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Aminophylline bioadhesive tablets attempted by wet granulation

C. Prudat-Christiaens, P. Arnaud*, P. Allain, J.C. Chaumeil

Université R. Descartes Paris V, Faculté des Sciences Pharmaceutiques et Biologiques, Laboratoire de Pharmacie galénique, Département de Pharmacotechnie, 4 avenue de l'Observatoire, 75270 Paris Cedex 06, France

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Abstract

The bioadhesive systems are new delivery systems used to reduce bioavailability problems resulting from a too short stay of the pharmaceutical form at the activity or resorption site. Aminophylline bioadhesive tablets were made by wet granulation with different polymers: Carbomers 934 P, 974 P, EX 55, sodium carmellose, hypromellose and hydroxypropyl cellulose (HPC). Wet granulation is a limiting factor for bioadhesion. The combination of polyacrylic acids with hypromellose or sodium carmellose increases bioadhesion and decreases drug release. Carbomer 974 P alone had a lower adhesion than Carbomer 934 P. Combinations Carbomer 934 P/hypromellose 100 gave the best adhesion properties and a slow release dissolution.

Keywords: Bioadhesion; Tablet; Bioadhesive polymers; Wet granulation; Dissolution

1. Introduction

The bioadhesive forms have led to a new research strategy. Some formulations are available commercially for local therapeutic use (Aftach™: triamcinolone acetonide; Pappel™: dipotassium glycine lysine), for systemic therapeutic use (Susadin™: nitroglycerine, Buccastem™: prochlorperazine) or for nasal administration (Rhinocort™: beclometazone dipropionate). These forms possess adhesion properties on a mucosa for a sufficient time to produce a therapeutic effect (Duchêne et al., 1988a). Bioadhesion is the property of a biological or synthetic material to adhere to a biological tissue for a given time. Specific bonds may be created, for example between glycoprotein (lectin) and sugar. The bioadhesion mechanism is used to solve bioavailability problems resulting from a too short stay of the pharmaceutical form at the absorption site (Duchêne and Ponchel, 1989; Lejoyeux et al., 1989).

The aim of this work was to formulate

* Corresponding author.

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Table 1
Formulae studied

Formula (mg)	1	2	3	4	5	6	7	8	9
Aminophylline	50	50	50	50	50	50	50	50	50
PVP 90	15	15	15	15	15	15	15	15	15
Calcium phosphate	100	100	100	100	100	100	100	100	100
Magnesium stearate	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2	0.2
Carbomer 934 P	16.5	17.5	21.5	26.5	17.5	17.5	0	0	0
Carbomer 974 P	0	0	0	0	0	0	17.5	0	0
Carbomer EX55	0	0	0	0	0	0	0	17.5	0
Hypromellose	0	10	50	100	0	0	10	10	0
HPC	0	0	0	0	0	10	0	0	0
Sodium carmellose	0	0	0	0	10	0	0	0	165
Tablet weight (mg)	181.7	192.7	236.7	291.7	192.7	192.7	192.7	192.7	330.2

aminophylline bioadhesive tablets that adhere to a biological support during an adequate time and give a controlled release (Peppas et al., 1987; Ponchel et al., 1987). The adhesion properties of different polymers (Carbomers 934 P, 974 P, EX 55, sodium carmellose, hypromellose or HPC), used either alone or in combination were studied in vitro. The adhesion of tablets formulated with the previous blends were then studied in vitro. Instead of using the usual method, i.e. direct compression, wet granulation was chosen to manufacture tablets with the aim of determining the interest and limitation of this process.

2. Materials and methods

2.1. Materials

The bioadhesives polymers used were hypromellose (MP812C, Aqualon France), hydroxypropyl cellulose (Klucel™ HFEP, Aqualon France), sodium carmellose (Blanose™ 7H4XF, Aqualon France), Carbomer 934 P (Carbopol™, BF Goodrich Rueil, France, molecular weight M_r 3 000 000), Carbomer 974 P (Carbopol™, BF Goodrich Rueil, France, M_r 3 000 000), Carbomer EX 55 (Carbopol™, BF Goodrich, Cleveland, USA). Aminophylline was used as a hydrophilic drug (Cooper, France).

