neurotensin analogues. The relative biological activity towards contraction of guinea-pig ileum was assessed using a 4 point assay procedure. The results are shown in Table 2.

The contractile activity was reduced by removing the *N*-terminal amino-acid but the shortest chain peptide NT_{8-13} still showed activity corresponding to one fifth of that of neurotensin. This suggests that the amino-acid in the *C*-terminal region seems to be more important for the contractile activity than that in the *N*-terminal region. The most interesting fact is that there is a chemical resemblance between NT_{6-13} and xenopsin, pyrGlu-Gly-Lys-Arg-Pro-Trp-Ile-Leu-OH, which was recently isolated from the frog skin (Araki, Tachibana & others, 1973). Xenopsin was found to have a moderate contractile activity on guinea-pig ileum with the threshold dose of $1{\cdot}25 - 6{\cdot}25 \times 10^{-5}$ M (Araki & others, 1973). In this experiment, both NT_{8-13} and NT_{6-13} produced considerable contraction on guinea-pig ileum at a dose of 2×10^{-7} M. Therefore our results suggest that Arg_8 and/or Tyr in *C*-terminal region are necessary for the contractile activity of neurotensin on guinea-pig ileum.

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The adhesion of film coatings to tablet surfaces-measurement on biconvex tablets

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The adhesion of a film coating to a tablet substrate has recently been quantified by measuring the force required to remove the film from a known area of the tablet surface using a specially designed tensile testing apparatus (Fisher & Rowe, 1976). In an attempt to obtain a direct measure of the adhesive forces the instrument was designed to remove the film normal to the tablet surface. This implies that the technique is only applicable to flat-faced tablets since during the testing of film-coated biconvex tablets, there is progressive removal of the film from around the edges of the tablet to the centre. This paper examines the possibility of using the apparatus in the measurement of the adhesion of film coatings to biconvex tablets.

Four sizes of tablets (6·25, 7·94, 10·0 and 11·11 mm diameter, biconvex and flat-faced) were prepared by compressing a standard placebo granule consisting of lactose, starch and magnesium stearate using an instrumented tablet machine (Type F3 Manesty Machines Ltd). To minimize porosity changes in the tablets all were compressed at a constant compression pressure of 200 MPa. The tablets were coated with a film formulation consisting of a mixture of four parts hydroxypropyl methylcellulose and one part ethylcellulose (Grade N7 Hercules Powder Co. Ltd.) with 20% w/w glycerol as plasticizer, applied as a 2·5% w/v solution dissolved in a dichloromethane–methanol (70 : 30% v/v) solvent mixture using either a 6 inch diameter Wurster column or 24 inch Accelacota Manesty Machines Ltd). To obtain a range of coatings with varying adhesions, three grades of hydroxypropyl methylcellulose were used, Pharmacoat 603, Pharmacoat 606 (Shinetsu Chemical Co. Ltd., Japan) and Methocel HG60 viscosity 50 (Dow Chemical Co., U.S.A.). The thickness of the film was approximately 30–40 μm and the tablets were stored at room temperature and 50° R.H. for two weeks before testing. Ten tablets were used for each measurement and the mean and standard deviation calculated. The work done in removing the film was calculated from the areas under the traces obtained from the ultraviolet recorder.

In all the experiments performed (Table 1) the forces required to remove the film from biconvex tablets were consistently lower than those required to remove the same film from the corresponding flat-

Table 1. *The forces required and the work done in removing three film formulations from a placebo tablet substrate.* The correlation coefficients were determined by the method of least squares.

