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Research paper

Bioadhesion of solid oral dosage forms, why and how?[1]

Dominique Duchêne *, Gilles Ponchel

Université de Paris-Sud, Châtenay Malabry, France

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Abstract

This review focuses on two kinds of bioadhesive solid oral dosage form: tablets for buccal administration, and nanoparticles for intestinal and more specifically colonic administration. For each of these dosage forms, the advantages of the form for drug delivery are presented as well as a short explanation of its bioadhesion mechanism and the bioadhesion evaluation methods. For bioadhesive tablets examples are given concerning the influence of tablet characteristics and of the surrounding medium on bioadhesion. For nanoparticles, examples are given concerning the influence of the nanoparticle surface charges and of the presence of lectins on their intestinal bioadhesion at various pH. © 1997 Elsevier Science B.V.

Keywords: Bioadhesion; Tablets; Nanoparticles; Investigation methods; Lectins; Buccal delivery; Intestinal delivery; Colonic delivery; Site-specific delivery

1. Introduction

Bioadhesion, which is classically defined as the ability of a material to adhere to a biological substrate, was presented for the first time as a pharmacotechnical tool some 12–15 years ago [1–4]. The biological substrate, a mucosa, corresponds to the site of either best activity or best absorption of the drug. At the very beginning, bioadhesion dealt mostly with the buccal or vaginal administration [5,6] of solid dosage forms and especially tablets [7,8]. This can be explained by the easy accessibility of the mucosae, and the simple process of tablet manufacture.

This new concept rapidly led to the idea that bioadhesion could be used advantageously to improve drug absorption through other administration routes, such as the nasal, ocular and colonic routes [9–14]. Obviously, the nature of the corresponding dosage form is adapted to the route concerned and can vary from hydrogels to micro- and nanoparticles. Furthermore, the classic bioadhesion mechanism (interpenetration of chains of the swollen bioadhesive polymer and of mucin), involved in the bioadhesion of tablets, is no longer encountered for the bioadhesion of micro- and nanoparticles and, especially for the intestinal and colonic route, the mechanism requires site-specific interactions.

The present paper deals with solid dosage forms devoted to oral administration with the main purpose of obtaining drug release at either the buccal level, or the intestinal level, and more particularly the colonic level.

2. Bioadhesive tablets for buccal delivery

Bioadhesive tablets for buccal administration are used to release a drug either for local or systemic activity. Local activity can be investigated either for the

* Corresponding author. Physico-chime, Pharmacotechnie, Biopharmacie, URA CNRS 1218, Faculté de Pharmacie, Université de Paris-Sud, Rue Jean Baptiste Clément, 92290 Châtenay Malbry, France. Tel.: +33 146835581; fax: +33 146835308.

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treatment of mycosic infection [15,16], aphthous stomatitis [5] and peridontal diseases [17], or for obtaining local anaesthesia [18]. Systemic activity is researched through buccal administration, because of the possibility for the drug to escape the hepatic first-pass effect. This route can therefore be used for the administration of drugs such as propranolol [19], testosterone [20] and peptides [21].

2.1. Mechanism of tablet bioadhesion

The mechanism by which a tablet can adhere to a biological surface is, in fact, a succession of phenomena, and demands a number of well-defined qualities from the bioadhesive polymer incorporated in the tablet [22].

First, it is necessary to have an intimate contact between the tablet and the mucosa. This is not too difficult to obtain with the buccal mucosa which is quite smooth compared with other mucosae, such as the vaginal mucosa [8]. In the mouth, a good contact can be obtained by exerting a slight pressure on the tablet at the surface of the mucosa. Such a contact is necessary to allow a good wetting of the tablet bioadhesive polymer by the mucosa moisture [23,24]. Moistening can lead to a second phenomenon can then occur: this is the swelling of the bioadhesive polymer, disentangling of the polymeric chains, leading to the interpenetration of the polymer and mucous chains. Charged polymers are very interesting from the swelling standpoint, because the charges between the polymer chains, and, furthermore, the ionic concentration inside the polymer network will create osmotic pressure resulting in a facilitated entrance of the water inside the network [25]. The third phenomenon is the creation of interfacial bonds between the interpenetrated chains. These bonds are of the secondary type, such as electrostatic forces, Van der Waals forces, hydrogen bonds and hydrophobic interactions and are relatively weak [25].

