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BIOADHESIVE TABLETS
INFLUENCE OF THE TESTING MEDIUM COMPOSITION ON BIOADHESION

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ABSTRACT

A bioadhesive tablet of metronidazole has been developed for oral or vaginal administration. The bioadhesive component is poly(acrylic acid) (Carbopol 934), and the matrix component is hydroxypropyl methylcellulose (HPMC K4M). The influence of the test medium was investigated in order to determine the adhesion of the tablet during routine use by the various routes. The parameter retained to evaluate adhesion was the adhesion work on a biological tissue. The factors whose influence was investigated were pH, ionic force and nature of cations, and type of biological substrate.

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INTRODUCTION

For some years, bioadhesive systems for various administration routes <1 to 4> have been the subject of increasing interest, and some of these systems are already on the pharmaceutical market. However, up to now, they generally contain only a small quantity of active ingredient.

In previous publications <5 to 7>, we showed that it is possible to develop a bioadhesive form exhibiting high adhesivity, even though it contains a high concentration of active ingredient (50%), and resulting in suitable controlled release <7>.

As this form is intended for local application, it was interesting to study the influence of various factors, such as pH, ionic strength and composition of the medium, and the type of biological substrate on the adhesiveness of the tablet.

The parameter retained to evaluate adhesion is the adhesion work of a system fixed on a biological tissue. This value is the most commonly used to study the rupture of adhesive joints <8,9>. In fact, it appears that this value is suitable for the quantification of the bioadhesive power of a given polymer <5 to 7>.

MATERIAL AND METHODS

Bioadhesive system

The bioadhesive system developed and studied here is a controlled-release matrix tablet containing 50% metronidazole (Rhône-Poulenc, Antony, France), 37.5% hydroxypropyl methylcellulose (HPMC) (Methocel K4M, Dow Chemical, Valbonne, France), and 12.5% poly(acrylic acid) (PAA) (Carbopol 934P, Goodrich, Cleveland, Etats Unis).

These powders were mixed in a Turbula apparatus (model T2G, Baschoffen, Basel, Switzerland), and tabletted on a single-punch

machine (EKO, Korsch, Berlin, West Germany). The tablets had an average weight of 250 mg, a hardness of 70 to 90 N, their diameter was 12 mm, and their thickness 2 mm.

Test media

The test media used were either buffered solutions or solutions with adjusted ionic concentration. For pH 5 to 8, the buffered solutions contained disodium phosphate and potassium hydrogenophosphate, and for pH 2, they contained 0.1 N hydrochloric acid and potassium chloride. Their osmolality was measured using an osmometer with Pelletier effect (Osmomat 30). The isotony was obtained by the addition of sodium chloride.

The solutions with adjusted ionic concentration were sodium chloride (0, 10, 25, 50, 75 and 100 g/l) and calcium chloride solutions (0, 5, 10, 20, 50 and 100 g/l). All the reagents were of analytical grade. The water used was distilled water (pH 6, conductivity 5.6 μS).

Biological tissues

The biological samples used were bovine vaginal and sublingual mucosa. They were taken immediately after the sacrifice of the animals at the slaughterhouse. They were frozen at -20 °C immediately after careful separation of the mucosa from the supporting muscular tissue. For the bioadhesive studies, the samples were thawed in an isotonic solution at pH 7.2.

Bioadhesive studies

Two methods were used in order to determine the force and work of adhesion of a tablet on a mucosa. The first one (Method No.1)

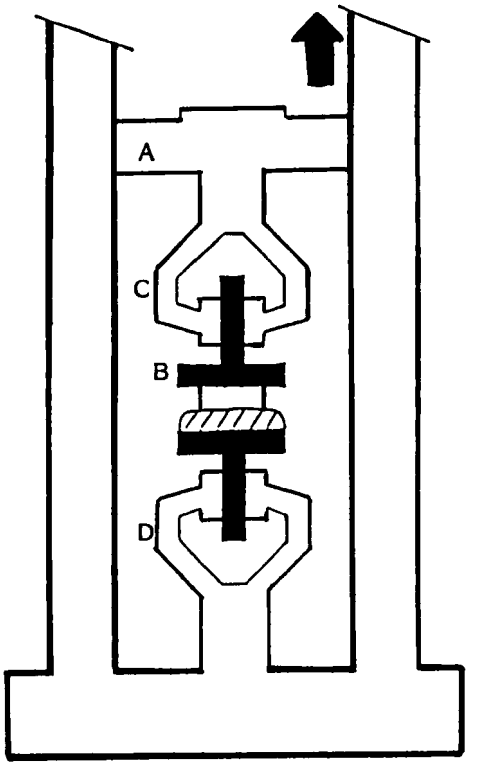

Figure 1 Apparatus employed for the determination of adhesion on biological tissues according to Method No.1

