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Bioadhesive analysis of controlled-release systems. III. Bioadhesive and release behavior of metronidazole-containing poly(acrylic acid)-hydroxypropyl methylcellulose systems

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Summary

Bioadhesive controlled release systems for the delivery of metronidazole were prepared by compression of hydroxypropyl methylcellulose with poly(acrylic acid), which served as the bioactive adhesive compound. The release behavior of systems containing 50 wt% metronidazole and various amounts of the two polymers was found to be non-Fickian. The bioadhesive strength of the bond formed between surface-preswollen systems and the sublingual bovine mucus was determined by novel tensile experiments and it was found to be dependent on the poly(acrylic acid) content.

Introduction

The development of bioadhesive controlled-release systems has been the subject of a large number of studies in recent years (Mikos and Peppas, 1986; Peppas and Buri, 1985; Longer and Robinson, 1986; Banker, 1980). Bioadhesive delivery systems, also known as mucoadhesive systems, are candidates for oral, buccal, sublingual and nasal administration of drugs.

Among various possible bioadhesive polymers, poly(acrylic acid), henceforth referred to as PAA, has been found to have significant adhesive interaction with certain types of mucus and mucin solutions or gels (Ishida et al., 1982; Ishida et al., 1983; Smart et al., 1984; Ch'ng et al., 1985).

In previous publications in this series (Ponchel et al., 1987; Peppas et al., 1987) we discussed the mechanisms that lead to the development of a strong bioadhesive bond between swollen PAA-containing tablets and bovine sublingual mucus. We examined the bioadhesive strength under both static and dynamic mechanical conditions and we investigated molecular parameters of the phenomenon using the interpenetration and fracture theories (Peppas and Buri, 1985; Kammer, 1983).

In this contribution we extend our previous analysis to a potentially bioadhesive controlled-release system containing increased amounts of drug and we examine the influence of this drug on the development of the bioadhesive bond. The model drug for these studies was metronidazole, a

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bacteriocide for anaerobic bacteria such as *Bacteroides fragilis* or *Clostridium perfringens* and a parasiticide for *Trichomonas vaginalis* or *Entamoeba histolytica*. Finally, in the development of these systems it was a goal of our project to concentrate on technologically acceptable methods of preparation, such as compression.

Materials and Methods

Preparation of the controlled-release systems

Tablets of the basic bioadhesive formulations were prepared by mixing hydroxypropyl methylcellulose, PAA and the drug in a mixer (Turbula, model T2G, Bachhofen, Basel, Switzerland) for 10 min. The hydroxypropyl methylcellulose (HPMC, Methocel K4M Dow Chemical Co., Midland, MI, U.S.A.) had a hydroxypropyl molar degree of substitution of 0.18–0.23, a methoxyl degree of substitution of 1.36–1.42, a number average molecular weight of 86,000 Da, a number average degree of polymerization (DP) of 460, and a viscosity of 4 Pa.s at 20 °C for its 2% aqueous solution.

PAA (Carbopol 934, B.F-Goodrich Co., Brecksville, OH, U.S.A.) had a number average molecular weight of 3×10^6 Da, a viscosity of 39.4 Pa.s at 25 °C for its 0.5% aqueous solution (pH = 3.0), a density of 1.41 g/cm^3, and a glass transition temperature of 105 °C. The drug was metronidazole (2-methyl-5-nitroimidazole-1-ethanol, I.B.P., Rhône-Poulenc, Antony, France) with a molecular weight of 171.16 Da.

Tablets were prepared in a compression apparatus (Frogerais AO, Ets. Frogerais, Vitry, France) by mixing 50 wt% of metronidazole with various amounts of HPMC and PAA as shown in Table 1. The final tablets had a weight of 250 mg, a diameter of 12 mm and thickness varying from 2 to 2.75 mm, depending on the formulation. In addition to these samples, drug-free tablets were prepared as shown in Table 1.

