ELSEVIER

International Journal of Pharmaceutics 114 (1995) 227–236

international journal of pharmaceutics

The potential use of tomato lectin for oral drug delivery: 3. Bioadhesion in vivo

Barbara Naisbett [1,*], John Woodley

Drug Delivery Group, Department of Biological Sciences, Keele University, Keele ST5 5BG, UK

Received 2 June 1994; accepted 20 July 1994

Abstract

^{125}I-labelled tomato lectin ([^{125}I]TL) was evaluated as a bioadhesive for oral drug delivery following intra-gastric administration to adult rats. It was compared with two control molecules, [^{125}I]polyvinylpyrrolidone ([^{125}I]PVP), an inert polymer, and ^{125}I-labelled bovine serum albumin ([^{125}I]BSA), a degradable protein of similar molecular weight. The intestinal transit, body distribution and degradation of the macromolecules were determined 1, 5, 10 or 24 h after oral feeding and the behaviour and patterns of distribution were compared. TL was found to be resistant to degradation, with 12% of the recovered dose appearing as high molecular weight fractions in the faeces after 24 h. After 1 and 5 h, 80 and 50% of the recovered activity was found in the gastrointestinal (GI) tract, respectively. Up to 20% of the radioactivity was associated with intestinal tissue at these time points. 100% of the PVP was recovered in the faeces after 24 h. At 1 and 5 h, virtually all the PVP activity was associated with intestinal washings. BSA was degraded completely during transit with 95% of the recovered activity found in the urine and 5% in the thyroid gland after 24 h. Although these results indicate that TL is resistant to degradation in the GI tract and that it adheres to intestinal tissue, little difference was seen in the transit times of TL and PVP. This may have been due to interactions of TL with intestinal mucus and could limit the potential of TL for use as an intestinal bioadhesive.

Keywords: Bioadhesion; Tomato lectin; Intestinal transit time; Oral drug delivery; Body distribution

1. Introduction

One of the major problems with oral drug delivery formulations is the speed with which they pass through the gastrointestinal tract. With a small intestinal transit time of less than 3 h, the contact time of a drug formulation, or its residence time within the small intestine, is often too short to allow complete absorption of a drug. Thus, a drug delivery system may pass rapidly through the small intestine, the area of maximum drug absorption, and arrive at the colon and release most of its drug there, at a non-optimal site. If the residence time of a drug in the small intestine could be increased, this may lead to improved drug absorption and allow less frequent dosing, thus approaching the goal of once-a-day therapy.

* Corresponding author.

[1] Present address: Leiden/Amsterdam Center for Drug Research, Division of Pharmaceutical Technology, Gorlaeus Laboratories, POB 9502, 2300 RA Leiden, The Netherlands. Tel. +31-71-274219; Fax+31-71-274277.

SSDI 0378-5173(94)00242-8

One approach to delaying intestinal transit has been the use of bioadhesives, although as most of these systems have been developed as gastroadhesives, the delay in transit is really an effect caused by a delay in gastric emptying (Fell et al., 1987; Read and Sugden, 1987; Harris et al., 1990). Bioadhesives have been used to promote dosage form residence time as well as improving intimacy of contact with various absorptive surfaces of biological systems. They can also act as platforms for controlled release dosage forms and may exert some control over the rate and amount of drug release and contribute to the therapeutic advantage of such systems (Gupta et al., 1990). Bioadhesives have been shown to work in the mouth and cervix, but authors dispute their effectiveness, particularly in the GI tract where strong shear forces may prevent adherence and mucus may interfere with the binding (Davis, 1985; Gruber et al., 1987).

To date, most intestinal bioadhesives have been based on synthetic polymers (Duchene et al., 1988; Leung and Robinson, 1990), which are usually known as 'mucoadhesives' because of their ability to attach to the intestinal mucus. Gupta (1990) suggested that most bioadhesive polymers bind to mucus and never penetrate deep enough to form a bond with the underlying epithelial cells. Our approach to bioadhesion, however, has been a biological one, utilizing carbohydrates exposed on the epithelial cell surface. The epithelium may become exposed when the mucus layer is interrupted, thus allowing bioadhesives access to the carbohydrates of the enterocyte surface.

Carbohydrates are found bound covalently to proteins and lipids to form glycoproteins and glycolipids, which are an integral part of the enterocyte membrane. The carbohydrate chains project out from the cell surface and form the glycocalyx or 'fuzzy coat', which is maintained and synthesized continuously by the underlying cells. These carbohydrates represent important binding sites for bacterial adhesion. For example, enterotoxigenic *Escherichia coli* attach to the intestinal epithelium via surface lectins on the pili (Festa, 1987; Gupta, 1990) and colonize the gut. Lectins, which are carbohydrate-binding proteins or glycoproteins that bind specific sugar residues, may be used as bioadhesives, following this model of bacterial adhesion, and research is now taking place to investigate the use of type I fimbriae from *E. coli* as intestinal bioadhesives for drug delivery (Caston et al., 1990).