2.2. Methods

2.2.1. Preparation of the tablets

Each tablet contained 50 mg of aminophylline. Povidone 90 (Cooper, France), dicalcium phosphate (Cooper, France) and magnesium stearate (Cooper, France) amounts were constant. Different amounts of each bioadhesive polymer were tested (Table 1).

The tablets were made by conventional wet granulation. After mixing and wetting, the resulting granules were sieved (2.5-mm holes), dried (50 ± 3°C) in an oven (24 h), calibrated (1.25-mm holes) then lubricated with magnesium stearate. Compression was performed with an alternative machine (Korch, Germany). The weight of the 9-mm-diameter flat tablets depended on the amount of polymer used, and they had a hardness (Schleuniger 2E, Frogerais, France) of approximately 150 N to avoid low disintegrating time.

2.2.2. Assays

2.2.2.1. Bioadhesion test. The bioadhesion (in vitro adhesion) was measured with a dynamometer DY 20B (Lhomargy, France), according to Charrueau et al. (1993). The dynamometer is made of two duralinox supports (26 mm diameter): the lower one is stationary while the upper one is mobile. The ascending speed was set to 20 mm/min. The detachment force of the polymer (N) and the adhesion work (mJ) as a function of extension

were measured. Adhesion work was evaluated by the area under the curve of the detachment force versus the extension. This method was used to test granules of bioadhesive polymers either alone or in combination (1.75/1 w/w) according to their respective percentages in the tablets. It was modified to test the tablets. The upper support was replaced by a Plexiglass disk (10 mm diameter) and the tablets were glued to the under support.

2.2.2.2. Water absorption test. The water absorption test of granules was performed according to Nogami's method as described by Charrueau et al. (1993). Water absorption is probably related to adhesion properties.

2.2.2.3. Dissolution test. The dissolution test was performed using the USP XXIII apparatus 2 at 50 rpm (Hanson Research Corporation Northridge, USA). The dissolution medium consisted of 1000 ml of purified water (pH 6.5) at 37 ± 0.5°C. The tablets were placed on the bottom of the vessel and pushed with a glass rod to make them adhere to the bottom of the glass vessel, so that only one side of the tablet was in contact with the dissolution medium. Six assays were performed for each formulation. At appropriate times, samples were automatically taken. The concentration of aminophylline released was measured with an UV spectrophotometer at 268-nm wavelength. The dissolution profiles and the $T_{50\%}$ (i.e. the time necessary for a 50% aminophylline dissolution) were compared using Student's t-test. The visual appearance of the tablets and their adhesion ability (i.e. ability to adhere to the bottom of the vessel) were observed during the dissolution test.

3. Results

The main problem of the wet granulation method was the wetting of the bioadhesive polymers. Beyond a 10% amount of Carbomer, a sticky and adhesive paste was obtained which did not allow any granulation.

Table 2
Detachment force (N) and adhesion work (mJ) obtained with polymers used alone

	Detachment force (N)	Adhesion work (mJ) (± SD)
Carbomer 934 P	73 ± 0.23	473 ± 77.1
Carbomer 974 P	67 ± 0.25	216 ± 17.5
Carbomer EX55	68 ± 0.1	289 ± 85
Hypromellose	65 ± 4.11	225 ± 23.5
HPC	72 ± 0.79	367 ± 154
Sodium carmellose	74 ± 0.75	406 ± 114.5

3.1. Adhesion assays

3.1.1. Polymer adhesion

3.1.1.1. Detachment force and adhesion work obtained with polymers used alone (Table 2). The detachment force reached 65–74 N and showed a good bioadhesion ability. The adhesion work varied with each polymer from 216 to 473 mJ. The detachment force of hypromellose was similar to that obtained with the best bioadhesive polymers (Carbomer 934 P, sodium carmellose). HPC, sodium carmellose, Carbomer 934 P had a high adhesion work. Carbomer 974 P appeared to be much lower than Carbomer 934 P. The adhesion work of hypromellose was low.

