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PHARMACEUTICAL AND MEDICAL ASPECTS OF BIOADHESIVE SYSTEMS FOR DRUG ADMINISTRATION

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ABSTRACT

Bioadhesion could lead to the solution of bioavailability problems resulting from a too short stay of the pharmaceutical dosage form at the absorption or activity level of the active ingredient. Bioadhesion stages are: intimate contact resulting from a good wetting of the bioadhesion surface and the swelling of the bioadhesive polymer, then penetration of the bioadhesive into the crevice of the tissue surface or interpenetration of bioadhesive chains with those of the mucus, and finally low chemical bonds. To date, the most important bioadhesive polymers are polycarbophil and Carbopol 934. Methods of studying bioadhesion are described as well as the existing bioadhesive dosage forms.

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INTRODUCTION

Bioadhesion may be defined, as has been done by various authors <1, 2>, as the ability of a material (synthetic or biological) to adhere to a biological tissue for an extended period of time. This definition includes a large number of adhesion phenomena <2>: the adhesion of various shellfish on rocks, the adhesion of cells on one another, and the adhesion of microorganisms on various mucosa substrates.

From a theoretical standpoint, bioadhesion may lead to the solution of bioavailability problems resulting from a too short stay of the pharmaceutical dosage form at the absorption level of the active ingredient. Some examples may be quoted <3,4>. Thus, in the case of sublingual administration, which is of great interest because it provides a possibility of avoiding either destruction by gastro-intestinal liquids (pH and enzymes) or hepatic first-pass inactivation, it is often difficult to maintain the tablet in a suitable place or even not to swallow it. In the case of administration by the digestive route, the stomach emptying and the whole intestinal peristaltism can unfortunately displace the active ingredient from its resorption site. For rectal administration with systemic activity intent, it might be important to maintain the pharmaceutical dosage form in the rectum lower part, where the haemorroidal veins escape from the hepatic pass. For vaginal administration, it is highly desirable that the dosage form is not eliminated too early from its activity site. For nasal administration, it is necessary to avoid displacement of the active ingredient by ciliary movement. And last, but not least, even for ocular administration, the guarantee of keeping in place the dosage form for a sufficiently long time is a condition for its activity. Bioadhesion therefore maintains the pharmaceutical dosage form for a clearly-defined time at its activity or resorption level. It is obvious that a release prolonged all over the duration of bioadhesion is a requisite criterion.

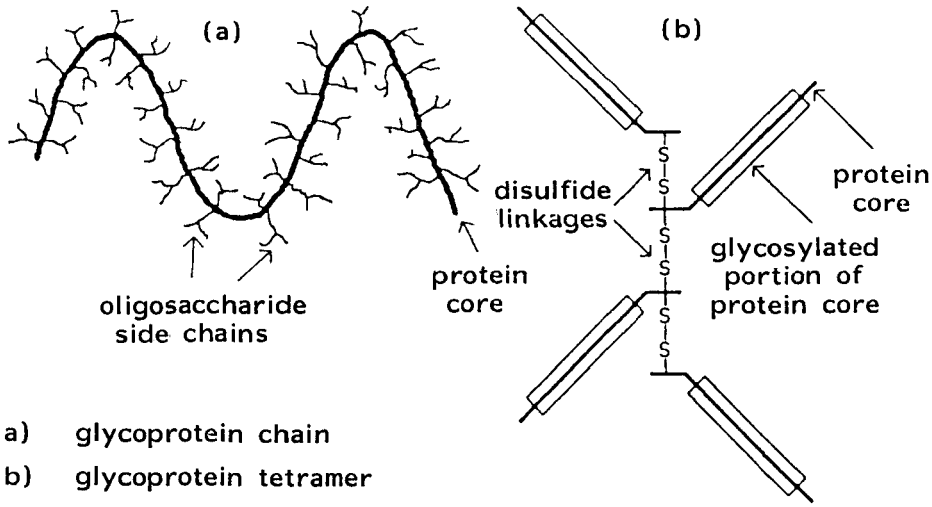
MUCOUS LAYER

The mucus is the layer covering the mucosa. It is secreted by the goblet cells. It is a highly viscous liquid, adhering to the epithelium. Its rôle is mucosa protection against various aggressions: mechanical, chemical, bacterial or viral. The understanding of bioadhesion and active ingredient diffusion mechanisms requires knowledge of the mucus.

Chemical composition

Besides water, which represents more than 95% of the mucus, its major components are glycoproteins (0.5 to 5%), lipids in low proportions, mineral salts (1%) and free proteins (0.5 to 1%) <2,4,5>. The exact mucus composition varies depending on its source.

Glycoproteins are the main mucus components, responsible for its viscosity, and adhesive and cohesive properties. Basically, glycoproteins consist of a protein core on which are attached oligosaccharide chains (diagram (a) in Figure 1). Glucidic chains essentially contain galactose, N-acetylgalactosamine, N-acetylglucosamine, sialic acid and fucose. Amino acids are principally serine, threonine and proline. Linkages between the protein core are of the O-glucidic type, between N-acetylgalactosamine and serine or threonine <5>. Many of the terminal residues in the oligosaccharide side chains are sialic acids, negatively charged at pH greater than 2.8, making the protein an anionic polyelectrolyte. Sulphate residues contribute equally to this negative charge <2>. The mucus gel structure is the consequence of the intermolecular association of glycoproteins in a polymeric network. Previously thought to be a tetramer (diagram (b) in Figure 1), the polymer is now believed to be a terminally linked chain with numerous cross-linkings <2>. It has been proposed that chains result from disulphide bonds (intrachain) and macromolecular associations are due to physical bonds stabilized by electrostatic interactions



(a) glycoprotein chain
(b) glycoprotein tetramer

Figure 1 Schematic representations of the mucus (According to <2> with permission)

(hydrogen bonding, salt linkage) or other non-covalent contacts between the oligosaccharide chains or between chains and the protein core of the molecule <4> (Figure 2). An appreciable proportion of the glycoprotein is not incorporated in the network, but is present as a soluble fraction, enhancing the viscosity of the interstitial fluid rather than conferring a solid/liquid character <6>.

Diffusion barrier

The mucus covers the epithelial surface with a layer of heterogeneous thickness, varying between 5 and 200 µm with an average of 80 µm. The mucus protective rôle is evident at the stomach level. Its protective effect would result particularly from its hydrophobicity and would protect the mucosa from the back diffusion of hydrochloric acid from the lumen to the epithelial surface <6>. The gastric mucus may act as an unstirred water layer, in which hydrogen ions diffusing from the lumen are neutralized by the bicarbonate of the surface epithelium secretion <6>. A dynamic equilibrium exists at

A entanglements
B molecular associations
C permanent crosslink
r average end-to-end distance between two junctions (molecular weight $\overline{M}_j$)

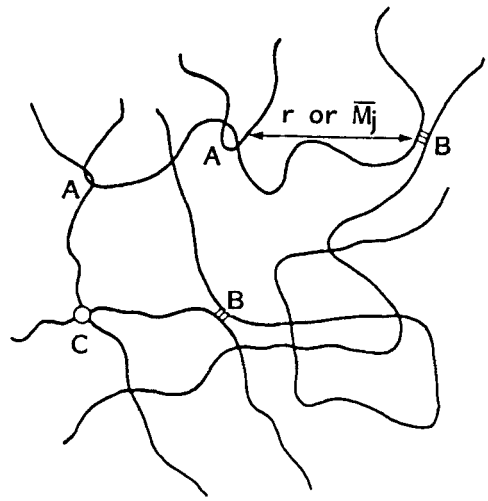


Figure 2 Crosslinked structure of the intestinal mucus network (According to <1,4> with permission)

the mucosal surface between a continuous erosion by proteolyse and mechanical abrasion and the equally continuous new mucus secretion <6>.