This paper describes the in vivo interaction of the non-toxic tomato lectin (TL), with the adult rat intestine after intra-gastric administration. This lectin has previously been shown to bind avidly to small intestinal gut rings in vitro, and to individual glycoproteins isolated from enterocyte brush border membranes (Naisbett and Woodley, 1994a). This binding was shown to be specific and inhibited by preincubation with competing sugars. In an improved in vitro culture system of gut sacs, TL has also been shown to be taken up by enterocytes by adsorptive endocytosis (Naisbett and Woodley, 1994b).

The strong bioadhesive properties of TL in vitro suggested that the lectin may have potential for increasing the intestinal residence time of drugs in vivo. The experiments described here were developed to follow the intestinal transit and body distribution of radiolabelled tomato lectin, [^{125}I]TL, after oral administration to adult rats. The behaviour and pattern of distribution were compared with radiolabelled polyvinylpyrrolidone ([^{125}I]PVP) and bovine serum albumin ([^{125}I]BSA), control macromolecules representing an inert polymer and a degradable protein, respectively.

2. Materials and methods

2.1. Tomato lectin

TL was purified by chromatofocusing and radiolabelled with Na^{125}I using Iodobeads, as described earlier (Naisbett and Woodley, 1994a). BSA was radiolabelled via the same method and [^{125}I]PVP was purchased from Amersham International, plc, U.K.

2.2. Transit time and body distribution

Radiolabelled substrate was administered (in 0.6 ml of 0.85% w/v NaCl) by intubation to the

stomach of lightly anaesthetised adult male Wistar rats (250–300 g) which had been starved for 24 h. Animals were allowed to recover and were kept in metabolic cages (with free access to food and water), to facilitate collection of urine and faeces, before killing at times up to 24 h. Blood was collected (50 μl) from the heart and immediately suspended in 1.0 ml of 1 M NaOH. The total blood volume was calculated from the estimate that for every 100 g of body mass, an adult rat contains 7.2 ml of blood (Seymour et al., 1987). The small intestine, stomach, caecum and large intestine were removed and each part washed out separately with 0.85% (w/v) NaCl. The intestinal tissues were weighed and digested in 1 M NaOH. Other organs were excised, weighed and digested in 1 M NaOH, faeces were suspended in 1 M NaOH and the remaining carcass was digested in 10 M NaOH. The intestinal washings, digested intestinal tissue, organs, carcass, urine and faeces were counted for radioactivity and the amount of radioactivity found in each part was calculated as a percentage of the total dose recovered.

Table 1 lists the organs which were removed routinely during these experiments.

2.3. Paper electrophoresis

Urine and faeces were analysed by paper electrophoresis, to indicate the amount of high and low molecular weight radiolabelled fragments produced by digestion during transit. Solutions of urine or faeces were loaded 5 cm from the end of a length of chromatography paper (Whatman No.1, 5 cm × 30 cm) and electrophoresed in 0.1 M barbitone/sodium barbitone, pH 8.6, in a Shandon-Southern electrophoresis tank for 20