The only problem when preparing a biaodhesive tablet is the choice of the right bioadhesive polymer which will be added to the normal tablet formulation. One of the most commonly employed polymers is poly(acrylic acid) which can confer bioadhesive properties to tablets for concentrations equal to (and over) 10% [26].

2.2. Evaluation of tablet bioadhesion

Generally, tablet bioadhesion is assessed by detachment tests occurring between the tablet and a substrate on which it has been previously applied [26]. A great number of such tests have been described, differing in either the nature of the substrate on which the tablet adheres, or by the detachment method.

The substrate can be artificial or natural. One of the most surprising artificial substrates is probably that constituted by a sieve canvas [27]. However, it seems preferable to work on a mucosa. But the choice is difficult: which kind of animal? which mucosa? Probably one resembling the one on which the tablet will be used. The problem is that the nature of the mucosa is very dependent on the animal and furthermore on the exact location on the mucosa considered. For example, when considering the buccal, sublingual, gingival and palatal mucosae, differences can be observed in thickness, keratinization, and intercellular lipid nature (Table 1) [28,29].

Furthermore, the problem of the presence, or absence of mucus is very important because, due to its biological turnover, it is a factor that decreases the possible bioadhesion duration. It is recognized as a parameter leading to low bioadhesion, and susceptible to important changes occurring after animal death and detachment from its normal substrate. For all these reasons some authors choose to work on mucosa free of mucus [30].

Detachment methods encountered in the literature can vary according to the detachment force direction: horizontal [31] or vertical. This latter possibility is the most commonly employed, but can differ by the detachment mechanism: spring balance connected to the tablet support [32], digital balance connected to a recorder [12], or universal tensile apparatus [17,18,33] (Fig. 1).

On a tensile apparatus, the tablet can be stuck on to one of the two supports and the test surface (mucosa) to the other. The tablet and the mucosa are put in contact with a given pressure for a given time. The tensile test starts so as to create a detachment force normal to the contact interface between the tablet and the mucosa. The advantage of using a tensile apparatus for carrying out detachment tests is that it allows not only the evaluation of the maximal detachment force, but also the recording of the detachment force as a function of the displacement of the mobile support, in other words as a function of elongation of the joint constituted by the interpenetrated bioadhesive polymer and mucin chains [34]. Such a method allows the calculation of different parameters such as the bioadhesion

Table 1
Characteristics of some human mucosae [29]

Location	Thickness (μm)	Keratinization	Intercellular Lipids
Buccal	500–600	No	Polar
Sublingual	100–200	No	Polar
Gingival	200	Yes	Non-polar
Palatal	250	Yes	Non-polar