Besides its gastric protection rôle against hydrochloric acid, the mucus constitutes, generally speaking, a diffusion barrier for molecules, and especially against drug absorption. Diffusion through the mucus layer depends largely on active ingredient physicochemical characteristics: molecule charge, hydration radius, ability to form hydrogen bonds, and molecular weight <5>. However, the mucus nature interferes also at the level of diffusion phenomena, especially by glycoprotein concentration, and by the cross-linking ratio, or, more accurately, the average molecular weight between two junctions in the mucus network, as shown by the following equation proposed by Peppas *et al* <7>:

$$\frac{D_{in}}{D_{iw}} = k\, c_m^{-1/3}\, \overline{M}_j \exp - \left[\frac{k' r_i^2}{(\frac{1}{c_m} - \overline{v})} \right]$$

where:

- D_{in} diffusion coefficient of the active ingredient through the mucus network,
- D_{iw} diffusion coefficient in water,
- k and k' two constants,
- c_m glycoprotein concentration in the mucus,
- $\overline{M}_j$ average molecular weight between two junctions in the mucus,
- r_i molecular radius of the diffusing active ingredient,
- $\overline{v}$ glycoprotein specific volume.

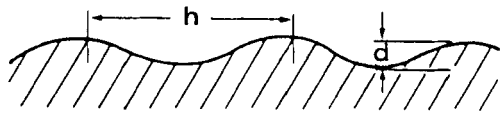
A large number of active ingredients may interact with the mucus <5>, particularly antibiotics <8 to 13>. It seems that the formation of insoluble complexes would occur, impeding resorption by the gastro-intestinal tract as well as by the submaxillary route.

BIOADHESION MECHANISM

For bioadhesion to occur, a succession of phenomena is required, whose rôle depends on the bioadhesive nature. Bioadhesion stages can be summarized as follows. First an intimate contact must exist between the bioadhesive and the receptor tissue. This contact results either from a good wetting of the bioadhesion surface, or from the swelling of the bioadhesive. When contact is established, the penetration of the bioadhesive into the crevice of the tissue surface then takes place, or inter-penetration of bioadhesive chains with those of the mucus. Low chemical bonds can then settle.

Intimate contact

The bioadhesive material has to penetrate the crevices of the tissue on which it is applied, and hence the tissue surface roughness is



d: depth h: width

Figure 3 Surface roughness of a soft tissue
(According to <1,4> with permission)

an important factor for bioadhesion. A rough surface may be defined by the aspect ratio of maximum depth, d, to maximum width, h (Figure 3) <4>. Insignificant roughness for adhesive purposes occurs when the aspect ratio takes values of $d/h < 1/20$. For higher values of this ratio, only highly fluid materials can penetrate the tissue anomalies, and therefore their viscosity and wetting power are of the greatest importance for satisfactory bioadhesivity.

When the bioadhesive material is solid, its swelling in contact with moisture is necessary in order to impart sufficient freedom to the constituent chains.

. Wetting theory

The spreading coefficient S of a liquid (subscript b) with the tissue substrate (t) in the gastric area (g), for example, under static conditions, is given by the following equation:

$$S_{b/g} = \gamma_{gt} - \gamma_{bt} - \gamma_{bg}$$

where:

. γ_{gt} interfacial tension between gastric contents and tissue,

. γ_{bt} interfacial tension between bioadhesive and tissue,

. γ_{bg} interfacial tension between bioadhesive and gastric contents.

For a bioadhesive material to displace the gastric contents and adhere spontaneously on the tissue, the spreading coefficient must be positive.

. Swelling

The rôle of water in the mechanism of bioadhesion, for a solid material, is of primordial importance <1,4>, as shown by Chen and Cyr <14>, who found that an optimum water content exists for maximum bioadhesion. Indeed, hydration of a colloid results in the relaxation of stretched, entangled or twisted molecules, which are able to liberate their adhesive sites giving them the possibility of creating bonds. It seems that the hydration of hydrocolloids causes dissociation of the already existing hydrogen bonding of the polymer. The polymer/water interactions may overwhelm the corresponding polymer/polymer interactions, favouring chain inter-diffusion. Water molecules form a double layer shielding any possible functional group interactions. The rupture of any interchain and intrachain associations increases the mobility of the macromolecules and facilitates their penetration in the surface crevices <4>.

Interpenetration

Interpenetration of chains from the bioadhesive polymer and mucus to a depth sufficient to create semi-permanent bonds corresponds to the diffusion theory discussed by Voyutskii <15>.

During chain interpenetration (Figure 4) <4>, the molecules of the bioadhesive and the glycoproteinic network are brought into intimate contact and, due to the concentration gradient, the bioadhesive polymer chains penetrate at rates which depend on the diffusion coefficient of a macromolecule through a crosslinked network and the chemical potential gradient. With crosslinked

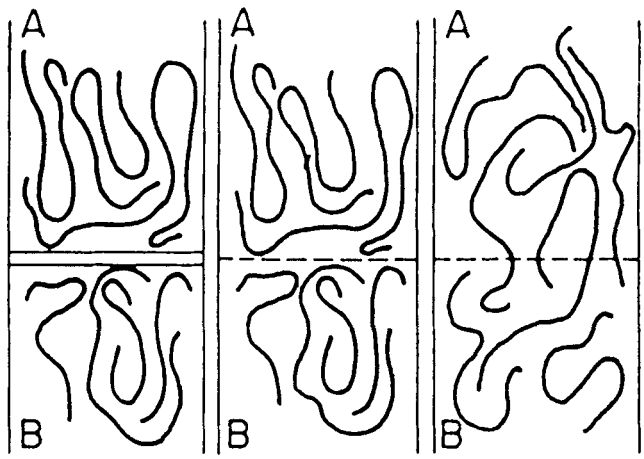


Figure 4 Chain interpenetration during bioadhesion of polymer A with the mucus B (According to <1,4> with permission)

polymers, interpenetration of large chains occurs with greater difficulty. However, smaller chains and chain ends may still contribute to interdiffusion <4>.

It is possible to determine the characteristic time for bioadhesion t by setting:

$$t = \frac{\ell^2}{D_b}$$

where:

- ℓ interpenetration depth,
- D_b bioadhesive material diffusion coefficient through the mucus.

Chemical interactions

Adhesion chemical bonds are of the primary or secondary type <2,4>. Primary chemical bonds have a covalent nature: their high strength

results in permanent bonds undesirable in bioadhesion. Secondary chemical bonds comprise a group of many different forces of attraction, including electrostatic forces, van der Waals forces, and hydrogen and hydrophobic bonds. Electrostatic attractions are due to Coulomb forces between molecules of opposite charge. Van der Waals forces are all the interactions between uncharged molecules. They can be attributed to three types of effect: polar (or Keesom) forces resulting from the orientation of permanent dipoles in two molecules, induction (or Debye) forces arising from a permanent dipole in another molecule, and dispersion (or London) forces resulting from instantaneous changes in the charge distribution around non-polar molecules. Hydrogen bonding occurs when a specific hydrogen atom from one molecule is associated with another atom from a second molecule. Hydrophobic bonding occurs when non-polar groups associate with each other in aqueous solution, due to the tendency of water molecules to exclude non-polar molecules. This type of force is far the most important in bioadhesion <2>.

Surface separation after bioadhesion

. Fracture theory

The fracture theory of bioadhesion attempts to relate the difficulty of separation of two surfaces after adhesion due to the adhesive bond strength. The fracture strength σ, equivalent to the bioadhesive bond strength, may be calculated by the following equation:

$$\sigma \cong \sqrt{\frac{E\epsilon}{L}}$$

where:

- . E Young's modulus of elasticity,
- . ϵ fracture energy,
- . L critical crack length upon separation of the two surfaces.

Thus, the stiffness of the material (i.e. the elastic modulus) can be used as a measure of bioadhesion. This theory assumes that, in a separation experiment, the failure of the bioadhesive bond occurs exactly at the interface. However, this almost never occurs <4>.