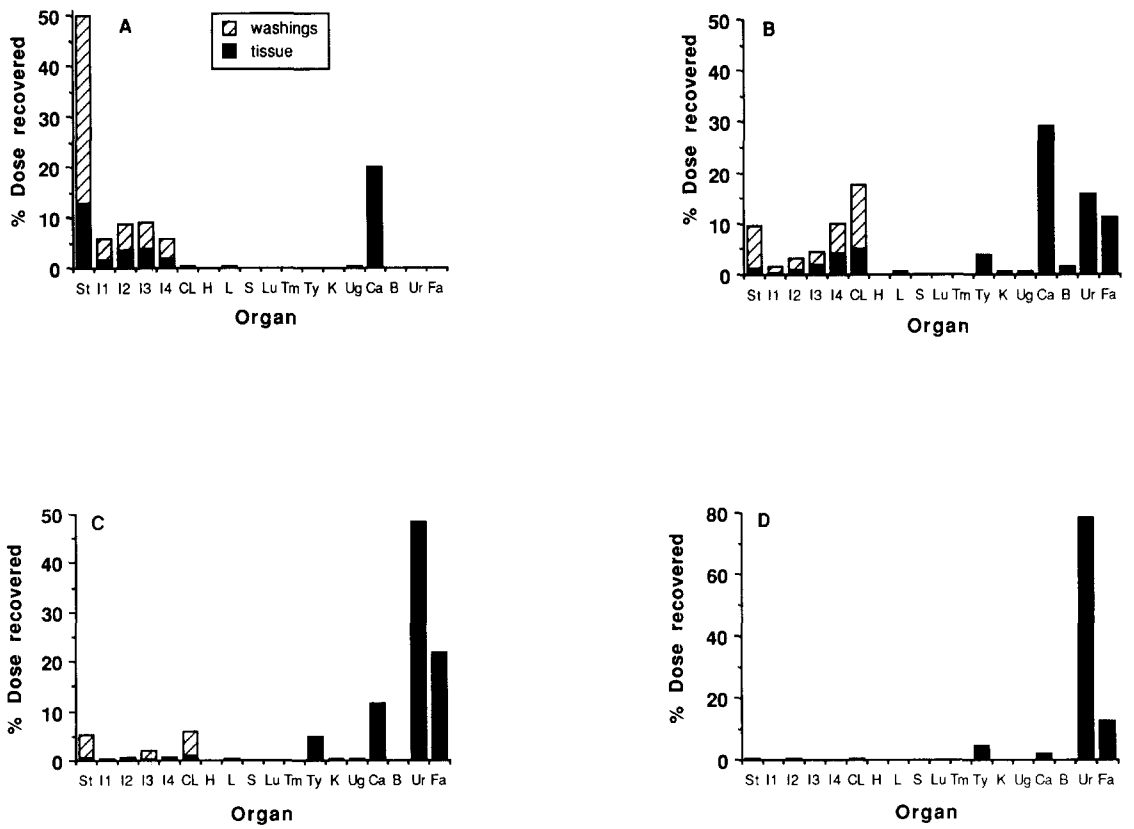

Fig. 1. [^{125}I]TL body distribution. (a) 1 h; (b) 5 h; (c) 10 h; (d) 24 h. Results are the mean of three animals.

Table 1
Organs removed during in vivo experiments

Organ	Symbol
Blood	B
Stomach	St
Small intestine part 1	I 1
Small intestine part 2	I 2
Small intestine part 3	I 3
Small intestine part 4	I 4
Caecum and large intestine	CL
Heart	H
Liver	L
Spleen	S
Lungs	Lu
Thymus	Tm
Thyroid	Ty
Kidneys	K
Urogenital tract	Ug
Urine	Ur
Faeces	F
Carcass	Ca

min at 13 mA, 400 mV. A total of four strips was electrophoresed each time to ensure that the current was consistent. The paper strips were then cut into strips of equal size (0.5 cm) and counted individually for radioactivity.

3. Results and discussion

3.1. Lectin body distribution

The distribution of radioactivity recovered following oral administration of ^{125}I-labelled tomato lectin is shown in Fig. 1a–d. Hatched bars show radioactivity associated with intestinal washings and solid bars indicate radioactivity found in the tissues. After 1 h (Fig. 1a), over 80% of the dose was recovered from the stomach and small intestine, with the greater part of this radioactivity