TABLE 1

Composition of systems studied

Code	Composition (in wt%)			Percentage (%) of PAA in polymer mixture
	HPMC	PAA	Metronidazole	
1	0	100	0	100
2	10	90	0	90
3	25	75	0	75
4	50	50	0	50
5	75	25	0	25
6	90	10	0	10
7	100	0	0	0
A	0	50	50	100
B	5	45	50	90
C	12.5	37.5	50	75
D	25	25	50	50
E	37.5	12.5	50	25
F	45	5	50	10
G	50	0	50	0

Bioadhesive experiments

The method of determination of the bioadhesive bond strength was a modification of the classical, constant extension rate tensile experiment utilizing a tensile tester (Instron, model 1026, Instron Ltd., High Wycombe, U.K.) as described in the first publication of this series (Ponchel et al., 1987).

Briefly, the two clamps of the tensile apparatus were equipped with cylindrical metallic supports of circular surface with a diameter of 14 mm. In a typical experiment, the tablet was secured on the upper support using a cyanoacrylate adhesive liquid (Pattex Express, Henkel, Gentilly, France). The biological tissue used in these studies was bovine sublingual mucus including a portion of the tissue, with a surface of ca. 15–20 cm^2 and a thickness of 2 mm. This tissue was frozen at −20 °C immediately after sacrifice of the animal. Before experimentation it was thawed at 4 °C in contact with an isotonic solution (Isoton II, Coultronics, Margency, France), containing 0.9 wt% NaCl in a pH = 7.2 buffer solution with quaternary ammonium and formaldehyde. This tissue was secured to the lower cylindrical support again by cyanoacrylate adhesive liquid.

During the experiment, 15 μl of water was placed on the tablet surface and the two surfaces (tablet and mucus) were brought in contact with a force of 0.5 N and kept in this condition for 10 min. As discussed before (Ponchel et al., 1987),

this preswelling time led to surface-swollen tablets with maximum adhesive characteristics. Then the tensile experiment was performed at a constant extension rate of 5 mm/min at 26 °C and a relative humidity of 60%.

During the experiment, the force was recorded as a function of elongation until the rupture (breaking) point. All studies were performed in triplicate.

Controlled-release experiments

Controlled-release experiments were conducted in a dissolution apparatus (Dissolutest, Prolabo, Paris, France) at 37 °C under perfect sink conditions. A volume of 1000 ml dissolution medium consisting of 0.1 N aqueous HCl solution (pH = 1.0) was used in each experiment at an agitation rate of 50 rpm. The metronidazole concentration was measured in a UV spectrophotometer (Safas 210, Monaco) at 238 nm. Six tablets of each formulation were tested.

Results and Discussion

Bioadhesive characteristics

To investigate the development of the bioadhesive bonding between the metronidazole-containing tablets and the bovine sublingual mucus we conducted a series of experiments using a modification (Ponchel et al., 1987) of the tensile experiment described before by Gurny et al. (1984).

Fig. 1 shows the variation of the force measured during the experiment as a function of elongation. All curves obtained were of similar shape. During the early portion of the tensile curve (curve AB) the force increased significantly with elongation and no contact surface disruption was observed. A plateau followed (curve BC) where there was partial detachment of the tablet from the tissue with simultaneous decrease of the contact area from its original value of $A_0 = 113$ mm^2. Finally, during the latter portion of the curve (CD) a major change of the contact area occurred until point D where total rupture (break) was observed.

As in the previous publication, to analyze the adhesive characteristics of these tablets with mucus we determined the work of adhesion, W_a, as the area under the typical curves such as the one shown in Fig. 1.

$$W_a = F \cdot l \quad (1)$$

Fig. 2 shows the effect of PAA content of the formulations tested on the work of adhesion observed. In general, as the PAA content increased, the work of adhesion increased significantly until

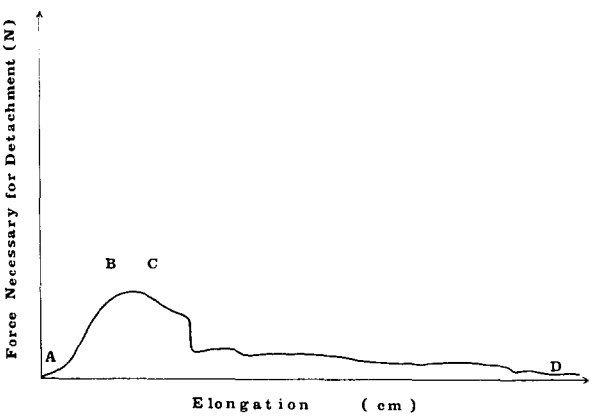

Fig. 1. Variation of the force necessary for detachment of an HPMC/PAA polymer tablet containing 50 wt% metronidazole from the bovine sublingual mucus surface at 26 °C as a function of elongation. The experiment was carried out with a tablet containing 12.5 wt% HPMC and 37.5 wt% PAA and surface-preswollen in water for 10 min.