. Fracture and interpenetration

Recently, Peppas <16> showed that bioadhesion results in a compromise between the chemical interaction theory between functional polymer groups (poly(acrylic acid)) and the mucus, at their interface, and the theory of polymer chain interpenetration in the mucus. Furthermore, the mean relaxation time of the polymer chains, determined by dynamic analysis, is a good indicator of the bioadhesive behaviour of the polymer <17>. Rupture does not occur at the interface between the polymer and mucus, but rather inside the mucus (Figure 5) <6,15>.

METHODS TO STUDY BIOADHESION

In order to classify polymers, and to assess bioadhesive preparations, various methods to study bioadhesion have been described.

Study of cellular modifications during interpenetration

The first method to study bioadhesion, described by Robinson <18>, consists of an investigation of the modifications of cultured epithelial cells due to interpenetration by polymer molecules. The method is the following. A fluorescent liposoluble probe, pyrene, which, localized in the lipid bilayer of the cell membrane, is added to a suspension of cultured human conjunctival epithelial cells. The addition of a polymer, bonding with the cell membrane, results in compression of the lipid bilayer, causing a change in fluorescence proportional to polymer binding. This can be explained by the

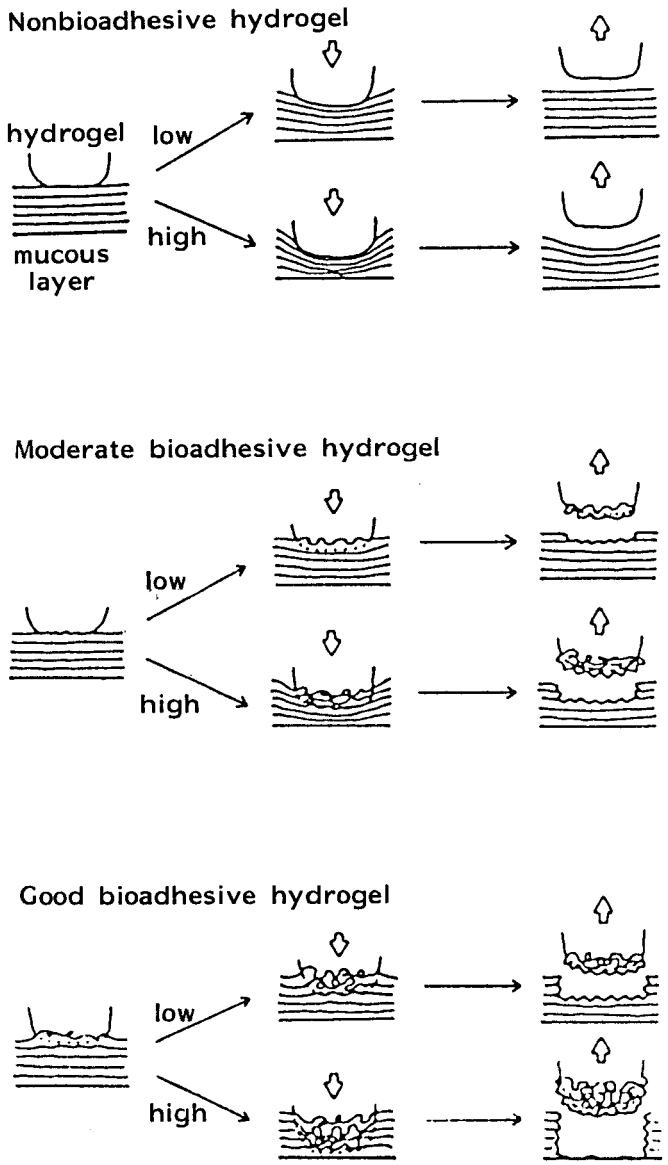


Figure 5 The interaction between mucous layers and hydrogels (According to <6> with permission)

fact that a photo-excited molecule of pyrene can react with a non-excited monomer to form a complex called an excimer. Excimer fluorescence is readily distinguished from monomer fluorescence. Lateral movement of the pyrene molecule in the membrane is closely related to the mobility of lipid molecules and, consequently, excimer formation is a diffusion-controlled process. Fluorescence intensities of monomer (M) and excimer (E) are related to the pyrene molecule diffusion coefficient in the lipid bilayer. Thus, by measuring and comparing E/M ratios for control and polymer-treated cells, it is possible to evaluate the effect of polymer treatment on membrane fluidity, i.e. polymer binding. The reduced E/M ratio by polymer treatment, $\Delta(E/M)$, is:

$$\Delta(E/M) = (E/M)_{control} - (E/M)_{polymer\text{-}treated}$$

Thus $\Delta(E/M)$ is a parameter suitable to compare quantitatively the ability of a polymer to increase viscosity, assuming that an increase in viscosity results from polymer binding or adsorption <18>.

It is also possible to obtain information on cell polarity from the peak ratio measurement of monomer fluorescence. In fact, the pyrene monomer is characterized by three well-defined peaks. Thus, the peak intensity ratio of II/I can be used as a measure of polarity of the probe environment. This ratio is referred to by Robinson as the P_y value <18>. Using this method, and measuring $\Delta(E/M)$ and P_y, Robinson tried to classify a large number of polymers according to their bioadhesiveness <18>.

Study of adhesion on artificial media

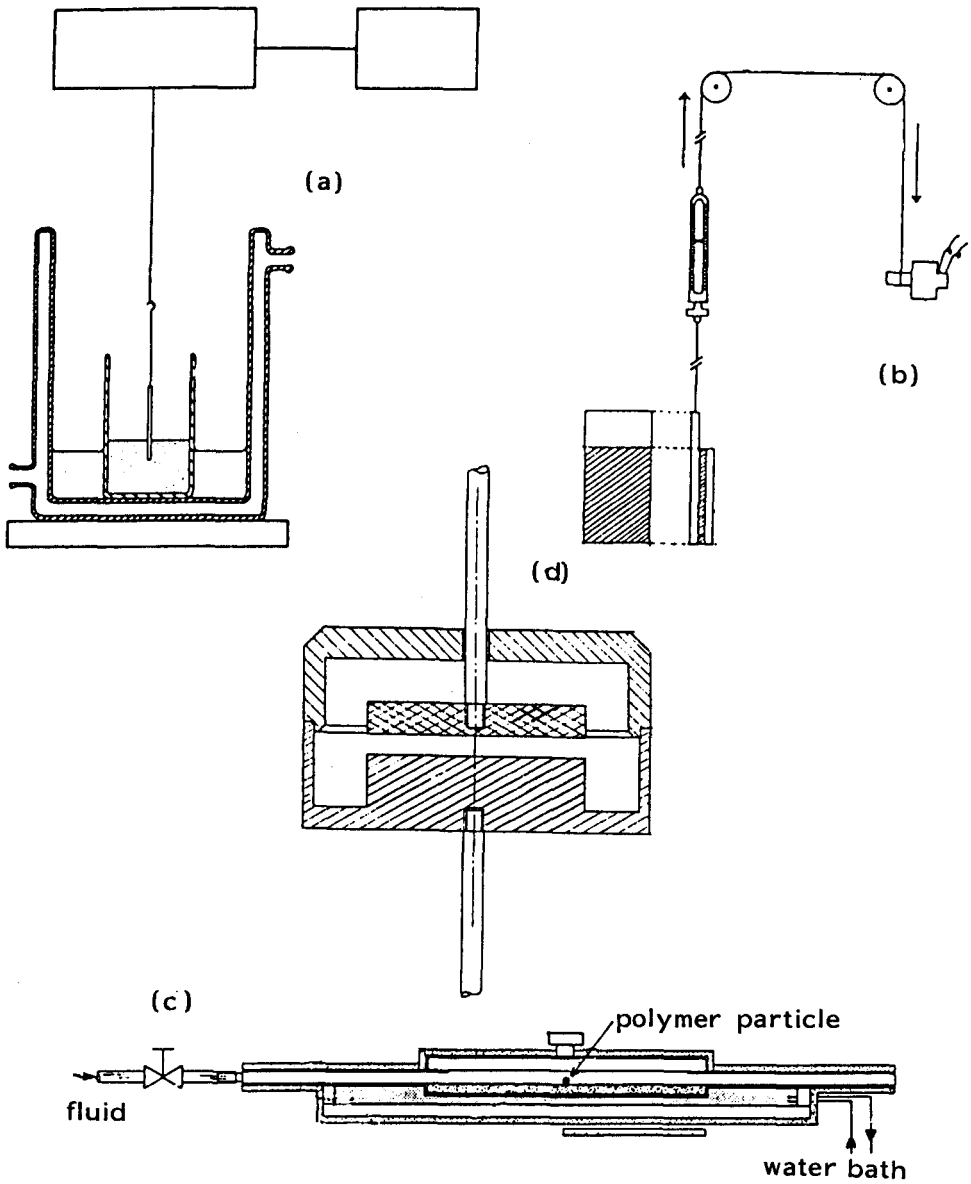
. Apparatus

Smart and Kellaway developed a method for the measurement of bioadhesiveness which is a modification of the Wilhelmy method for