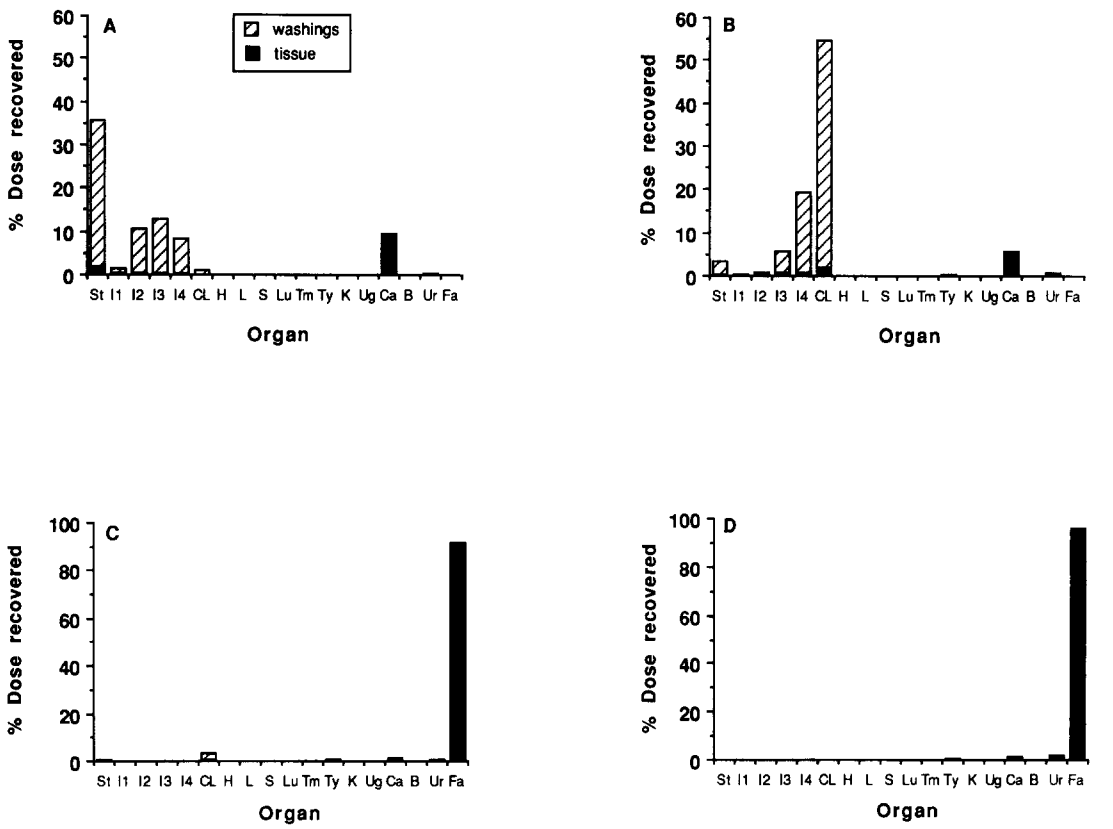

Fig. 2. [^{125}I]PVP body distribution. (a) 1 h; (b) 5 h; (c) 10 h; (d) 24 h. Results are the mean of three animals.

being found in the stomach. Although the majority of the activity was recovered from gut washings rather than gut tissue, tissue-associated activity accounted for 20% of the recovered dose. 20% of the dose was recovered from the carcass.

After 5 h (Fig. 1b), gastric-associated radioactivity had fallen to less than 10% and caecum and large intestine accounted for almost 20% of the dose. However, GI radioactivity still accounted for almost 50% of the recovered dose and approx. 14% of this was associated with gut tissue. Activity was also found in the blood, urine and thyroid gland and 30% of the dose was found in the carcass. This indicated breakdown and uptake of lectin fragments by the gut. However, over 10% of the dose was recovered in the faeces. After 10 h, a residual amount of lectin was found in the GI tract, the majority of this activity being found in the intestinal washings (Fig. 1c). 5% was retained in the stomach and 5% in the caecum and large intestine. The majority of the dose after 10 h was recovered from the urine, thyroid gland and carcass and over 20% in the faeces.

After 24 h (Fig. 1d), 80% of the dose was found in the urine, 12% in the faeces and the remainder in the carcass and thyroid. Samples of faeces after 24 h dosing were analysed by paper electrophoresis to determine whether TL was still in a high molecular weight form.

3.2. PVP body distribution

[^{125}I]PVP was used as a control inert, non-metabolizable polymer to follow and compare the transit time of the labelled macromolecules. Results are shown in Fig. 2a–d.

1 h after feeding [^{125}I]PVP (Fig. 2a), over 70% of the dose was recovered in the gastrointestinal