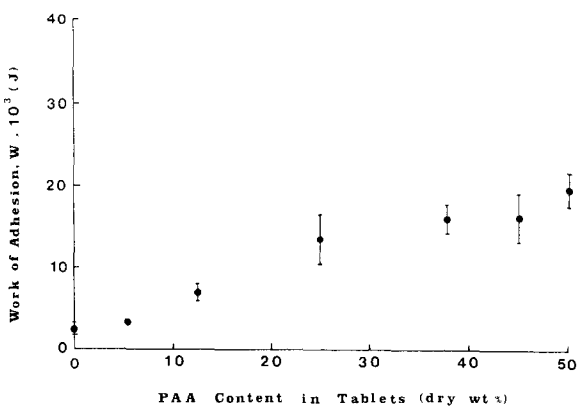

Fig. 2. Work of adhesion, W_a, between metronidazole-containing PAA/HPMC tablets and bovine sublingual mucus at 26 °C as a function of the dry PAA content, for systems with water-preswollen surface (for 10 min). The amount of metronidazole was kept constant at 50 wt%.

TABLE 2

W_a for metronidazole-containing and pure tablets containing PAA in contact with bovine sublingual mucus at 26 °C

PAA wt% content	W_a ($J \times 10^3$)	
	Without drug	With 50 wt% drug
0	3.38 ± 1.21	2.29 ± 1.30
10	9.64 ± 1.27	3.10 ± 0.16
25	12.42 ± 7.18	6.86 ± 1.98
50	16.63 ± 4.00	13.35 ± 6.06
75	19.39 ± 1.63	16.28 ± 3.51
90	22.98 ± 5.23	16.50 ± 5.91
100	–	19.61 ± 4.23

PAA wt% content is expressed as percentage of only the polymer components. Values are means ± S.D.

about 25 wt% PAA where it remained constant. As discussed before (Ponchel et al., 1987), all studies were done with tablets that had been preswollen at their surface for 10 min. This swelling time was selected because of its maximum bioadhesive characteristics.

In the previous publication (Ponchel et al., 1987) we concluded that due to the strong penetrating characteristics of the uncross-linked PAA chains in the bovine mucus, excessive amounts of PAA were not necessary to achieve the maximum bioadhesive strength (as judged by the magnitude of the work of adhesion) and that only about 30–40 wt% PAA (based on dry polymer) was sufficient. The results of our bioadhesive analysis with the metronidazole-containing tablets indicate that the presence of 50 wt% drug had only a small effect on the bioadhesive strength formed. The comparison of the adhesion work of the drug-free and drug-containing systems shown in Table 2 indicates a decrease of 10–20% of the work of adhesion due to the presence of the drug.

Controlled-release behavior

Fig. 3 shows the results of metronidazole release as a function of time for a series of tablets with a wide range of compositions and PAA contents. The results are expressed as normalized quantity of drug released, M_t/M_∞, vs release time.

In general, as the PAA content increased there was an increase in the amount of drug released. This phenomenon is explained by the swelling behavior of the HPMC/PAA systems. These systems are swellable in water and a minimum time of 1–2 h is needed for their complete swelling. Therefore, during this early portion of the release kinetics the behavior is similar for all systems. Following this period, tablets containing high amounts of PAA swell in general faster (Ponchel et al., 1987). Thus, the higher release rates for the tablets with high PAA content are an indication of the higher and faster swelling of PAA which would lead to a higher drug diffusion coefficients in them.