3.1.1.2. Detachment force and adhesion work for polymer combinations (Table 3). Polymer combinations presented a lower detachment force (45–

Table 3
Detachment force (N) and adhesion work (mJ) for polymer combinations

	Detachment force (N)	Adhesion work (mJ) (± S.D.)
Carbomer 934 P/ sodium carmellose	64 ± 1.76	270 ± 8.51
Carbomer 934 P/ hypromellose	45 ± 1.12	93 ± 29.53
Carbomer 934 P/HPC	61 ± 2.46	271 ± 92.8
Carbomer 974 P/ hypromellose	63 ± 4.11	214 ± 65.2
Carbomer EX55/ hypromellose	64 ± 3.12	262 ± 38.9

Table 4
Detachment force (N) and adhesion work (mJ) of granules

	Detachment force (N)	Adhesion work (mJ)
Carbomer 934 P	71 ± 0.25	471 ± 69.1
Sodium carmellose	72 ± 0.67	453 ± 67.5
Carbomer 934 P/ sodium carmellose 10	67 ± 0.83	587 ± 57.5
Carbomer 934 P/ hypromellose 10	63 ± 0.2	557 ± 100.5
Carbomer 934 P/ hypromellose 50	67 ± 0.4	869 ± 85.7
Carbomer 934 P/ hypromellose 100	69 ± 0.27	916 ± 71.5
Carbomer 934 P/ HPC 10	68 ± 0.25	1223 ± 216.9
Carbomer 974 P/ hypromellose 10	63 ± 1.24	662 ± 81.2
Carbomer EX55/ hypromellose 10	66 ± 1.63	842 ± 286.3

64 N) and adhesion work (93–270 mJ) than polymers used alone.

All the values were around 61–64 N except for Carbomer 934 P/hypromellose (45 N). The adhesion work was similar (210–270 mJ) for all formulations except for Carbomer 934 P/hypromellose (93 N).

3.1.2. Granule adhesion

Granule adhesion values (63–71 N) confirmed our previous observations on the dry polymers or polymer combinations (Table 4). Wet granulation did not modify the bioadhesive properties of the polymers. The detachment force and the adhesion work increased with the amount of hypromellose (formulae 1–4). Carbomer 934 P/hypromellose 100 and 50 and Carbomer 934 P and sodium carmellose alone had the highest detachment force. The better formulations in term of adhesion work were the combinations of Carbomer 934 P/HPC 10, Carbomer 934 P/hypromellose 50–100 and Carbomer EX 55/hypromellose 10.

3.1.3. Tablet adhesion

The detachment force (2.2–5.5 N) and the adhesion work (1.6–9.6 mJ) values were lower for the tablets than for the granules (Table 5). This may be explained by the measurement technique. Tablet adhesion was measured on one side of the tablet (0.392 cm^2) while that of the polymer powders or the granules was measured on the surface area (2.7 cm^2) of the apparatus. Carbomer 934 P had a low adhesion work. By contrast, the hydration of granules was greater than that of tablets. Hypromellose significantly increased the adhesion work of the tablets containing Carbomer 934 P and, in 50 and 100 mg doses, gave the highest adhesion forces. Sodium carmellose showed good bioadhesive properties in granule form. Carbomer 974 P in combination with hypromellose was more adhesive than Carbomer 934 P/hypromellose 10. The combinations Carbomer 934 P/hypromellose 50 or 100 and sodium carmellose presented the highest adhesion work.

3.2. Water absorption assays

All of the polymers were hydrated very quickly in water, reaching equilibrium at 1 min. Carbomer 934 P granules (formula 1) absorb a low volume of water (2 ml).

Table 5
Detachment force (N) and adhesion work (mJ) of tablets

	Detachment force (N)	Adhesion work (mJ)
Carbomer 934 P	2.4 ± 0.26	3.0 ± 0.1
Sodium carmellose	3.9 ± 0.67	4.0 ± 0.31
Carbomer 934 P/ sodium carmellose 10	3.2 ± 0.37	1.6 ± 0.12
Carbomer 934 P/ hypromellose 10	2.2 ± 0.28	3.3 ± 0.1
Carbomer 934 P/ hypromellose 50	4.5 ± 0.54	6.7 ± 0.15
Carbomer 934 P/ hypromellose 100	5.5 ± 0.5	9.6 ± 0.16
Carbomer 934 P/ HPC 10	3.1 ± 0.37	3.1 ± 0.18
Carbomer 974 P/ hypromellose 10	3.2 ± 0.38	1.6 ± 0.14
Carbomer EX55/ hypromellose 10	2.8 ± 0.35	2.9 ± 0.28

