage form (C) to be tested was fixed to the bottom of the fine adjustment screw (A) in the adjustable holder (B) straddling the pan. The tablet or capsule was lowered until in contact with the moist mucosal surface (without pressing on it) and left for 1 min. The additional weight (m) required for complete separation of the dosage form from the oesophageal strip was recorded and used to calculate the detachment force ($F = m \cdot g$).

Measurement of film coat thickness

An epi-fluorescence microscope fitted with an eye-piece graticule was used. Cross-sections of tablet samples were prepared and the coat thickness measured directly.

Results and Discussion

The forces required to detach proprietary tablets and capsules are shown in Figs. 2–4. The mean forces for sugar-coated and uncoated tablets were low, varying between 0.5 and 2.5 mN while those for capsules were higher, lying between 25 and 88 mN. This is in agreement with the results of Marvola and co-workers (1982, 1983), and the more recent data of Swisher et al. (1984) who used a similar isolated oesophagus technique.

Large variations in adhesivity were noted between film-coated preparations (Fig. 4); some displayed high detachment forces, which varied between 45 and 90 mN, while other film-coated tablets showed lower forces of detachment. The highest recorded detachment forces were recorded for Osmosin tablets; in one experiment a force of 120 mN, the limit of the apparatus, failed to detach the tablet for 15 min although the oesophageal mucosa had become separated from the underlying muscle (Fig. 5). On removal of the coloured outer hydroxypropylmethylcellulose (HPMC) film coat on Osmosin, the mean force of adhesion of the tablet was substantially reduced to about 3 mN (Fig. 4).

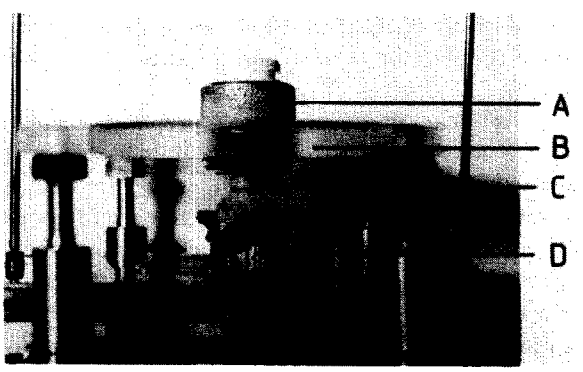

Fig. 1. Apparatus for measurement of adhesiveness of solid dose forms to oesophageal tissue: (A) fine adjustment screw, (B) adjustable plastic holding frame, (C) test specimen, (D) plastic stub with attached strip of porcine oesophagus.

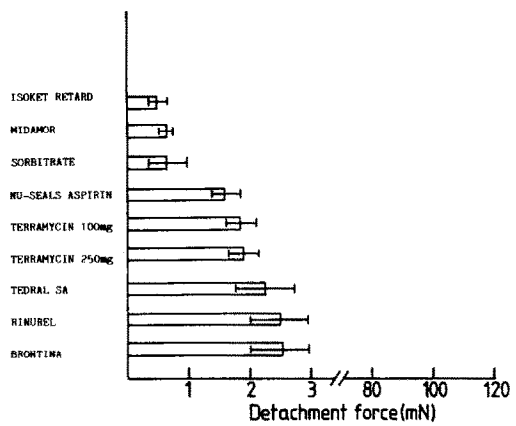

Fig. 2. Forces required to detach proprietary uncoated and sugar-coated tablets from oesophageal tissue (bars indicate range, $n \geqslant 6$).

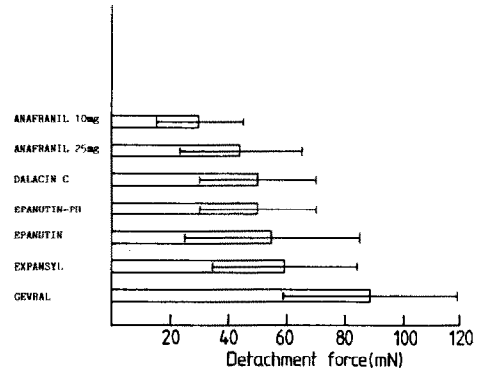

Fig. 3. Forces required to detach proprietary hard-shell gelatin capsules from oesophageal tissue (bars indicate range, $n \geqslant 6$).