the measurement of superficial tension <19>. The apparatus (diagram (a) in Figure 6) consists of a glass plate, 11 mm wide, suspended from a microbalance. A 5 mℓ glass phial (20 mm internal diameter by 33 mm deep) containing the mucus sample is placed in a water-bath at 20 °C. This is placed on a platform that can be mechanically moved up and down at a rate of 1 mm/min. The platform is raised until the glass plate penetrates the mucus or model gel to touch the base of the container. The plate is then left in contact with the mucus for 7 minutes before the platform is lowered at 1 mm/min. The maximum force recorded by the microbalance and displayed on a y/t recorder when the plate is detached from the mucus is noted. For the study of bio-adhesive polymers, glass plates are coated by dipping in a 1% solution of the test material, and oven-drying at 60 °C to constant weight.

A similar method was used by Nagai <20> to measure the adhesiveness of oral mucosa ointments (diagram (b) in Figure 6). The method consists in covering a 2.5 × 5 cm glass plate with ointment 0.3 to 0.4 mm thick, and measuring the force necessary to shear another glass plate sliding on the ointment at a speed of 140 cm/min.

An interesting method is the one resulting from collaboration between Purdue University and Geneva University <21>, because it tends to simulate the real behaviour of a gastro-intestinal bioadhesive system on the mucus. The apparatus (diagram (c) in Figure 6) consists of a thin channel about 15 cm long by 4 cm wide, and 0.5 cm deep, filled with a mucin solution, gel or natural mucus. The channel is thermostated and equipped with a transparent cover which can be removed by a handle. The system is connected through a valve to a fluid source which may be a gas or a viscoelastic liquid. The channel is placed on an optical microscope. For the experiment, a single spherical polymer particle of known weight is placed on the surface of the mucin using a Pasteur pipette, and the



(a) Smart and Kellaway apparatus (<19> with permission)
(b) Nagai *et al* apparatus (<20> with permission)
(c) Peppas and Mikos apparatus (<21> with permission)
(d) Gurny *et al* apparatus (reproduced from Gurny R., Meyer J.M. and Peppas N.A. Biomaterials, 1984, 5, 336-340, by permission of the publishers, Butterworth and Company (Publishers) Limited ©) <22>

Figure 6 Apparatuses for *in vitro* determination of bioadhesion

lid is closed. The volumetric flow rate (and the superficial velocity) of the fluid is then adjusted to physiological conditions, and the motion of the particle is followed with a fast-frame camera. The distance travelled by the particle is measured, as well as the time for detachment and the type of motion (rolling, sliding, jumping).

Gurny *et al* <22> developed a tensile method using an Instron tester equipped with a special cell for the determination of the adhesive bond strength (diagram (d) in Figure 6). The cell is constructed of two Plexiglas discs, each 10 cm in diameter, connected in their centres by permanently-fixed metallic bars perpendicular to the discs. The bars are fixed to the tensile tester. The two discs are enclosed in two cylindrical chambers. In the experiment, the bioadhesive preparation (gel) is hydrated with an equal amount of artificial saliva for 120 minutes, and placed between the two discs held at an initial distance of 2 mm. The equipment is started and the discs are pulled at an extension rate of 0.1 mm/min. The stress/strain curves are recorded.

. Artificial biological medium

As mentioned, some of the previous apparatuses require the use of an artificial biological medium: mucus or saliva.

Smart and Kellaway <19> describe a 'homogenized' mucus prepared with crude mucus samples, obtained by scraping guinea-pig intestines more or less contaminated with heterogeneous cellular material. These samples are mixed with an equal volume of distilled water, stirred slowly for 24 h at 4 °C, and then centrifuged. The supernatant and sedimented solids are discarded and the middle gel layer retained.

An artificial saliva is described by Fusayama *et al* <23>. It contains:

. Na_2S	0.0008 g
. $Mg_2P_2O_7$	0.0008 g
. mucin	2.0000 g
. Na_2HPO_4	0.3000 g
. $CaCl_2$	0.3000 g
. KCl	0.2000 g
. NaCl	0.2000 g
. distilled water q.s.	500 mℓ

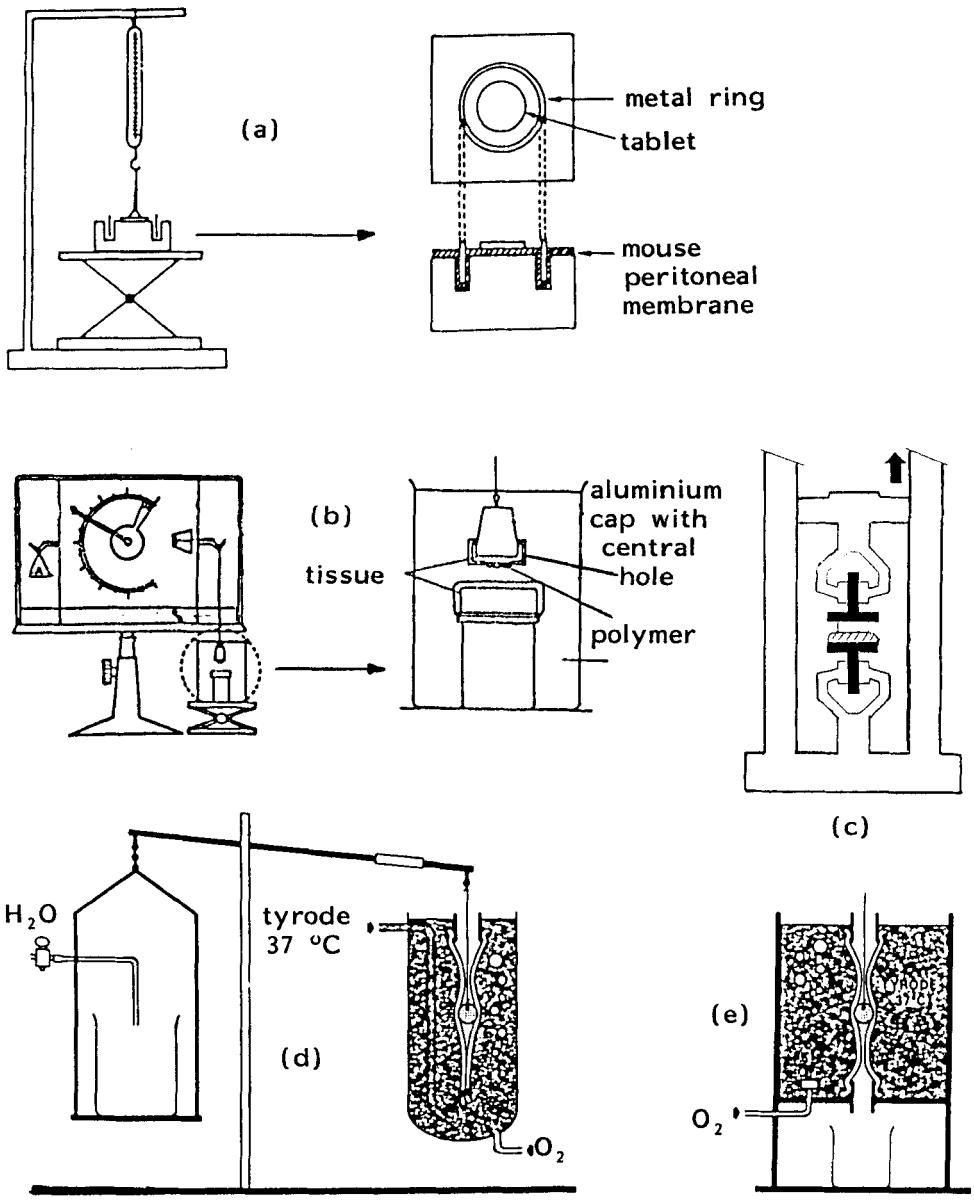
Study of adhesion on biological tissues

In order to be as close as possible to the real use conditions of bioadhesive systems, it was necessary to work on the same tissues as those for which the bioadhesive systems are developed.
These experiments are carried out either *in vitro* (or more precisely *ex vivo*) or *in vivo*.