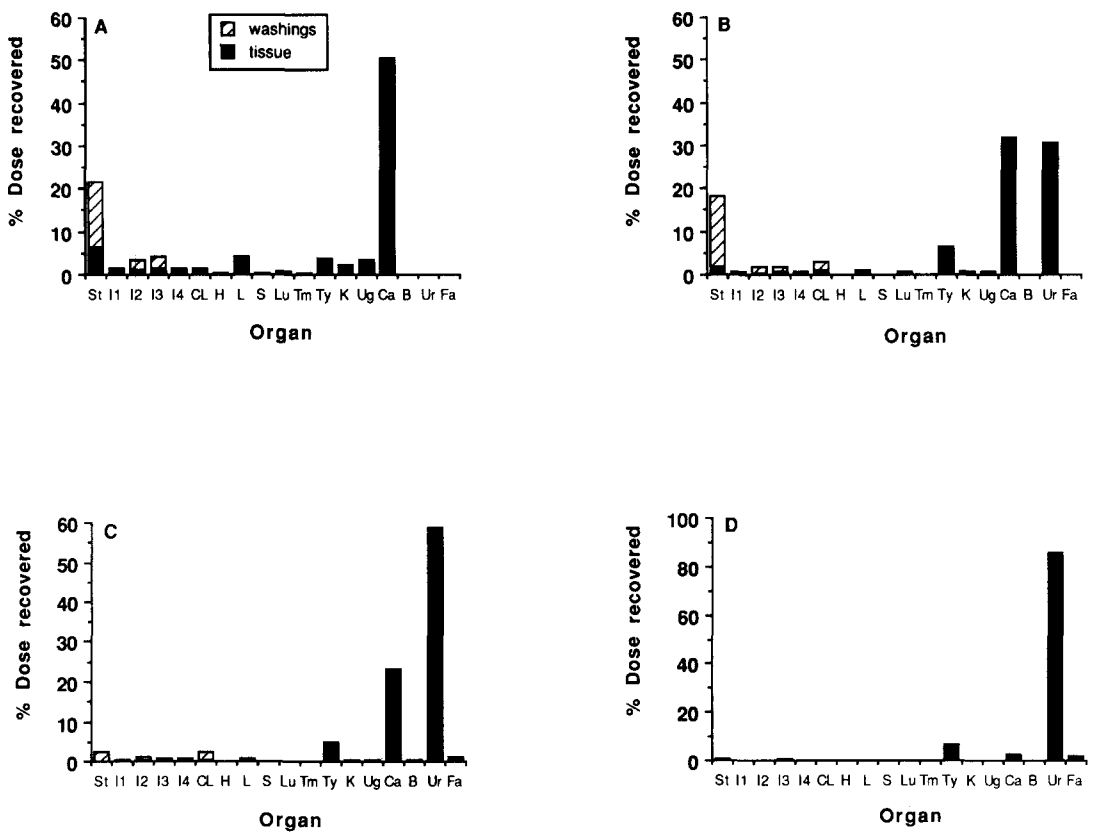

Fig. 3. [^{125}I]BSA body distribution. (a) 1 h; (b) 5 h; (c) 10 h; (d) 24 h. Results are the mean of three animals.

tract. Virtually all of this radioactivity was associated with gut washings and, except for the stomach, there was little or no tissue association. This was in contrast with lectin which showed significant tissue association. 10% of the dose was found in the carcass.

After 5 h (Fig. 2b), almost 90% of the PVP remained in the GI tract. 80% was found in the fourth part of the small intestine, caecum and large intestine in contrast with lectin which showed a more even distribution over the whole length of the intestine, with up to 10% of the lectin remaining in the stomach.

A small amount of activity (< 2%) was discovered in the urine and the thyroid gland after 5 h. Whilst PVP was thought to be an inert polymer, it was possible that a small amount of the [^{125}I] label may have been non-covalently bound to the polymer and dissociated from the polymer during transit. Although it has been postulated that there are deiodinases in the intestine which remove iodide from macromolecules (particularly proteins) (Jones, 1977), there has been no direct evidence to show their presence. [^{125}I]PVP was purchased from Amersham International Plc. and there was a possibility that some of these batches were not monodisperse and there may have been fragments which were below 40 KDa molecular weight and which may have been small enough to appear in the urine. This would not explain the appearance of radioactivity in the thyroid, which is thought to be due to the uptake of free iodide.

After 10 h (Fig. 2c), almost 100% of the recovered dose was found in the faeces, with a residual amount (< 2%) in the caecum and large intestinal washings. This pattern was echoed by the graph showing body distribution of PVP after 24 h (Fig. 2d), where almost 100% of the dose was found in the faeces.

3.3. BSA body distribution

[^{125}I]BSA was used in this system to determine the body distribution of a degradable macromolecule (protein) with a similar molecular weight to the lectin, and to compare its distribution pattern with that of tomato lectin. Results are shown in Fig. 3a–d.

1 h after feeding [^{125}I]BSA (Fig. 3a), 30% of the dose was recovered from the gut (mainly from the washings), and 55% found in the carcass. BSA was distributed widely amongst the other organs; liver, thyroid, kidneys and uro-genital tract. This indicated rapid degradation by the gut and uptake of small fragments into the bloodstream. However, very little radioactivity could be found in the blood samples.

After 5 h (Fig. 3b), 20% of the dose remained in the gut, most of this being associated with the stomach washings. Less than 10% was tissue-as-

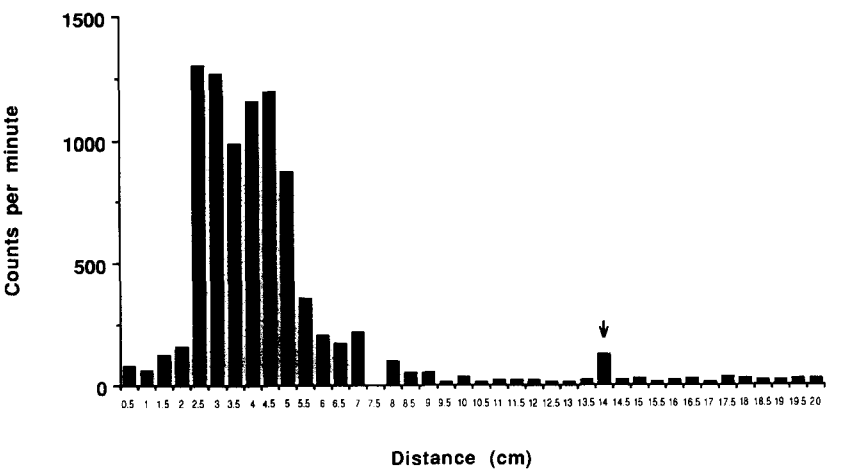

Fig. 4. Paper electrophoresis of faeces 24 h after oral administration of [^{125}I]TL.

sociated. The thyroid showed 7% accumulation, whilst 60% of the dose appeared in the urine and carcass.