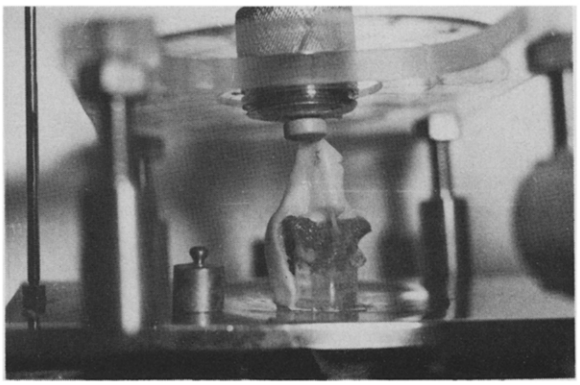

Fig. 5. Adhesiveness of an Osmosin tablet: the HPMC-coated tablet adhered sufficiently strongly to the moist mucosa to separate it from the muscle layer at 120 mN.

Our interest in the adhesivity of moistened dosage forms was aroused by reports of oesophageal ulceration with film-coated tablet formulations of emepronium bromide (Cetiprin). However, it appeared that the manner in which Cetiprin tablets disintegrated was of greater significance

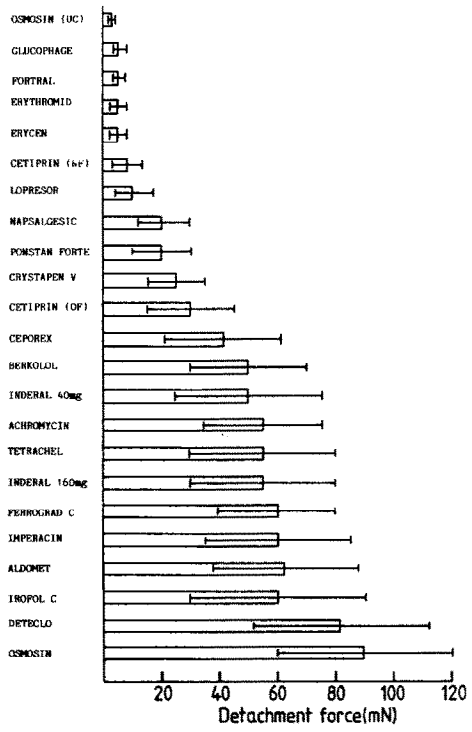

Fig. 4. Forces required to detach proprietary film-coated tablets from oesophageal tissue (NF/OF = new/old formulation, UC = uncoated; bars indicate range, $n \geqslant 6$).

than the adhesivity of the film-coat used in the formulation (Al-Dujaili et al., 1983). At about the same period problems of gastrointestinal ulceration with the OROS system formulation of indomethacin (Osmosin), came to light (Committee on Safety of Medicines, 1983). Cursory examination found the moistened tablet to be extremely adhesive to touch, suggesting that one aspect of the problem might be the adhesiveness of the dosage form to gastrointestinal tissue. While the data presented here was being collated, Swisher et al. (1984) reported measurements of the adhesion of Osmosin to an isolated oesophageal preparation; although the methods of assessment are not directly comparable, it was interesting to note that the substantial differences in adhesivity of coated and uncoated Osmosin tablets shown by our method was reflected in their more elaborate technique (i.e. 90 and 3 mN, and 43 and 3 g, respectively).