was described in a previous work <5>. It enables the study of tablet adhesion with respect to the quantity of liquid at the interface. The apparatus employed was a universal tensile apparatus (Instron, model 1026, Instron Limited, High Wycombe, UK) (Figure 1).

It consisted of a gantry equipped with a vertically mobile crosspiece (A), supporting a test cell (B) with a pneumatic clamp (C). A second clamp (D) was fixed to the stand directly below the first one. The whole apparatus was placed in an air-conditioned room (25 °C, 60% RH). The tablet and mucosa were

stuck on to cylindrical copper supports (12 mm in diameter) with a cyanoacrylate type glue (Loctite Super Glue, Framet, Senlis, France). The mucosa support was maintained by the lower clamp. The tablet support was fixed similarly to the upper clamp, in such a way that the tablet and mucosa surfaces were rigorously parallel. 15 µl of buffered solution were spread on the mucosa surface. The crosspiece was then lowered, in order to maintain a contact between the tablet and the mucosa, with a force of 0.5 N. After 10 minutes, the crosspiece was raised at constant speed (5 mm/min). The detachment force was recorded as a function of displacement, up to the total separation of the two surfaces. The adhesion work was given by the area under the curve/force necessary for detachment/ elongation.

The second method (Method No.2) was derived from the first. It was used to conduct the same experiments when the whole tablet/ mucosa system was dipped in a liquid medium of variable composition. The tablet was stuck to a Teflon support (14 mm in diameter), which was maintained by a glass cylinder on the bottom of a 400 ml beaker. The whole beaker/Teflon support assembly replaced the lower clamp of the previous apparatus. The beaker was filled with 300 ml of the test medium, and the surfaces (tablet and mucosa) were put in contact. All the other parameters (contact force and time, room temperature, displacement speed of the crosspiece) were the same as in the previous method.

RESULTS AND DISCUSSION

Influence of pH

First of all, the influence of pH was investigated by limiting the hydration of the tablet/mucosa system by controlling the quantity of the liquid medium (Method No.1). The biological support was bovine sublingual mucosa. Three solutions of pH 2, 5 and 8 isotonized with sodium chloride were the test media. The

Table 1
Influence of pH on the adhesion work of a bioadhesive tablet on bovine sublingual mucosa according to Method No.1
(Average of five determinations)

solution pH	2	5	8
work (mJ)	3.9 ± 2.3	3.6 ± 1.4	3.5 ± 1.5

Table 2
Influence of pH on the adhesion work of a bioadhesive tablet on bovine sublingual or vaginal mucosa, according to Method No.2
(Average of five determinations)

solution pH	2	5	7	8
work (mJ):				
. sublingual	0.5 ±0.3	0.2 ±0.05		0.5 ±0.4
. vaginal	0.4 ±0.1		0.5 ±0.2	

results (Table 1) show that the pH has no significant influence on system bioadhesion.

Since this lack of variation could result from the small quantity of liquid at the interface, the experiment was then carried out by dipping the whole system in a buffered solution (Method No.2). Sublingual and vaginal mucosa were the biological tissues employed. The results (Table 2) clearly show a decrease in adhesion work compared with the previous results in Table 1.

This could result from a greater hydration of the interface. The differences between the various measurements are not significant. The bioadhesion of the system seems to be only poorly (or not at all) sensitive to the pH of the medium in which it is immersed. This could be the result of a too slow action of the solution medium on the system tested (low quantity of ions, slow diffusion

Table 3
Influence of the ionic strength on the bioadhesive power of a tablet on bovine sublingual or vaginal mucosa, according to Method No.2
(Average of five determinations)