10 h post-dosing (Fig. 3c), the majority of the radioactivity was found in the urine and carcass, with a trace amount in the gut and the liver. The thyroid again accumulated almost 7% of the activity. A small amount of the dose was also recovered from the faeces (< 2%). This may have been due to some BSA remaining undigested or, more likely, faeces may have been contaminated by urine due to ineffective separation of urine and faeces by the metabolic cage apparatus.

After 24 h (Fig. 3d), almost 95% of the dose was recovered in the urine and 5% in the thyroid gland. Residual activity was found in the carcass and again, slight contamination of the faeces was seen.

3.4. Recovery of material in the faeces

Samples of faeces were analysed by paper electrophoresis after 24 h feeding experiments with tomato lectin, to determine whether the radioactivity measured was present as high or low molecular weight species.

Fig. 4 shows the appearance in the faeces of ^{125}I-labelled lectin or ^{125}I-labelled lectin fragments. The position of free [^{125}I]iodide, which was co-electrophoresed on separate strips, is marked with an arrow on the profile as a reference. The profile of activity shows most of the radioactivity to be confined to a large high molecular weight peak with some spreading about the peak. This shows that the activity in the faeces represents essentially undegraded or high molecular weight fragments of lectin.

If a radiolabelled non-degradable macromolecule is given as an oral dose, it will be expected to remain intact throughout its passage through the GI tract and appear as high molecular weight species in the faeces. Very little radioactivity would be expected in other body compartments. In contrast, if a degradable macromolecule is administered orally, it will undergo substantial enzymatic degradation with subsequent uptake into the circulation of di- and tripeptides and amino acids. These degradation products are eventually excreted by the kidneys (molecular mass cut off < 50 kDa, depending on molecular size, charge and shape; Smith et al., 1983), and appear as relatively small molecular weight fractions in the urine. Any free [^{125}I]iodide will appear in the thyroid gland which can accumulate ingested iodide at 25–40 times the plasma concentration (Smith et al., 1983). Very little radioactivity would be expected in the faeces.

In this study, PVP and BSA were used as model non-degradable and degradable macromolecules, respectively, in order to compare their body distribution patterns with that of tomato lectin, which was thought to resist digestion to some extent in the GI tract (Kilpatrick et al., 1985). As PVP is an inert polymer, it was also thought to be a good model for measuring GI transit time as it would show little or no interaction with GI mucus or gut mucosa.

The results obtained show that PVP is a good model for a non-degradable, inert macromolecule. 100% of the dose recovered appeared in the faeces, with little radioactivity being found outside the GI tract. Furthermore, radioactivity in the gut was mainly found in the washings fraction and very little was tissue-associated.

BSA showed typical results of a degradable protein. Within 1 h, although the majority of the dose was in the carcass, other organs, including the liver and thyroid, showed the presence of radioactivity. Virtually no BSA was present in the faeces and almost 100% of the dose was recovered in the urine after 24 h.

Body distribution of orally administered tomato lectin displayed characteristics of both non-degradable and degradable macromolecules. After 24 h at least 12% of the dose was found in the faeces and this was shown by paper electrophoresis to be high molecular weight material (Fig. 4). However, the majority of the radioactivity was found in the urine at this time point, and this showed very small labelled fragments on paper electrophoresis (data not shown). 5% of the dose was also found in the thyroid. In summary, whilst tomato lectin was degraded to a large extent by gastrointestinal enzymes during transit, it also demonstrated some resistance to digestion.

3.5. Radioactivity in the carcass

With both BSA and tomato lectin, the observation was made that, whilst virtually no radioactivity could be detected in any of the blood samples at any time point, a large proportion of the doses recovered up to 10 h was found in the carcass. This discrepancy may have been due to the very small (50 μl) samples of blood taken. The radioactivity in the carcass however was assumed to be from the blood volume of the animal as all major organs had been removed although some of the dose may have accumulated in one or a few tissues which were digested with the carcass.

This does not explain radioactivity found in the carcass of rats fed PVP after 1 and 5 h (10 and 6%, respectively). No PVP was found in the urine so it is unlikely that radioactivity in the carcass represents PVP in the blood or other organs remaining in the carcass. There is the possibility that some of the radioactive dose may have been delivered into the oesophagus rather than the stomach and occasionally animals were found to have retained some radioactive material in their mouths.