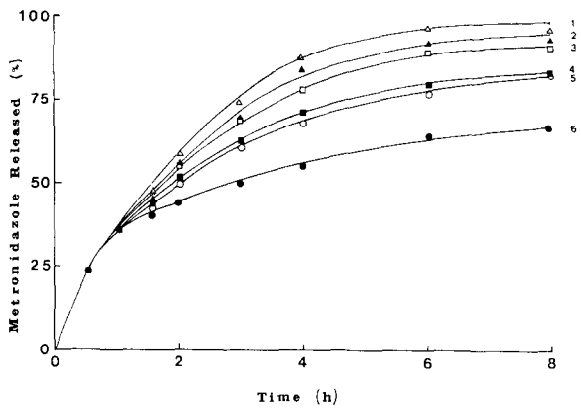

Fig. 3. Normalized metronidazole release, M_t/M_∞, as a function of release time, t, for originally dry, swellable HPMC/PAA containing a constant quantity of 50 wt% metronidazole. Curve 1: 37.5 wt% PAA; Curve 2: 45 wt% PAA; Curve 3: 25 wt% PAA; Curve 4: 12.5 wt% PAA; Curve 5: 0 wt% PAA; Curve 6: 5 wt% PAA.

To further examine this kinetic behavior the results of Fig. 3 were analyzed according to Eqn. 2, where n is a diffusional exponent (Peppas, 1985), characteristic of the drug transport mechanism.

$$\frac{M_t}{M_\infty} = kt^n \tag{2}$$

In all cases this exponent was calculated as $n = 0.76 \pm 0.05$ indicating a non-Fickian release behavior controlled by a combination of a diffusion and a chain relaxation mechanism. The latter relaxation mechanism is the result of the relatively slow swelling of the tablets which leads to a transition of the overall system from the glassy to the rubbery state. Thus, it would have been unreasonable to expect here a kinetic release behavior

expressed by a time-dependence of square-root-of-time ($n = 0.5$ in Eqn. 2) as would have been the case for conventional, non-swellable tablets.

The results presented here indicate that the bioadhesive bond strength appears within the first 10 min of the swelling process. However, swelling continues for several hours and the kinetic release behavior of metronidazole is controlled by a combination of diffusion and HPMC/PAA chain relaxation. The large initial amounts of metronidazole do not seem to affect the overall bioadhesive strength, indicating once more that the controlling mechanism of bioadhesion of swollen, PAA-containing tablets is the penetration of PAA chains in the glycoproteinic network of the mucus. In fact, the change of the work of adhesion from drug-free to drug-containing tablets of the same polymer composition is of the order of 10–20%, indicating that the small molecules of metronidazole have little or no effect on the macromolecular mechanism of PAA penetration in the mucus.

What is perhaps more surprising, is the unusual release behavior of metronidazole in these swelling-controlled release systems. In fact, this is the first time, to our knowledge, that a highly non-Fickian release behavior is reported for a swelling-controlled release system containing such large amounts of drug. Until now, it had been generally believed (e.g., Lee, 1983) that significant amounts of drug usually interfere with the macromolecular chain relaxation process, thus leading to a suppression of the relaxational mechanism and observation of only a diffusional mechanism. Consequently, swelling-controlled release systems with large initial amounts of drug loading (usually more than 30 wt%) gave Fickian diffusional release ($n = 0.5$ in Eqn. 2).

The methodical studies of Lee (1983) which first led to the conclusion that large amounts of drug are detrimental to a non-Fickian (or even zero-order) release behavior in swelling-controlled release systems were performed with a crosslinked poly(2-hydroxyethyl methacrylate) polymer, which is known to swell only moderately at temperatures between 20 and 37 °C. It is then plausible that the unusual non-Fickian release behavior observed in our case, even with 50 wt% metronidazole present, is the result of the very high degree of swelling attained by the systems studied and the rather slow relaxation process observed.

Conclusions

In conclusion, a new bioadhesive system for the release of metronidazole was developed using HPMC and PAA in various amounts. It was found that this system behaves as a swellable system and that its release behavior is controlled by diffusion and chain relaxation.

The new system showed significant bioadhesive characteristics in contact with bovine sublingual mucus. These characteristics increased as a function of PAA content and levelled off at about 25 wt% PAA.

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