10, 50 and 100 mg of hypromellose (formulae 2, 3 and 4) increased the water absorption volume of the granules to 6, 8 and 9 ml, respectively. The sodium carmellose (formula 9) granule absorption was highest in relation to the chemical properties of this cellulose product (10 ml). Water absorption increased with increasing amounts of hypromellose.

Formulae 5–8 absorbed the same quantity of water (about 6 ml).

3.3. Visual appearance of tablets in water

The visual appearance of the tablets in water during the dissolution test varied according to their composition. The tablets that inflated the most, lost their shape and disintegrated in 30 min were the sodium carmellose ones. Those containing high amounts of hypromellose (50 and 100 mg), or a polymer combination with sodium carmellose 10, showed the most swelling in 2 h and showed deformations in 20 h. These tablets had the highest adhesion properties.

3.4. Dissolution test

The release of aminophylline was slow, and lasted for about 15 h (Fig. 1). $T_{50\%}$ values were between 180 and 290 min. Carbomers 974 P and EX 55, mixed with hypromellose (10 mg), had similar dissolution rates. Carbomer 934 P with HPC (formula 6) decreased the dissolution rate, as expected from the HPC properties. HPC absorbed water slowly and had a dissolution rate similar to a Carbomer 934 P/50 mg hypromellose combination.

Fig. 2 shows the influence of hypromellose in tablets containing Carbomer 934 P/hypromellose combinations. Carbomer 934 P with a low amount hypromellose (10 mg) (formula 2) increased the dissolution rate. Increasing the amount of hypromellose (50 and 100 mg) decreased the dissolution rate. Hypromellose absorbed water and caused swelling of tablets. It appeared to be a gelification barrier at the surface, decreasing the dissolution rate.

Carbomer 934 P/sodium carmellose 10 combinations showed the lowest dissolution rate

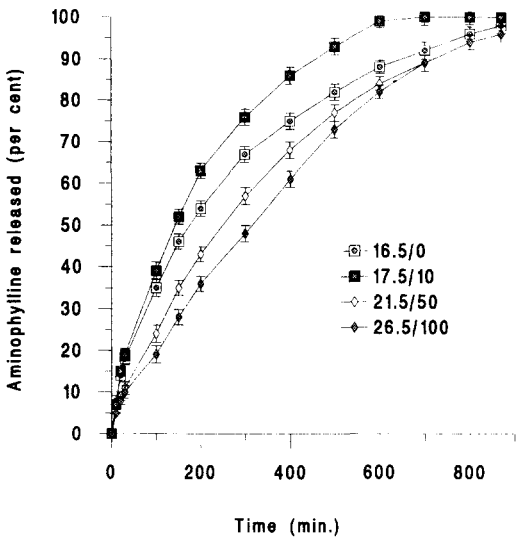

Fig. 1. Aminophylline released (%) vs. time of different tablets manufactured with four different bioadhesive polymers (error bars = ± SD).

($T_{50\%} = 290$ min) whereas sodium carmellose alone gave a rapid disintegration time (30 min). Carbomer 934 P/hypromellose combinations gave the highest dissolution rate.

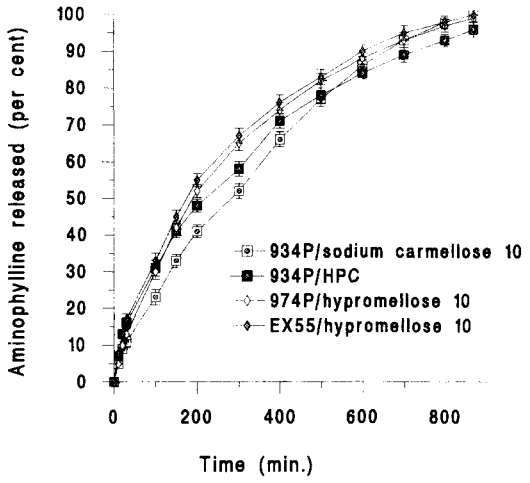

Fig. 2. Influence of the amount of hypromellose (0–100 mg) in combination with Carbomer 934 P in tablets. Aminophylline released (%) vs. time (error bars = ± SD).