Formulation	Diam. of tablet	Force required to remove film N		Correlation coefficients d^2 *vs* force		Work done in removing film mJ		Correlation coefficients d^2 *vs* work done	
		Flat	Biconvex	Flat	Biconvex	Flat	Biconvex	Flat	Biconvex
Pharmacoat 603 (Coated on Wurster)	6·25	1·288 ± 0·345	0·785 ± 0·117			0·782 ± 0·253	0·534 ± 0·117		
	7·94	1·692 ± 0·312	1·053 ± 0·092	0·995	0·930	1·222 ± 0·459	0·850 ± 0·135	0·982	0·965
	10·0	2·844 ± 0·516	2·027 ± 0·447			2·293 ± 0·520	2·077 ± 0·075		
	11·11	3·357 ± 0·443	1·869 ± 0·197			2·443 ± 0·381	2·108 ± 0·278		
Pharmacoat 606 (Coated on 24 inch Accelacota)	6·25	1·560 ± 0·247	0·925 ± 0·133			1·009 ± 0·270	0·746 ± 0·197		
	7·94	2·484 ± 0·593	1·742 ± 0·415	0·995	0·929	2·018 ± 0·494	1·725 ± 0·482	0·981	0·973
	10·0	3·358 ± 1·002	2·957 ± 0·408			3·155 ± 1·271	3·608 ± 0·938		
	11·11	4·045 ± 0·622	2·699 ± 0·259			3·429 ± 0·858	3·694 ± 0·399		
Methocel HG60 visc 50 (Coated on 24 inch Accelacota)	6·25	1·629 ± 0·180	0·939 ± 0·102			0·894 ± 0·254	0·725 ± 0·254		
	7·94	2·374 ± 0·486	2·053 ± 0·465	0·992	0·886	1·507 ± 0·428	1·954 ± 0·513	0·987	0·966
	10·0	2·993 ± 0·543	2·492 ± 0·497			1·967 ± 0·435	2·394 ± 0·543		
	11·11	3·482 ± 0·629	2·468 ± 0·221			2·629 ± 0·669	3·287 ± 0·332		

faced tablets. These forces increased with the diameter of the tablet but whereas there was a direct relation between the forces and the square of the diameters for flat-faced tablets, a maximum was reached in the case of biconvex tablets and no such correlation was found. Measurements of the work done showed no maximum and were directly related to the square of the diameter for both flat-faced and biconvex tablets.

In any evaluation of adhesion it is generally assumed that the adhesion is uniform over the total area of the film/substrate interface and therefore any measurement must reflect this in that it must be proportional to the surface area of contact between the film and substrate. The area of the convex surface of a tablet is given by the formula $2\pi r_w h$ where r_w and h are the radius and height respectively of curvature. Since this area is directly related to the area of the equivalent diameter flat-faced tablet (the factor in this case was calculated as 1·047), the square of the diameter of a tablet is directly related to the surface areas of both tablets. The correlation between the work done in removing the film and the square of the diameter suggests, therefore, that this mode of analysis gives a more accurate and quantitative measure of the film/substrate adhesion than a direct force measurement, although for flat-faced tablets either is satisfactory.

However, one small anomaly still exists in that the work done in removing the film from biconvex tablets is either smaller (in the case of small diameter tablets) or insignificantly different (in the case of the larger diameter tablets) than that in removing the film from flat faced tablets even although the biconvex tablets have a marginally greater area of contact. This discrepancy may well be due to either or both of the following reasons:

(i) differences in the physical properties (smoothness, microporosity) of the actual surface in contact with the film, although no significant differences in the porosity of the tablets could be detected using mercury pycnometry (all were within the range 13·3–16·0%). Even if as is generally accepted, the surface porosity at the crown of a biconvex tablet is marginally greater than at the edges, due to force variation on compression, a slight increase in the adhesion would be expected for these tablets rather than the decrease reported;

(ii) differences in the way the film is removed during the test. In the case of biconvex tablets there is a shearing action due to peeling while in the case of flat-faced tablets the action is mainly tensile.

The results show that if biconvex tablets are to be used for testing, as would probably be the case during product development, the work done in removing the film gives a much more accurate and quantitative measure of the adhesion than direct force measurement. Although the results have been presented as a work done in removing the film, this can easily be converted to the work of adhesion—defined as the work done in removing unit area of film—by correction for the surface area.

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