. Study of *ex vivo* bioadhesion

Nagai was probably the first to describe an apparatus with the purpose of measuring the adhesiveness of an insulin solid dosage form for oral mucosa <24>. The apparatus (diagram (a) in Figure 7) requires the use of mouse peritoneal membrane on which the insulin dosage form is fixed for 10 minutes, and then wrenched with a spring balance.

Robinson <6,25> uses the same type of system with rabbit stomach mucosa (diagram (b) in Figure 7) immersed in test solution. The mucosa is secured on a fixed holder (bottom) and on a mobile holder (top) so as to leave apparent on the latter only a 10 mm diameter surface of mucosa. This surface is coated with hydrated polymer, and raised in contact with the mucosa of the upper holder. After 1 minute of contact with a pressure due to the upper holder weight <1,8>, the upper holder, connected to a modified tensiometer, is



(a) Nagai *et al* apparatus (<24> with permission)
(b) Robinson apparatus (According to <25>)
(c) Ponchel and Touchard apparatus (According to <26>)
(d) and (e) Marvola apparatus (According to <27>)

(b) (d) and (e) Reproduced with permission of the copyright owner, the American Pharmaceutical Association

Figure 7 Apparatuses for determination of *ex vivo* bioadhesion

raised with a force increasing at a constant rate of 10 mg/s until the polymer detaches from the mucus.

Ponchel, Touchard *et al* <16,26> developed a system very similar to that of Nagai. The tensile apparatus is an Instron tester (diagram (c) in Figure 7). The mucosa employed is ox subiingual mucosa which is stuck on the holder connected to the lower clamp of the tester. A tablet made with the bioadhesive polymer is stuck on the holder connected to the upper clamp of the tester. The force necessary for detachment is continuously recorded, and enables the calculation of adhesion work.

It is necessary to mention the two systems developed by Marvola <27> in order to measure the adhesion of a dosage form to the oesophagus (here it is not a question of bioadhesive systems, but a disadvantage of certain classical formulations). These apparatuses (diagrams (d) and (e) in Figure 7) use segments of pig oesophagus maintained at 37 °C in oxygenated tyrode solution. The solid dosage form (tablet or hard gelatin capsule) under study is attached to a prescription balance, and inserted in the oesophagus. It is then progressively detached by increasing the charge on the opposite tray of the balance.

Swisher *et al* <28> as well as Al-Dujaili and Florence <29> employ analogous methods for the same purpose.

. Study of *in vivo* adhesion

Robinson <25>, in order to investigate the gastro-intestinal transit of bioadhesive beads, developed an *in vivo* method in the rat (Figure 8). After anaesthesia of the rat and abdominal incision, the stomach is carefully lifted from the abdominal cavity and opened along a few mm. A capsule containing the bioadhesive material labelled with ^{51}Cr, or control product, is inserted into

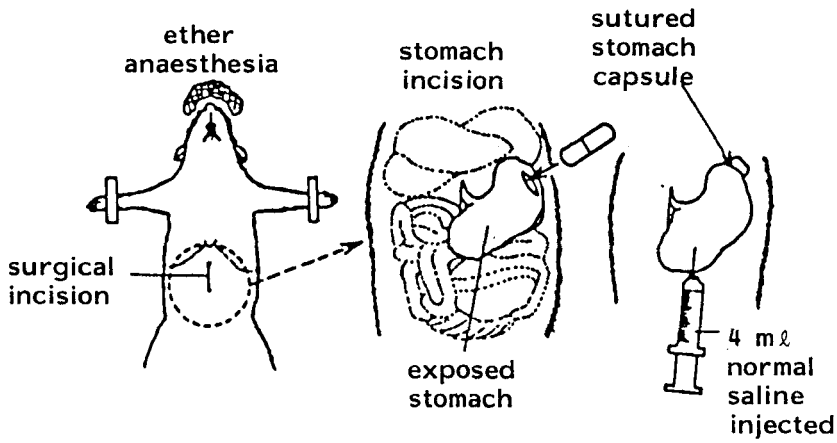


Figure 8 Robinson method for determination of *in vivo* bioadhesion (According to <25>)

the stomach. The opening is then tied and the stomach replaced in the abdominal cavity. 4 mℓ of a normal saline solution are injected into the stomach to assist in dissolution of the gelatin capsule. The external incision is closed and the anaesthesia interrupted. At selected time intervals, the rats are sacrificed, and the stomach and small intestine removed. The intestine is cut into 20 equal segements and the radioactivity is measured in each segment and the stomach.

Davis <30>, with his scintigraphic method, followed the gastro-intestinal transit of a bioadhesive form. It seems that there are some bioadhesion irregularities with the consequence of a lack in accurate and durable localization of the bioadhesive form.

BIOADHESIVE POLYMERS

In his first technique for measuring bioadhesiveness by the change in fluorescence of pyrene bonded to the cell lipid layer,

Robinson tried to classify cationic, anionic and neutral polymers using the P_y and $\Delta(E/M)$ values <18>. Interpretation of results is not always easy. However, Robinson concluded that polyanions are better than polycations, for both bioadhesiveness and toxicity reasons. Among polyanions, poly(acrylic acid) seems to have the best bioadhesion characteristics, for high proportions, because of the importance of $\Delta(E/M)$. Gelatin, arbitrarily placed with neutral polymers, presents a large decrease in the E/M ratio, corroborating its bioadhesive character. Most of the neutral polymers have important $\Delta(E/M)$ and P_y values, compared with other polymers, but it is not possible to conclude prematurely in a high bioadhesive potential because they can easily be washed off and eliminated from their adhesion site.

With the purpose of acquiring a better knowledge of the relationship between polymer structure and bioadhesive potential, Robinson synthesized a series of anion crosslinked swellable polymers of the polycarbophil family <25>, and measured their *ex vivo* bioadhesion <25>. It appears (Table 1) that poly(acrylic acid/divinylbenzene), polycarbophil and poly(acrylic acid-2,5-dimethyl-1,5-hexadiene) have high bioadhesive characteristics, whereas poly(2-hydroxyethyl methacrylate) or poly(HEMA), Amberlite 200 and gelatin result in poor or non-existent bioadhesive qualities. It is necessary to point out that the rôle of pH on bioadhesion is of great importance, the maximum of adhesion being observed for pH 5 to 6. It appears from this study <25> that bioadhesiveness increases with an enhancement of the charge density and with a simplification of the polymer structure (Table 1). When hydrogels become more hydrophobic, such as poly(HEMA), they tend to interact with each other, thus reducing interaction with the mucous layer. The absence of bioadhesive properties of Amberlite beads and crosslinked gelatin microcapsules is thought to be due to the lack of chain flexibility necessary for physical entanglement with the mucin molecules.