NaCl		sublingual mucosa		vaginal mucosa	
g/l	ionic strength	maximum force F (N)	work W (mJ)	maximum force F (N)	work W (mJ)
0	0	1.9 ±0.6	0.6 ±0.3	2.8 ±0.6	1.0 ±0.5
10	0.17	2.5 ±0.7	0.8 ±0.3	2.2 ±0.7	0.5 ±0.2
25	0.43	1.4 ±0.6	0.3 ±0.1	3.3 ±1.0	1.4 ±0.8
50	0.87	1.5 ±0.3	0.3 ±0.1	1.8 ±0.4	0.4 ±0.1
75	1.32	0.8 ±0.4	0.2 ±0.05	1.4 ±0.6	0.4 ±0.3
100	1.77	0.9 ±0.3	0.2 ±0.1	2.3 ±0.9	0.7 ±0.4

at the interface), or to the small quantity of PAA (12.5% of the bioadhesive tablet), which is the only constituent whose bioadhesive character is liable to change with pH.

Influence of ionic strength

The maximum detachment force and bioadhesive work of the system immersed in sodium chloride solutions were recorded using sublingual and vaginal mucosa. With sublingual mucosa, the adhesion parameters (Table 3) decrease significantly with an increase in sodium chloride concentration. The vaginal mucosa, which possesses a more abundant mucus, gives results which are less clear (Figure 2).

In order to evaluate the rôle of PAA on this loss of adhesiveness, tablets of pure PAA and pure HPMC were tested in extreme

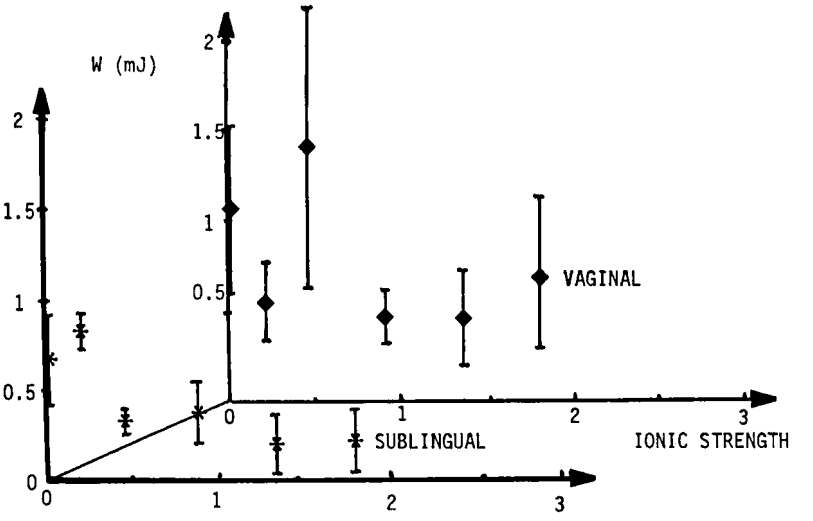

Figure 2 Influence of ionic strength (NaCl) on the bioadhesive work of a tablet on boving sublingual and vaginal mucosa

concentrations of sodium chloride solutions (0 and 100 g/l). The results (Table 4) are interesting for various reasons.

PAA adhesion is very sensitive to the presence of ions. In solution, PAA disentangles due to the action of its partly ionized carboxylic groups. The addition of cations to the solution shields these charges, and results in the recoiling of the macromolecule on itself <10 to 14>. In this new form, the PAA molecule cannot easily diffuse and penetrate into another hydrogel. Furthermore, the quantity of free groups capable of giving secondary chemical bonds with the biological tissue groups decreases significantly, and it is these phenomena that seem to be at the source of PAA bioadhesion <5 to 7, 15 to 19>.

On the other hand, ionic strength has little effect on HPCM adhesion (it is a non-ionic polymer). It is therefore possible to assume that the loss of adhesion of the system containing

Table 4
Influence of ionic strength on the bioadhesive power of pure PAA and pure HPMC tablets, on bovine sublingual mucosa, according to Method No.2
(Average of five determinations)

NaCl		PAA		HPMC	
g/l	ionic strength	F (N)	W (mJ)	F (N)	W (mJ)
0	0	7.6 ±1.7	3.9 ±1.2	2.4 ±0.8	0.8 ±0.4
100	1.77	2.4 ±1.1	2.1 ±0.7	2.3 ±0.8	0.6 ±0.3

metronidazole (Table 4) stems from the loss of bioadhesive power of the included PAA. It is interesting to note that the presence of an abundant mucus (vaginal mucosa) seems to protect the system against the influence of the surrounding medium.