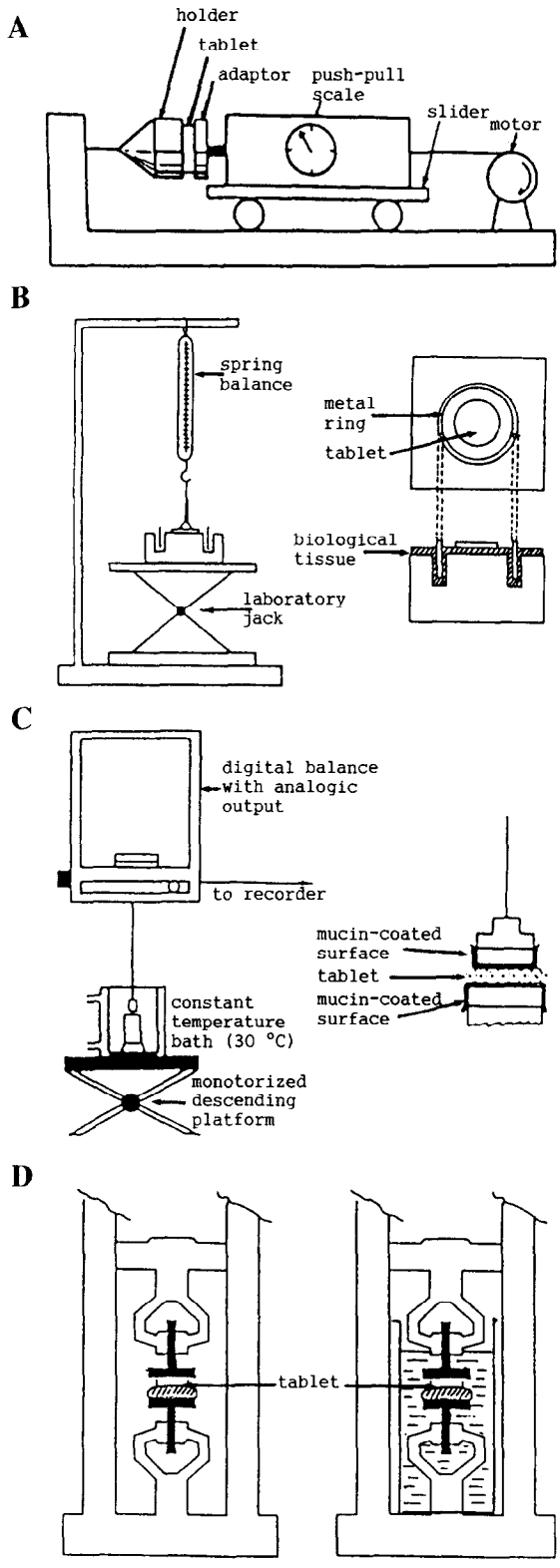

Fig. 1. Apparatuses for evaluation of bioadhesion by the means of detachment force. A. Horizontal detachement force [31]; B. Spring balance with vertical detachment force [32]; C. Digital balance connected to a recorder [12]; D. Universal tensile apparatus: left, dry medium; right, liquid medium [34]. Reproduced with permission of the copyright owners (Pharmaceutical Society of Japan, Elsevier Science Ltd.).

work and the fracture energy [26,34]. The bioadhesion work is represented by the area under the detachment force/displacement curve, and the fracture energy is the bioadhesion work with respect to the surface unit: bioadhesion work/initial surface between tablet and mucosa.

2.3. Factors affecting tablet bioadhesion

Using a tensile apparatus we investigated the bioadhesion of a metronidazole tablet on bovine sublingual mucosa.

First we investigated the influence of bioadhesive polymer (poly acrylic acid) concentration. It appeared that if the bioadhesion work increased regularly with an increase in poly acrylic acid, the detachment force was almost constant between 25 and 90% of this polymer. This indicates that the detachment probably occurs at the level of mucus glycoprotein chains rather than at the tablet/mucosa interface [26], showing the strength of the bioadhesion bonds following the set-up of the bioadhesive tablet.

We also investigated the influence of the contact time when placing the tablet on the mucosa [26]. This period corresponds to a pre-swelling necessary for bioadhesive polymer chain disentanglement and the establishment of an intimate contact between poly acrylic acid and mucin chains. It appears that there is an optimal pre-swelling time, after which the bioadhesion work is stabilized or decreases slightly. This can be the consequence of water migration from the tablet periphery to the centre with a consecutive interface drying.

We were also interested in the influence of the surrounding medium on bioadhesion, a factor particularly important for buccal bioadhesion, resulting from possible changes due to food or drink. We investigated the influence of pH, which is well known to modify the swelling of poly acrylic acid, an increase being observed between pH 2 and 7. For the bioadhesion studies, we deposited a drop of test medium on to the mucosa surface before placing the tablet in contact with the mucosa. We demonstrated that, in such conditions, there was no influence of the pH when increased from 2 to 8, which is probably explained by the buffer capacity of poly acrylic acid, and the small amount of liquid penetrating the tablet [7,26]. To overcome this drawback, we carried out the same experiment on the same system but completely immersed in test medium. In such conditions, the adhesion work is significantly decreased, but there is no noticeable influence of pH [7] (Table 2).