Table 1

Bioadhesive characteristics of a series of anionic crosslinked swellable polymers of the carbophil family

(According to <25>, reproduced with permission of the copyright owner, the American Pharmaceutical Association)

test material	weight required for detachment (mg)	force (dyn)	force/area (dyn/cm²)
polycarbophil	855 ±55	838 ±54	1061 ±68
polymer of acrylic acid/ divinylbenzene	876 ±57	858 ±58	1086 ±71
polymer of methacrylic acid/ divinylbenzene	306 ±45	300 ±44	380 ±56
polymer of acrylic acid/ 2,5-dimethyl-1,5-hexadiene	864 ±56	847 ±55	1061 ±68
poly(HEMA) poly(2-hydroxyethyl methacrylate)	30 ±8	29 ±8	37 ±10
Amberlite 200 resin beads	0	0	0
crosslinked gelatin microcapsules	0	0	0

Robinson once more, trying to assess the bioadhesion possibilities during gastro-intestinal transit, compares polycarbophil, poly-(methacrylic acid/divinylbenzene) and Amberlite <25>. It is the polycarbophil which has the best bioadhesive qualities (Table 2 and Figure 9). It should be noted that bioadhesion can occur in the stomach as well as in the small intestine. For the appearance of bioadhesion, there must be some free binding site on the surface of the polymer available for bioadhesion. This can only occur when the surface of the polymer is not fully covered with mucus when it is discharged from the stomach, or when the mucus layer is degraded during transit through the gastro-intestinal tract. Thus it would seem difficult to expect an exclusively gastric bioadhesion, and this is confirmed by the works of Davis <30>.

Table 2

Bioadhesive characteristics of polycarbophil, poly(methacrylic acid/divinylbenzene) and Amberlite

(According to <25>, reproduced with permission of the copyright owner, the American Pharmaceutical Association)

time (h)	stomach	small intestine	total
^{51}Cr polycarbophil			
1	96.9 ±1.2	3.1 ±1.2	100
2	91.3 ±2.5	8.1 ±2.5	100
4	84.8 ±2.4	15.2 ±2.4	100
6	78.3 ±1.5	21.7 ±1.5	100
10	54.6 ±1.0	17.2 ±6.0	71.8
17	37.0 ±3.4	17.4 ±2.18	54.4
24	9.0 ±3.2	12.4 ±3.59	21.4
^{51}Cr polymer methacrylic acid/divinylbenzene			
2	82.3 ±3.8	17.7 ±3.8	100
4	69.0 ±4.7	31.0 ±6.7	100
6	64.1 ±5.4	35.9 ±5.4	100
8	33.9 ±5.6	44.5 ±6.6	78
16	8.3 ±2.7	14.8 ±4.2	23.1
Amberlite 200 beads			
1	95.8 ±1.9	4.2 ±1.9	100
2	62.4 ±3.3	37.6 ±3.3	100
3	26.8 ±5.4	73.2 ±5.4	100
4	11.8 ±3.5	88.2 ±3.5	100
6	3.6 ±1.2	29.1 ±9.7	82.7
8	3.8 ±1.4	47.0 ±10.2	50.8

Other systematic studies of bioadhesion have been performed by Marvola <31,32>. Their purpose was different from that of the above studies, because it concerns the assessment of the rôle of formulation factors on oesophagal drug bioadhesion. The work deals more especially with the effects of film coating agents. It appears that the least adhesive tablets were those coated with sugar, whereas hydroxypropylmethyl cellulose and particularly

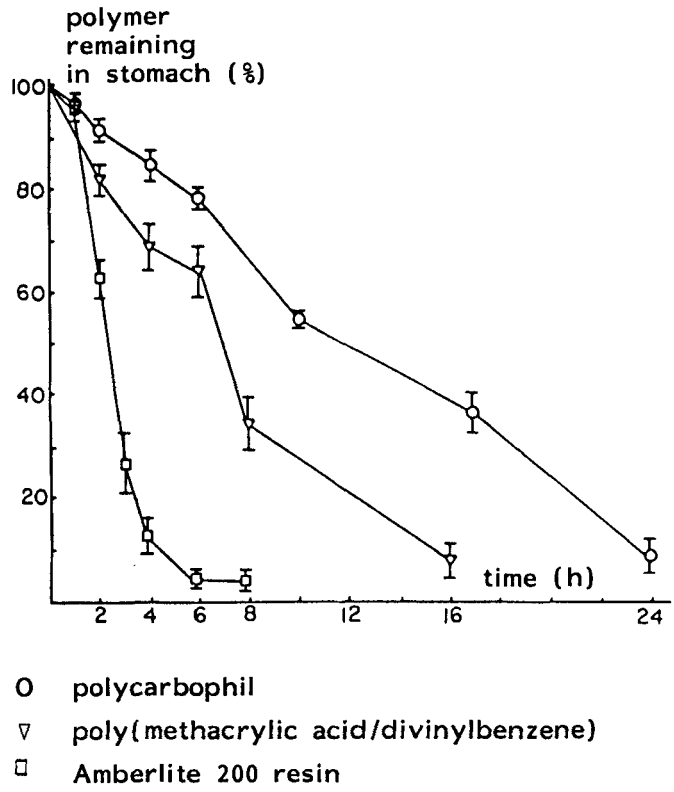


Figure 9 Rat gastro-intestinal transit of polymers
(According to <25>, reproduced with permission of the copyright owner, the American Pharmaceutical Association)

ethyl cellulose are considerably more adhesive. The effect of additives is quite poor. However silicic acid decreases bioadhesion and, on the contrary, polyethylene glycol, highly bioadhesive by itself, increases the bioadhesion of filmcoating agents, when used as a plasticizer.

Other studies have been undertaken to classify bioadhesive polymers <14,19>. They are summarized in Table 3 <2>. They show the important bioadhesion power of carboxymethyl cellulose and of Carbopol 934.

Table 3

Bioadhesive characteristics of various polymers
(According to <2>, with permission)

substance	mucoadhesive force	adhesive performance
Carmellose (carboxymethylcellulose)	193	excellent
Carbomer 934 (Carbopol)	185	excellent
polycarbophil	-	excellent
tragacanth	154	excellent
sodium alginate	126	excellent
hydroxyethylcellulose	-	excellent
karaya gum	125	good
gelatin	116	fair
guar gum	-	fair
pectin	100	poor
Povidone (poly(vinylpyrrolidone))	98	poor
acacia	98	poor
Macrogol (polyethylene glycol)	96	poor
psyllium	-	poor

Besides these classifications, it should be noted that Nagai <24,33 34> used a mixture of Carbopol 934 and hydroxypropyl cellulose, and Duchêne *et al* <16,17,35> used a mixture of Carbopol 934 and hydroxypropylmethyl cellulose. In both cases, Carbopol was the bioadhesive agent and the cellulosic derivative was the hydrophilic matrix. Peppas employed a copolymer: poly(HEMA-co-NVP) <36>, and Gurny *et al* <22> worked with a polyethylene gel containing sodium carboxymethyl cellulose.

FACTORS AFFECTING BIOADHESION

The bioadhesive power of a polymer or of a series of polymers is affected by the nature of the polymer and also by the nature of the surrounding media.

Polymer-related factors

. Molecular weight

As mentioned by Gurny *et al* <22>, it seems that the bioadhesive force increases with the molecular weight of the bioadhesive polymer, up to 100,000, and beyond this level there is not much effect. It is clear that, to allow chain interpenetration, the polymer molecule must have an adequate length. It is also necessary to consider the size and configuration of the polymer molecule. Hence, for example, with polyethylene oxide, adhesive strength increases even up to molecular weights of 4,000,000: these polymers are well-known to contain molecules of highly linear configuration, which contribute to interpenetration. On the other hand, with dextran, molecules with molecular weights as high as 19,500,000 do not exhibit better bioadhesion than molecules with a molecular weight of 200,000.