The comparison of the bioadhesive power of the two polymers (Table 4) is interesting. It appears that, for a given detachment force (PAA and HPCM both in a 100 g/l sodium chloride solution), PAA adhesion work is three times higher than that of HPCM. It is hence necessary to produce three times as much energy to detach the system containing PAA than for that containing HPMC. Hence system adhesivity is described more precisely by adhesion work than by simple maximum detachment force.

Influence of divalent cations

The effect of divalent cations on the mucus is well known. By linking themselves with the mucin macromolecule negative charges of the mucus sialic acid, the divalent cations cause a fall in mucus viscosity by shrinkage of its polymeric chains <18,20>.

A similar effect may be observed with PAA <14,21>. In order to study the influence of divalent cations on the bioadhesion of the system studied, the same test was carried out as before, using, for

Table 5
Influence of divalent cations (Ca^{2+}) on the bioadhesive power of a tablet on bovine sublingual or vaginal mucosa, according to Method No.2
(Average of five determinations)

NaCl		sublingual mucosa		vaginal mucosa	
g/l	ionic strength	F (N)	W (mJ)	F (N)	W (mJ)
0	0	1.9 ±0.6	0.6 ±0.3	2.8 ±0.9	1.0 ±0.5
5	0.13	1.0 ±0.6	0.3 ±0.1	2.4 ±1.0	0.7 ±0.5
10	0.27	1.1 ±0.5	0.2 ±0.1	2.9 ±0.7	1.1 ±0.5
20	0.54	1.2 ±0.6	0.3 ±0.2	1.7 ±1.0	0.8 ±0.5
50	1.39	1.5 ±0.6	0.4 ±0.2	2.0 ±0.8	0.5 ±0.3
100	2.77	1.5 ±0.7	0.3 ±0.2	2.9 ±0.7	0.9 ±0.

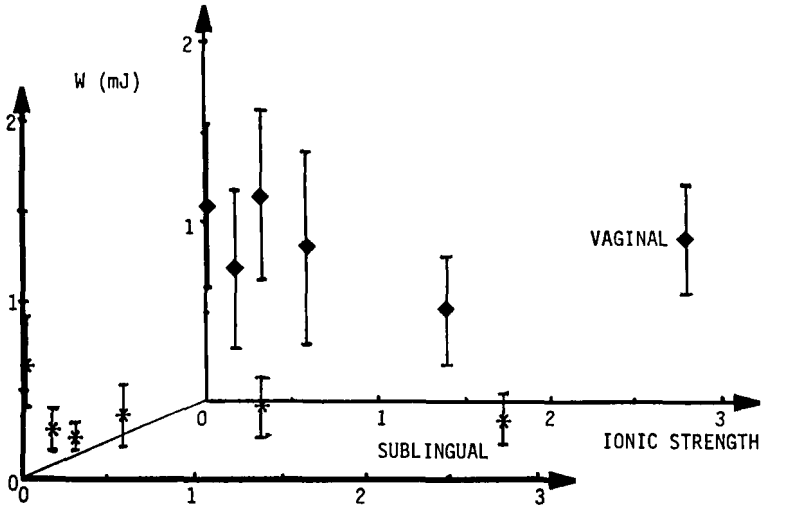

Figure 3 Influence of divalent cations (Ca^{2+}) on bioadhesive work of a tablet on bovine sublingual and vaginal mucosa

test media, calcium chloride solutions with increasing concentrations. The results (Table 5 and Figure 3) indicate that the adhesion parameters (detachment force and adhesion work) fall with the addition of a small quantity of calcium chloride, when the experiment is carried out on sublingual mucosa. The results obtained with vaginal mucosa, richer in mucus, do not lead to significant differences. Once more, it seems that the presence of a large layer of mucus protects the bioadhesive system/mucosa entity from all effects of the surrounding medium. The mucus covering the swelled layer of the bioadhesive tablet appears to act as a diffusion barrier, thus delaying the effect of ions contained in the external medium.

CONCLUSION

This study indicates that the adhesion work of a bioadhesive system, fixed on a biological tissue, is a good indicator if its bioadhesive power. On the other hand, the sensitivity of PAA bioadhesiveness to the ion environment impedes its use in bioadhesive systems containing ion-rich active ingredients. Furthermore, it seems that the presence at the interface of a large quantity of mucus protects the bioadhesive system from the effects of the surrounding medium.

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