3.6. Transit time

Although these experiments have shown that tomato lectin can resist degradation to some extent during transit, it is more difficult to determine from these data whether the lectin could be used effectively to delay GI transit time. When compared with PVP, there is only 50% lectin in the GI tract after 5 h but 90% of PVP present. This would seem to imply that PVP has a slower transit time than lectin, but these data need to be analysed carefully. Although only 50% of the lectin remains in the GI tract after 5 h, 50% has been metabolised (that is, degraded and taken into the circulation). 50% of the lectin has therefore been 'taken out' of the model and is unavailable to the GI tract. Thus, it would seem difficult to draw any definite conclusions about transit time from a comparison of a non-degradable macromolecule with a partially degradable macromolecule, as metabolism of the latter complicates the data.

Table 2
Lectin and PVP % dose recovered (gastrointestinal tract = 100% dose recovered)

	1 h		5 h		10 h		24 h	
	T [a]	W [b]	T	W	T	W	T	W
(i) Lectin								
Stomach	16.31	46.41	2.67	17.89	3.45	32.01	4.42	23.76
SI [c] part I	2.13	5.02	0.65	3.04	1.59	1.59	4.97	4.42 [e]
SI part II	4.53	6.58	2.19	4.66	2.19	2.52	2.76	20.44 [e]
SI part III	4.76	6.65	3.84	5.59	1.46	10.56	3.31	7.73 [e]
SI part IV	2.52	4.75	8.89	12.58	1.99	3.45	2.21	5.52
CLI [d]	0.11	0.23	11.21	26.80 [e]	6.44	32.74 [e]	2.76	17.68 [e]
(ii) PVP								
Stomach	2.53	48.50	0.56	3.55	1.12	8.31	0	15.15
SI [c] part I	0.57	1.53	0.05	0.36	6.29	0.67	0	0
SI part II	0.69	14.33	0.12	0.57	0.90	2.25	0	0
SI part III	0.56	17.93	0.74	5.91	0.90	3.15	0	0
SI part IV	0.60	11.32	0.75	22.19	0.67	3.60	3.03	3.03
CLI	0.14	1.31	2.32	62.88	13.71	58.43	18.18	60.61

[a] Tissue-associated radioactivity.
[b] Washings-associated radioactivity.
[c] Small intestine.
[d] Caecum and large intestine.
[e] $p < 0.05$ (after tissue and washings activities have been summed together).

However, it is possible to re-analyse the lectin and PVP data to allow a direct comparison of the two macromolecules. Data can be recalculated from the radioactivity recovered in the GI tract alone. The radioactivity, (in terms of cpm) recovered in the GI tract was summed and this was recorded as 100%. The radioactivity in each separate part of the GI tract was then calculated as a percentage of the total dose recovered from the entire GI tract. This would then allow the degraded lectin to be compared directly with the non-degradable PVP. These data are shown in Table 2.

From Table 2, it can be seen that after 1 h, although there was no significant difference in the distribution of the total amount of radioactivity along the GI tract for lectin and PVP, 30% of the lectin radioactivity was tissue-associated, but only 5% of the PVP was found with the tissue. After 5 h, there was a greater amount of lectin in the stomach than PVP, and it appeared that most of the PVP had entered the caecum and large intestine. Of this recovered dose, again, 30% of the lectin was still associated with the mucosa, compared with only 4% of the PVP.

10 and 24 h data were less clear. Although there was significantly more lectin in the stomach and more PVP in the caecum and large intestine after 10 h, the small intestinal fractions showed little difference. 24 h data did show a statistically significant difference ($p < 0.05$) for small intestine parts I–III, with more lectin recovered there than PVP. Again, a proportion of this lectin activity was tissue-associated whereas little or no PVP was found in the tissue fraction. There was also a clear difference in dose associated with the caecum and large intestine, with much more PVP being recovered from these portions of the GI tract than tomato lectin. However, the actual amount of lectin and PVP in the GI tract at 10 and 24 h was residual and the data recalculated at these time points were based on very low cpm and thus subject to error. These re-analysed data, however, did show some evidence of prolonged gastrointestinal residence time for tomato lectin, although the effect was not dramatic. An important point which should be stressed, however, is that a measurable percentage of the lectin dose found in the GI tract was associated with the gut tissue, but almost 100% of the PVP and the majority of the BSA was recovered in the gut washings.