Concentration of active polymer

Bremecker <37> relates that there is an optimum concentration of polymer corresponding to the best bioadhesion. In highly concentrated systems, the adhesive strength drops significantly. In fact, in concentrated solutions, the coiled molecules become solvent-poor, and the chains available for interpenetration are not numerous. This result seems to be of interest only for more or less liquid bioadhesive forms <22>. Duchêne and Peppas, for solid dosage forms such as tablets, showed that the higher the polymer concentration, the stronger the bioadhesion <16,26,38>.

. Swelling

This characteristic is related to the polymer itself, and also to its environment. As mentioned earlier, interpenetration of chains is easier as polymer chains are disentangled and free of interactions.

Swelling depends both on polymer concentration and on water presence. It must be remembered that, when swelling is too great, a decrease in bioadhesion occurs <22>. Such a phenomenon must not occur too early, in order to lead to a sufficient action of the bioadhesive system. Nevertheless, its appearance allows easy detachment of the bioadhesive system after the discharge of the active ingredient.

Environment-related factors

. pH

The absorption of water by a polymer, and hence its swelling, depends to a great extent on the pH (Figure 10). Bioadhesivity is also dependent on this factor (Figure 11) <6>. However, as can be seen when comparing the figures, when the pH varies, polycarbophil swelling is not the dominant factor for bioadhesion. In any case, there is an optimal pH for polymer adhesion <25>.

Applied strength

It is obvious that, to place a solid bioadhesive system, it is necessary to apply a defined strength. Whatever the polymer, poly(acrylic acid/divinylbenzene), poly(HEMA) <6> or Carbopol 934 <16,26>, the adhesion strength increases with the applied strength or with the duration of its application, up to an optimum (Figure 12).

BIOADHESIVE DOSAGE FORMS

Numerous patents concern various applications of bioadhesiveness related to the administration route, the dosage form, the additives or the active ingredients. On the other hand, there are only few commercially-available bioadhesive systems, but research works for real therapeutic applications are numerous.

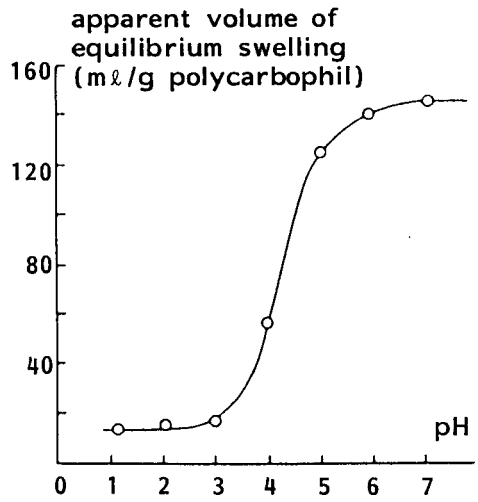


Figure 10 Apparent volume of equilibrium swelling of polycarbophil at various pH

(According to <6> with permission)

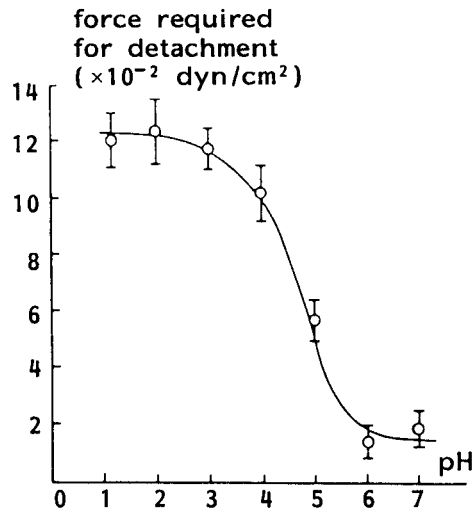


Figure 11 Effect of pH on *in vitro* bioadhesion of polycarbophil to rabbit stomach tissue

(According to <6> with permission)

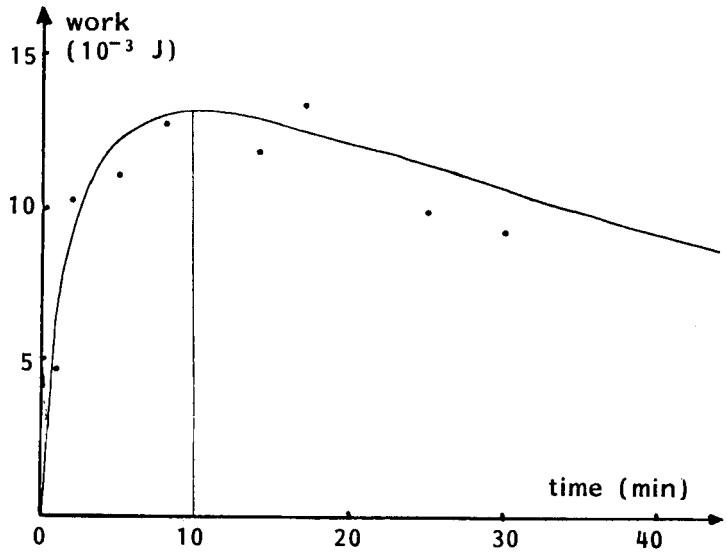


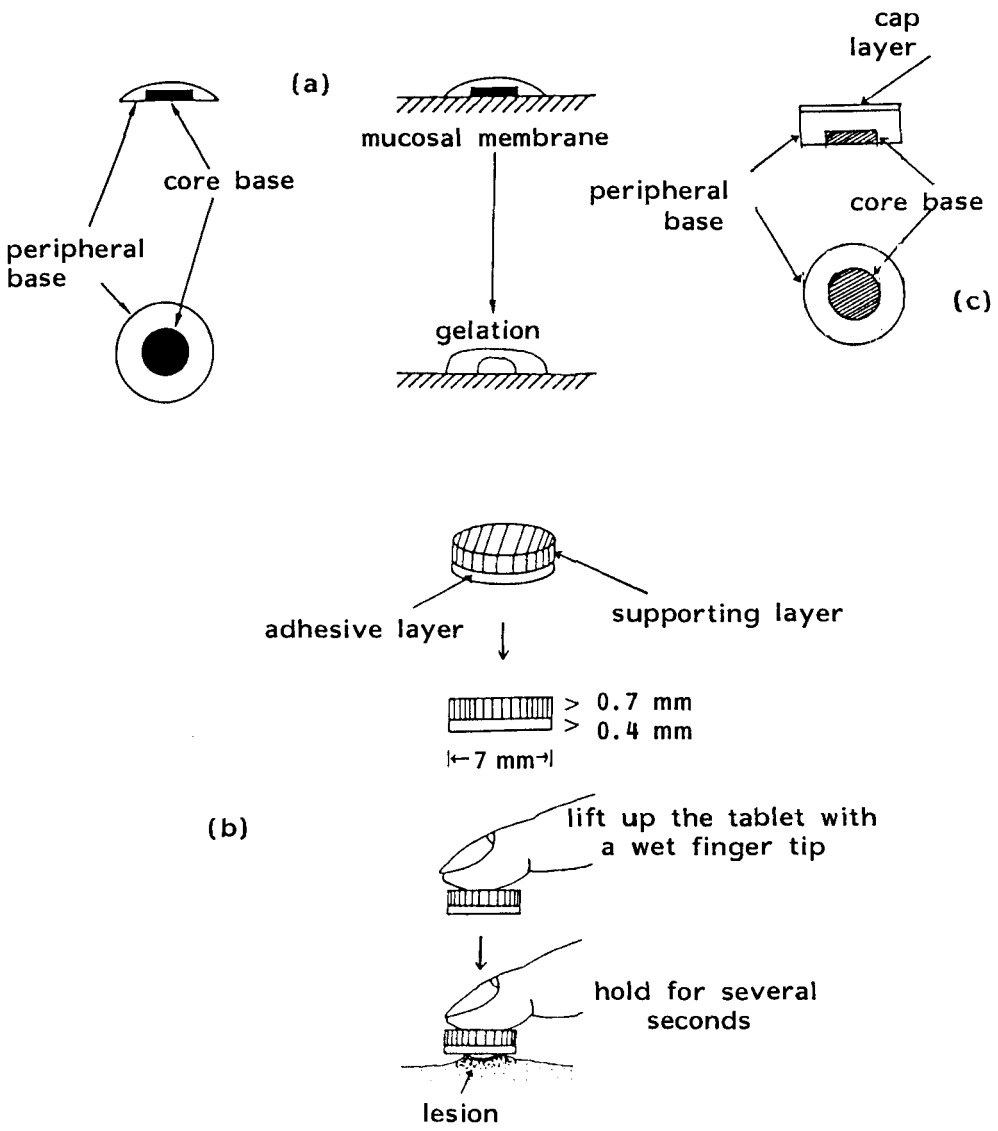
Figure 12 Effect of duration of applied strength on bioadhesion (According to <26>)

Buccal administration

By buccal administration, the activity sought may be systemic or local.