Working again in a liquid medium, we looked at the influence of the ionic strength, by varying the concentration in NaCl of the test medium from 0 to 100 g/l. On the buccal mucosa, a loss of bioadhesion was observed with an increasing ionic strength. This is easily explained by the fact that the addition of cations to the

Table 2
Influence of pH on the adhesion work of a bioadhesive tablet on bovine sublingual mucosa, after placing of a drop of the test medium at the surface of the mucosa (Dry), or after complete immersion in the testing medium (Liquid) [7]

Solution pH	2	5	8
Work (mJ)			
Dry	3.9 ± 2.3	3.6 ± 1.4	3.5 ± 1.5
Liquid	0.5 ± 0.3	0.2 ± 0.05	0.5 ± 0.4

Average of five determinations.

partly ionized carboxylic groups of poly acrylic acid shields these charges and results in the recoiling of the polymer, which cannot then interpenetrate the mucin chains (Table 3) [7]. The influence of the cation nature also has to be considered. When the same experiment is carried out with $CaCl_2$ solutions, a rapid fall in bioadhesion is observed with low calcium concentrations (Table 4) [7].

Tablet porosity was presented as the driving force in the bioadhesion process due to a suction effect. We studied this parameter on poly acrylic acid of different molecular weights, and tableted under low (75 N), medium (140 N) and high (200 N) compression forces, in order to obtain high, medium and low porosity [35]. Whatever the porosity, the bioadhesion work did not vary significantly. However a net influence of the molecular weight was observed, with an increase in bioadhesion from 450 000 to 750 000 molecular weight, followed by a progressive decrease (Table 5) [35]. Interpretation of these results is complicated by the fact that an increase in poly acrylic acid molecular weight does not automatically mean an increase in polymer chain length, due to the fact that only the first members of the series are linear polymers, and that, for higher molecular weights, not only ramifications but also cross-linkings appear.

3. Bioadhesive solid dosage forms for intestinal administration

Bioadhesive solid dosage forms for intestinal administration can be very interesting for drugs presenting a narrow absorption window, for which it might be necessary to prolong the residence time at or before this absorption window. However, numerous drugs are inactivated in the gastro-intestinal tract, because, for example, of the stomach pH, presence of proteolytic or peptidolytic enzymes, and also the hepatic first-pass effect. From this standpoint, it would be interesting to target a drug directly to the colon, allowing it to circumvent most of the previous drawbacks [14]. To obtain such a targeting, the solid dosage form can be protected from stomach and small intestine degradation by pH-sensitive [36–38] or bacterial degradable polymers [39–41].

One more advantage of the colon is the transit time. Whatever its variability, in all cases it is much longer than the transit through the small intestine, and it increases the likelihood of drug absorption. To take advantage of this transit time, it is necessary to try to make it as long as possible to allow the maximum absorption of the drug loaded in the delivery device. This can be obtained by preparing bioadhesive forms.

3.1. Design of solid drug delivery systems for intestinal administration

To prepare bioadhesive forms for the intestinal tract means that all the active content will be released at the same place on the mucosa. In order to prevent irritation or ulceration, it is safer to prepare particulate forms than monolithic forms, the particles covering a larger mucosa surface.

Particles, after adhesion, will be subjected to a washing out by the hydrodynamic forces of the intestinal content. The effect of the intestinal flow will be the rolling of adhesive particles, this motion and the consecutive detachment will be decreased by using small particles: nanoparticles [42].

Table 3
Influence of NaCl ionic strength on the detachment force and adhesion work of a bioadhesive tablet on bovine sublingual mucosa, in liquid medium [7]

	NaCl (g/l)					
	0	10	25	50	75	100
	Ionic strength					
	0	0.17	0.43	0.87	1.32	1.77
Force (N)	1.9 ± 0.6	2.5 ± 0.73	1.4 ± 0.6	1.5 ± 0.3	0.8 ± 0.4	0.9 ± 0.3
Work (mJ)	0.6 ± 0.3	0.8 ± 0.3	0.3 ± 0.1	0.3 ± 0.1	0.2 ± 0.05	0.2 ± 0.1

Average of five determinations.

Table 4
Influence of $CaCl_2$ ionic strength on the detachment force and adhesion work of a bioadhesive tablet on bovine sublingual mucosa, in liquid medium [7]

	$CaCl_2$ (g/l)					
	0	5	10	20	50	100
	Ionic strength					
	0	0.13	0.27	0.54	1.39	2.77
Force (N)	1.9 ± 0.6	1.0 ± 0.6	1.1 ± 0.5	1.2 ± 0.6	1.5 ± 0.6	1.5 ± 0.7
Work (mJ)	0.6 ± 0.3	0.3 ± 0.1	0.2 ± 0.1	0.3 ± 0.2	0.4 ± 0.2	0.3 ± 0.2

Average of five determinations.