From the in vitro data presented in previous papers (Naisbett and Woodley, 1994a,b), it would be expected that TL would bind avidly to the gut and show a much increased GI residence time when compared with these controls as TL binding to gut rings showed an 11- and 6-fold increase above PVP and BSA, respectively. However, this effect was less obvious in vivo. The GI tract in vivo is lined with a covering of mucus, which is rich in carbohydrate and is known to contain N-acetylglucosamine, and it is likely that, in vivo, the lectin may simply be binding to the glycoproteins in the gastrointestinal mucus and travelling down the GI tract bound to the mucus (propulsed by peristalsis), and thus never 'seeing' the enterocyte surface. This would result in no significant increase in GI transit time. Lehr et al. (1991) have estimated mucus turnover time in rats to be between 47 and 270 min, although other authors have postulated a turnover of between 17–24 h (Festa, 1987). This could represent a crucial physiological factor for bioadhesive dosage forms. In vitro, there was little or no mucus present in either gut ring or gut sac preparations, which would enable the lectin to have better access to the enterocyte surface glycoproteins.

In conclusion, whilst these data show clearly that tomato lectin is resistant to digestion in the GI tract and that it adheres to gut tissue in vivo, the transit time of the lectin shows only a small increase compared with controls, although data are difficult to interpret due to metabolism of the macromolecules.

References

Caston, A.J., Davis, S.S. and Williams, P., The potential of fimbrial proteins for delaying intestinal transit of oral drug delivery systems. *Proc. Int. Symp. Controlled Release Bioact. Mater.*, 17 (1990) 313–314.

Davis, S.S., The design and evaluation of controlled release systems for the gastrointestinal tract. *J. Controlled Release*, 2 (1985) 27–38.

Duchene, D., Touchard, F. and Peppas, N.A., Pharmaceutical and medical aspects of bioadhesive systems for drug administration. *Drug Dev. Ind. Pharm.*, 14 (1988) 283–318.

Fell, J.T., Harris, D., Sharma, H.L. and Taylor, D.C., The use of muco-adhesive polymers to modify the gastro-intestinal transit of oral pharmaceutical formulations. *Polym. Reprints*, 28 (1987) 145–146.

Festa, D., Sticky solutions for delivering drugs. *New Sci.*, 14th May (1987).

Gruber, P., Longer, M.A. and Robinson, J.R., Some biological issues in oral, controlled drug delivery. *Adv. Drug Del. Rev.*, 1 (1987) 1–18.

Gupta, P.K., Leung, S.-H.S. and Robinson, J.R., Bioadhesives/mucoadhesives in drug delivery to the gastrointestinal tract. In Lenaerts, V. and Gurny, R. (Eds), *Bioadhesive Drug Delivery Systems*, CRC Press, Boca Raton, 1990, pp. 65–92.

Harris, D., Fell, J.T., Taylor, D.C., Lynch, J. and Sharma, H.L., GI transit of potential bioadhesive systems in the rat. *J. Controlled Release*, 12 (1990) 55–65.

Jones, R.E., De-iodination of labelled protein during intestinal transmission in the suckling rat. *Proc. R. Soc. Lond. B.*, 199 (1977) 279–290.

Kilpatrick, D.C., Pusztai, A., Grant, G., Graham, C. and Ewen, S., Tomato lectin resists digestion in the mammalian alimentary canal and binds to intestinal villi without deleterious effects. *FEBS Lett.*, 185 (1985) 26–35.

Lehr, C.-M., Poelma, F.G.J., Junginger, H.E. and Tukker, J.J., An estimate of turnover time of the intestinal mucus gel layer in the rat in situ loop. *Int. J. Pharm.*, 70 (1991) 235–240.

Leung, S.-H.S. and Robinson, J.R., Polymer structure features contributing to mucoadhesion: II. *J. Controlled Release*, 12 (1990) 187–194.

Naisbett, B. and Woodley, J.F., The potential use of tomato lectin for oral drug delivery: 1. Lectin binding to rat small intestine in vitro. *Int. J. Pharm.*, 107 (1994a) 223–230.

Naisbett, B. and Woodley, J.F., The potential use of tomato lectin for oral drug delivery: 2. Mechanism of uptake in vitro. *Int. J. Pharm.*, 110 (1994b) 127–136.

Read, N.W. and Sugden, K., GI dynamics and pharmacology for the optimum design of controlled-release oral dosage forms. *CRC Crit. Rev. Ther. Drug Carrier Systems*, 4 (1987) 221–263.

Seymour, L.W., Duncan, R., Strohalm, J. and Kopecek, J., Effect of molecular weight of *N*-(2-hydroxypropyl) methacrylamide copolymers on body distribution and rate of excretion after subcutaneous, intraperitoneal and intravenous administration to rats. *J. Biomed. Mater. Res.*, 21 (1987) 1341–1358.

Smith, E.L., Hill, R.L., Lehman, I.R., Lefkowitz, R.J., Handler, P. and White, A., *Principles of Biochemistry: Mammalian Biochemistry*, McGraw-Hill, London, 1983, p. 760.