Systemic activity

Nagai <24,39,40> tried to develop an oral mucosal adhesive dosage form capable of solving problems of repeated parenteral administration of insulin. Since insulin is destroyed by the digestive tract, the adhesive form is designed to allow insulin diffusion only through the buccal mucosa (diagram (a) in Figure 13). Insulin and sodium glycocholate are dispersed in a cocoa-butter core 5 mm in diameter and 1 mm thick. The core is coated on one of its faces and laterally by a bioadhesive cap, constituted of hydroxypropyl cellulose and Carbopol 934 (1:2), slowly compressed on a hydraulic press, so as to cover the core. Unfortunately,



(a) adhesive dosage form of insulin (According to <24> with permission)

(b) adhesive tablet for the treatment of aphta (According to <39> with permission)

(c) adhesive dosage form of lidocaine (According to <34> with permission)

Figure 13 Buccal bioadhesive dosage forms developed by Nagai

even if insulin is well resorbed through the buccal mucosa, its blood level remains too weak to allow real development of this form.

Schor <41> developed a nitroglycerin bioadhesive tablet (Susadrin or Suscar) used for the treatment of angina pectoris.

. Local activity

With much more success than for insulin, Nagai developed a bioadhesive tablet for aphtous stomatitis <39,40>. The tablet (diagram (b) in Figure 13) is of small dimensions, 7 mm in diameter and 1.1 mm thick. It is a bilayer tablet. The upper coloured layer consists of lactose and has no adhesive property, its rôle being to prevent active ingredient (triamcinolone acetonide) diffusion out of its activity site (aphta) and to allow an easy placing of the bioadhesive tablet. The lower layer, which contains the active ingredient, is made with hydroxypropyl cellulose and Carbopol 934, and constitutes the bioadhesive layer. This tablet, commercially available under the name of 'Aftach', resulted in the awarding to Professor Nagai of the Japan National Invention Prize in 1984.

For the treatment of aphtae, Nagai <20> also studied a prednisolone ointment, whose bioadhesive base is, for example, a mixture of Carbopol and white petrolatum or Carbopol and hydrophilic petrolatum.

Nagai <34,39,40> also developed a bioadhesive tablet in order to produce a local anaesthesia for toothache. This tablet (diagram (c) in Figure 13) consists of a core containing the active ingredient, lidocaine, blended with a freeze-dried mixture of hydroxypropyl cellulose and Carbopol 934. The core is coated laterally and on the upper part with a bioadhesive mixture of hydroxypropyl cellulose and Carbopol, and directly compressed with

a hydraulic press. Finally, a third layer is applied, consisting of a freeze-dried mixture of hydroxypropyl cellulose and Carbopol added to magnesium stearate (1:1). This dosage form may be expected to afford a long-acting local anaesthesic action, especially if lidocaine can be advantageously replaced by dibucaine, in order to obtain a better anaesthesia.

It should be noted that Yotsuyanagi <42> uses tetracaine as the local anaesthetic in a buccal bioadhesive film containing hydroxypropyl cellulose and triacentin. This film also contains thiamphenicol.

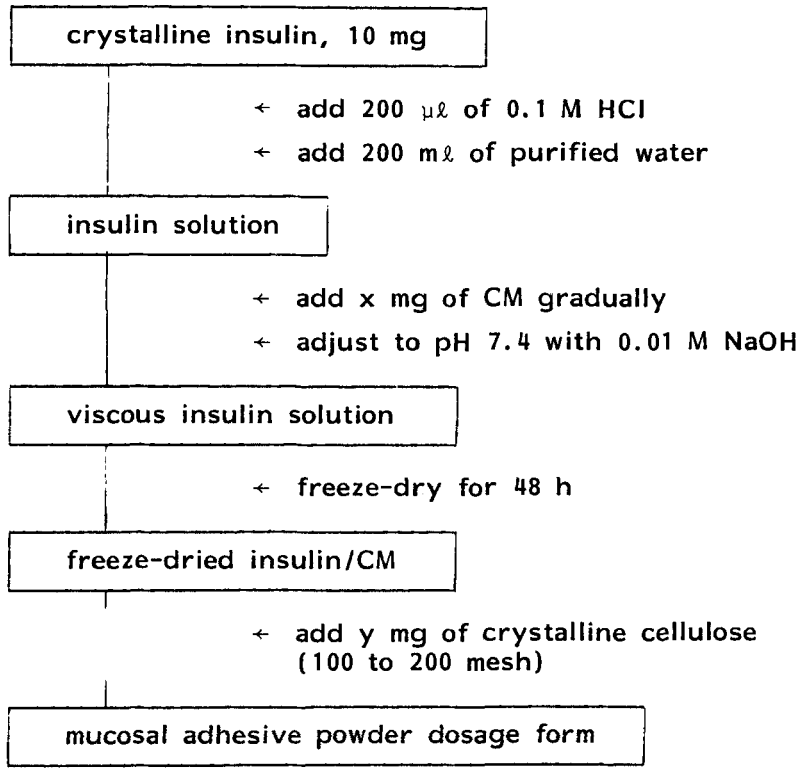
Numerous patents have been filed concerning various oral bioadhesive forms presented as tablets <43,44,45>, powders <43>, granules <43>, microcapsules <46,47>, and also films and tapes generally constituted with an active layer and a neutral layer <48 to 51>.

Gastro-intestinal administration

The search for a bioadhesive system that adheres at a defined level of the gastro-intestinal tract is essentially the work of Robinson <46,52>. He proposes the administration of capsules containing beads of albumin and chlorothiazide as a prolonged release form, and the same sized polycarbophil particles as the adhesive agent.

Cervix administration

Nagai <33,39,40,53> developed more or less bioadhesive forms for the treatment of uterine or cervical cancers: carcinoma colli. These forms, stick-shaped, have a base of hydroxypropyl cellulose and Carbopol, and contain bleomycin <33,53>, carboquone or 5-fluorouracil <53>. The stick is inserted in the cervix, where it adheres to the mucosa, and where it can release its active ingredient over and above 24 h.



formula:	x	y
H	0	90
I	10	80
J	50	40
K	90	0

Figure 14 Nagai's nasal mucosal adhesive powder for insulin (According to <39> with permission)

Nasal administration

The utilization of the nasal route for the administration by transmucosal penetration of active ingredients destroyed by other routes is a method that is currently expanding considerably. Nagai <39,40,43> proposes this route for the administration of various active ingredients in powder form. The administration of insulin seems to be possible. A freeze-dried powder with Carbopol (Figure 14) results in the same insulin blood concentration

as an intravenous injection dosed three times more. So penetration is really noticeable. Nagai <39> has published works on the development of a powder called 'Rhinocort' containing beclomethazone dipropionate and hydroxypropyl cellulose for the treatment of allergies.

Ocular administration

Bioadhesive forms currently proposed for ocular administration are rather rare. However, Robinson <46> has forecast, in a patent, the use of films or laminates for the ocular route.

CONCLUSION

The basic works dealing with bioadhesion, the good knowledge of polymers, and the great number of patents that exist indicate that drug administration by the transmucosal route, using bioadhesive systems, is the reality of tomorrow.

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