It has been demonstrated that it is not possible to obtain intestinal bioadhesion by administration of a simple blend of particulate drug to a bioadhesive polymer [3]. However, microspheres obtained by dispersion of poly acrylic acid in polyglycerol ester of fatty acid have a prolonged gastro-intestinal transit time compared with simple polyglycerol ester of fatty acid microspheres, or with these microspheres coated with poly acrylic acid [43].

Another method that has been intensively investigated uses the concept of site specificity based on the affinity between sugars and lectin. Two ways are possible: either the use of a sugar targeted to a lectin from the intestinal tract [44–46], or the use of a lectin targeted to a sugar from the intestinal mucus glycoprotein (β-galactose, α-*N*-acetylgalactosamine, α-*N*-acetylglucosamine, α-fucose, α-*N*-acetylneuraminic acid) [47,48]. In the latter case, the lectins employed are from tomato [47,48], mycoplasma or asparagus [48].

3.2. Investigation of nanoparticle bioadhesion

There are many methods described in the literature allowing the in vitro evaluation of particles adhering on to an intestinal mucosa [49–51]. They use a segment of intestine fixed on an inclined support, and a dispersion of bioadhesive particles is then poured on the upper part of the intestine segment. The quantity of particles adhering to the mucosa is quantified by comparing the steady-state inflow and outflow concentration of particles. Because of the possibility of altering the mucosa during its excision and preparation, in situ methods have been proposed. They consist of connecting an intestine segment to two cannulas and perfusing a suspension of bioadhesive particles [52,53].

One of the problems of these techniques is the correct evaluation of particle concentration, especially in the case of a latex. For such products we have developed a turbidimetric method [54]. This technique is based on the fact that, for particles with a diameter close to the wavelength of the incident light, the turbidity (τ) is related to the diameter (D) and the number of particles (N) in suspension (Eq. (1)). The equation is governed by a constant (K), function of the relative size of the particle to the wavelength of the light in the medium (α), and of the ratio of the refractive index of the particles to that of the medium (m) (Eq. (2) and Eq. (3)):

$$\tau = \pi K D^2 N/4 \quad (1)$$

$$\alpha = \pi n_0 D/\lambda \quad (2)$$

$$m = n/n_0 \quad (3)$$

One of the most widely used turbidimetric techniques consists in the determination of the specific turbidity (π/C). For a monodispersed latex suspension, π/C can be written (Eq. (4)):

$$(\pi/C) = [3/2\ K(\alpha, m)]/\rho D \quad (4)$$

where C is the latex concentration expressed as mass of polymer per volume, and ρ is the polymer density.

For polystyrene latex particles with diameters from 100 to 1000 nm, a very good correlation was demonstrated between concentrations assessed by the turbidimetric and gravimetric methods [54].

Whatever the value of this method, it requires knowledge of the refractive index of the particles, and does not allow a direct evaluation of the particles really adhering to the mucosa. Methods using fluorescent nanoparticles have been proposed to localize nanoparticles at the mucosa surface [55,56]. Despite their advantages, they require a modification of the nanoparticle surface. In order to overcome this drawback, we developed a method in which we used a Fourier transform infrared spectroscopy/attenuated total reflection (FTIR/ATR) method for direct quantification of absorbed polystyrene nanoparticles (chosen as model nanoparticles) on rat intestinal mucosa [57]. The results obtained by this technique can be correlated with those obtained by the turbidimetric dosage of particles after mucosa denaturation.