It is clear that film-coated preparations can adhere tenaciously to oesophageal mucosa. It is not possible in many cases to identify the nature of the film-coats and hence little can be said about the mechanisms of adhesion, which remain poorly understood (Park and Robinson, 1984). Marvola et al. (1983) found that excipients such as lactose, titanium dioxide and talc increased the tackiness of HPMC and ethyl cellulose film-coats. It is apparent that the formulation of a film-coat as well as its polymeric composition determines the degree of adhesiveness. The times taken for com-

TABLE 4

DISSOLUTION TIMES OF FILM-COATS ON COMMERCIAL TABLET FORMULATIONS IN AQUEOUS MEDIA [a]

Brand name	Time (min)
Achromycin	4
Aldomet	1
Deteclo	3
Erycen	> 40
Erythromid	1–2
Ferrograd C	4
Inderal 40 mg	2
Lopresor	2
Osmosin	2
Tetrachel	2–3

[a] pH 1.2 and 7.5 buffer at 37°C in the BP 1980 rotating-basket dissolution apparatus.

plete loss of film-coat on some commercial formulations rotated in aqueous media (using the epi-fluorescence microscope for measurement of film thickness) are shown in Table 4. Although in general the rates of solution of coatings are such that they are unlikely to persist until dosage forms reach the intestine (and effective tablet disintegration would ensure the loss of coat integrity), the rapid transference of solid dosage forms into the oesophagus suggests that problems could arise with tacky systems having slowly-dissolving coatings, the consequences of delaying descent in this way are particularly serious in cases when non-disintegrating sustained release formulations contain irritant drugs.

The ex vivo experiments reported here cannot replace studies in human subjects but they can indicate potentially abnormal behaviour. Some preliminary human oesophageal transit experiments using experimental formulations and gamma-scintigraphy showed the mean transit times to the lower part of the oesophagus for uncoated tablets and No. 4 and 000 hard-shell capsules were 5, 3 and 10 min, respectively; the mean detachment forces ± S.D. for these dose forms were 18 ± 6, 28 ± 10 and 48 ± 16 mN, respectively. The two capsules showed the anticipated rank order but our data were not sufficiently numerous to permit better correlations. In the following paper (Al-Dujaili et al., in press) an in vitro technique which allows investigation of the factors affecting adhesivity of experimental dosage forms coated with films of known composition is described.

References

Al-Dujaili, H., Salole, E.G. and Florence, A.T., Drug formulation and oesophageal injury. *Adv. Drug React. Ac. Pois. Rev.*, 2 (1983) 235–256.

Al-Dujaili, H., Florence, A.T. and Salole, E.G., In vitro assessment of the adhesiveness of film-coated tablets. *Int. J. Pharm.*, in press.

Chopra, S.K. and Tawashi, R., Tack behaviour of coating solutions. III. *J. Pharm. Sci.*, 74 (1985) 746–749.

Committee on Safety of Medicines, *Current Problems* No. 11 (1983), Committee on safety of Medicines, London.

Florence, A.T., Salole, E.G. and Al-Dujaili, H., Osmosin tablets. *Pharm. J.*, 232 (1984) 308.

Kikendall, J.W., Friedman, A.C., Oyewole, M.A., Fleischer, D. and Johnson, L.F., Pill-induced oesophageal injury: case reports and review of the medical literature. *Dig. Dis. Sci.*, 28 (1983) 174–182.

Marvola, M., Rajaniemi, J., Marttila, E., Vahervuo, K. and Sothmann, A., Effect of dosage form and formulation factors on the adherence of drugs to the esophagus. *J. Pharm. Sci.*, 72 (1983) 1034–1036.

Marvola, M., Vahervuo, K., Sothmann, A., Marttila, E. and Rajaniemi, M., Development of a method for study of the tendency of drug products to adhere to the esophagus. *J. Pharm. Sci.*, 71 (1982) 975–977.

Park, K. and Robinson, J.R., Bioadhesive polymers as platforms for oral-controlled drug delivery: method to study bioadhesion. *Int. J. Pharm.*, 19 (1984) 107–127.

Swisher, D.A., Sendelbeck, S.L. and Fara, J.W., Adherence of various oral dosage forms to the esophagus. *Int. J. Pharm.*, 22 (1984) 219–228.