Table 5
Influence of porosity on the detachment force and the adhesion work of poly acrylic acid (Carbopol®) tablets [35]

Polymer	Molecular weight	Porosity	Detachment force ± S.D. (N)	Adhesion work ± S.D. (mJ)
Carbopol 907	450 000	High	5.42 ± 2.15	1.74 ± 1.29
		Medium	6.14 ± 0.99	1.81 ± 0.67
		Low	6.25 ± 1.84	1.82 ± 0.56
Carbopol 910	750 000	High	6.74 ± 1.22	4.77 ± 0.41
		Medium	6.00 ± 0.94	4.14 ± 0.39
		Low	7.10 ± 0.82	4.39 ± 0.62
Carbopol 941	1250 000	High	5.42 ± 1.83	3.00 ± 1.22
		Medium	6.78 ± 1.87	3.15 ± 0.95
		Low	6.04 ± 2.27	3.09 ± 0.86
Carbopol 934P	3000 000	High	4.43 ± 2.26	1.86 ± 0.45
		Medium	6.45 ± 1.99	2.27 ± 0.67
		Low	6.17 ± 1.81	2.01 ± 0.32
Carbopol 940	4000 000	High	5.75 ± 1.54	1.92 ± 0.96
		Medium	6.05 ± 1.23	1.68 ± 0.83
		Low	7.00 ± 1.37	2.78 ± 1.31

3.3. Bioadhesion of nanoparticles to intestinal mucosa

Working first on model polystyrene nanoparticles, we investigated the influence of the surface properties and particle sizes, and the pH of the suspension medium on mucoadhesion on rat intestinal mucosa [58]. Polystyrene latexes under investigation were surfactant-free carboxylate and amino latexes (Polybead Carboxylate Microspheres, PCM, and, Polybead Amino Microspheres, PAM, respectively), and carboxylate latex with adsorbed sodium dodecyl sulphate (CML). The size of the nanoparticles varies from 0.2 to 2.0 μm. Generally it was found that adsorption was higher for the amino than for the corresponding carboxylate latexes, since the repulsion forces between mucus and particles, and between the particles themselves, were smaller (Table 6). At pH 7.4, all latexes were two or three times less adsorbed than at pH 6 and 4.5, due to repulsion forces of the negatively-charged mucous layer. The adsorption barrier was smaller for the less negatively-charged amino latexes. At pH 6, adsorption was increased not only by a decrease in the repulsion forces, but also by the hydrophillic character of the latex surface. In this case, hydrogen bonds could be the driving adhesive force (Table 6). A general conclusion about the influence of particle size was more difficult to draw, because the high specific surface of the smaller latexes leads not only to reduced adsorption due to more repulsion forces between the adsorbed particles, but also to stronger adhesion of the particles (Table 6). The situation is very complex since several factors interact at the same time [58].

Table 6
Latex adsorption on apparent surface of rat mucosa [58]

Latex	pH 4.5 (g/m^2)	pH 6 (g/m^2)	pH 7.4 (g/m^2)
PCM-200	n.d.	0.660 ± 0.154	n.d.
CML-350	n.d.	0.558 ± 0.057	n.d.
PAM-500	0.754 ± 0.065	0.979 ± 0.124	0.460 ± 0.112
PAM-750	0.813 ± 0.147	0.880 ± 0.058	0.384 ± 0.092
PCM-750	0.611 ± 0.047	0.924 ± 0.062	0.226 ± 0.091
PAM-1000	0.817 ± 0.098	0.954 ± 0.078	0.265 ± 0.091
PCM-1000	0.670 ± 0.082	0.779 ± 0.038	0.215 ± 0.105
PCM-2000	0.947 ± 0.112	0.930 ± 0.130	0.263 ± 0.100

Particle diameter is mentioned in nm after abbreviation of the latex name.

Our subsequent work dealt with lectin/polystyrene nanoparticle conjugates. The lectins investigated were *Lycopersicum esculentum* lectin (tomato lectin, TL), *Lotus tetragonolobus* lectin (asparagus pea lectin, AL) and *Mycoplasma gallisepticum* lectin (bacterial adhesin, ML). Lectins were associated to polystyrene nanoparticles either by covalent coupling (the carbodiimide method for carboxylated polystyrene and the glutaraldehyde method for amino polystyrene nanoparticles), or by the simple adsorption method. All the methods lead to fixation of lectins on the nanospheres, with, however, slightly better fixation efficiency for the covalent method [59]. The activity of the lectin/polystyrene nanoparticle conjugates and bovine serum albumin/polystyrene nanoparticle conjugate (control, BSA) were tested with pig gastric mucin. All the lectin/polystyrene nanoparticles were able to interact with pig gastric mucin. The conjugates prepared by the covalent techniques gave a higher performance than the conjugates obtained by adsorption, but the difference was not significant (Fig. 2) [59].

The influence of pH, which was investigated on blank polystyrene nanospheres, was also investigated on nanospheres functionalized with the above-mentioned lectins. Interaction with mucin decreases with a pH increase from 3.0 to 7.4. Interaction was lower with functionalized amino polystyrene than with carboxylated polystyrene [60]. An example of pig gastric mucin

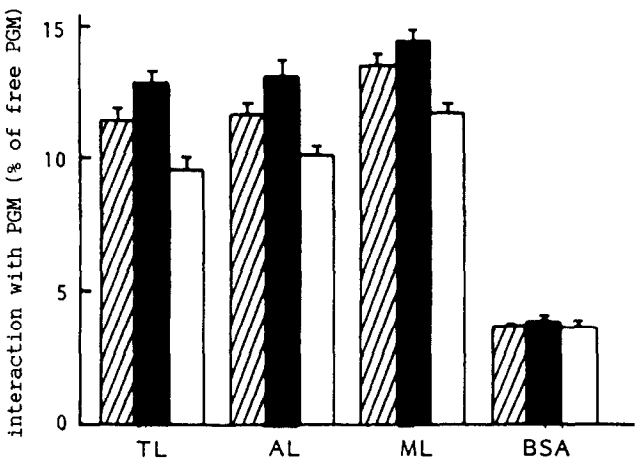

Fig. 2. Influence on the preparation method of lectin/polystyrene nanoparticles on their interaction with pig gastric mucosa [59]. □ Adsorption method (PCM-750); ■ glutaraldehyde method (PAM-750); ▨ carbodiimide method (PAM-750). Reproduced with permission of the copyright owner (Elsevier Science Ltd.).

adsorption on functionalized amino (PAM) and carboxylated (PCM) polystyrene as a function of pH is given in Fig. 3. By comparison with polyelectrolyte adsorption, it can be concluded that mucin adsorption on functionalized polystyrene nanospheres was probably driven by non-ionic interactions [60].

Variations in the sugar composition of the glycoproteins in the mucus layer or in the cell membrane along the gastro-intestinal tract having been observed, it was interesting to study ex vivo the specificity of bioadhesion of three different lectin/nanosphere conjugates to various structures of intestinal mucosa [61]. Working with the same three lectins as previously, it appeared that tomato lectin conjugates were more specific for the mucous gel layer and therefore for intestinal regions without Peyer's patches. On the other hand,

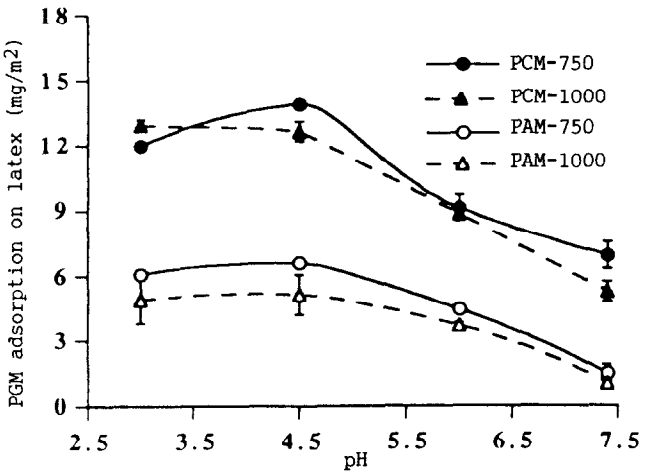

Fig. 3. Influence of pH on pig gastric mucosa adsorption on carboxylate (PCM) and amino (PAM) polystyrene nanoparticles [60]. Reproduced with permission of the copyright owner (Academic Press, Inc.).

the mycoplasma and asparagus lectin conjugates were more specific of the Peyer's patches. These specific interactions were probably mediated by receptors localized at the surface of the M-cells which are situated in the Peyer's patches [61].

4. Conclusion

Bioadhesion is a method which has great potential for pharmaceutical technology and pharmaceutical dosage form design. It can be adapted to almost all the administration routes, and the examples presented here show that the bioadhesion technique and mechanism are a function of the administration route considered. Starting by mechanical interpenetration for bioadhesive buccal tablets, it is site specificity and molecular recognition which are the main influencing factors in intestinal bioadhesion.

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