4. Discussion

The wet granulation method has many advantages over the direct compression method (homogeneity, lower cross-contamination risks, powder flowing, compression). But it is a limiting factor in the manufacturing of bioadhesive tablets, because of the wetting process. The proportion of polyacrylic acid (Carbomer 934 P) may not exceed 10% of the total without getting a sticky and adhesive paste. The adhesion work increased with the amount of bioadhesive polymers (Duchêne et al., 1988b). Therefore, 10% Carbomer in the wet granulation method was insufficient to obtain the same bioadhesion value than by a direct compression process (Duchêne et al., 1988a).

4.1. Adhesion

Carbomer 934 P alone had higher adhesion than Carbomer 974 P. In combination with hypromellose, the results were different. There is no relation between the adhesion properties of granules and those of tablets.

The adhesion work is a more significant parameter than the detachment force to measure adhesion (Duchêne and Ponchel, 1989). The adhesion work takes into account both force and elongation (Duchêne and Ponchel, 1989). The Carbomer 934 P/hypromellose (50 and 100 mg) combination had the best adhesion properties for granules and tablets. Increasing amounts of hypromellose improved the viscosity of the gel (made from granules) and therefore its bioadhesion (Duchêne et al., 1988a; Garcia-Gonzalez et al., 1992). Ionic polymers (sodium carmellose) are more adhesive than non-ionic polymers (hypromellose) due to their carboxyl or alcohol groups. This was modified after a granulation process and adhesion properties decreased. Several hypotheses may explain why the adhesion values are lower for tablets than for granules:

(a) The hydration state was different. A gel was made with the granules, whereas only three drops of water were dropped onto the tablet surface. The lower hydration state of the tablets limited the stretching of polymeric chains and their interpenetration, therefore hindering the bioadhesion mechanism (Duchêne and Ponchel, 1989; Lejoyeux et al., 1989);

(b) The porosity was lower for the tablets than for the granules, because cohesion forces between granules are greater within a tablet. This suggests a lower hydration ability, which is not favourable to bioadhesion (Duchêne et al., 1988a);

(c) The contact surface was lower for tablets than for gels.

These hypotheses demonstrate that it is difficult to evaluate bioadhesion for each tablet. However, it can be pointed out that hypromellose significantly increased Carbomer 934 P tablets adhesion. The detachment force or adhesion work and the amount of hypromellose were linearly correlated.

(d) The presence of magnesium stearate in tablets and not in granules could also explain the phenomenon. According to Bottenberg et al. (1989), 1% of magnesium stearate makes a hydrophobic film around the polymeric particles, preventing the polymer/stay interaction, and decreasing bioadhesion.

4.2. Absorption of water by granules

Increasing the amount of hypromellose enhanced the water absorption of the granules. The better the hydration state, the better the adhesion. This confirms that hypromellose enhanced the adhesion of Carbomer 934 P tablets. Sodium carmellose, a very hydrophilic polymer, absorbed a high level of water but gave a relatively low adhesion work, probably by formation of a low viscous gel. Combinations with Carbomer 934 P reduced the water absorption and increased the adhesion work.

4.3. Visual appearance of tablet in water

Tablets which have the best adhesion properties were those which inflated and swelled most. The optimal combination with hypromellose was in favour of bioadhesion. Carbomer 934 P tablets avoid deformation in water due to their small capacity to absorb water. Carbomer 934 P combined with hypromellose may form a complex by hydrogen bonds which decrease the swelling (Garcia-Gonzalez et al., 1992), and tablets using polymer alone have the highest swelling.

Table 6
$T_{50\%}$ of the different formulae

Carbomer 934 P	180 ± 10
Sodium carmellose	Disintegration in 30 min
Carbomer 934 P/sodium carmellose 10	290 ± 15
Carbomer 934 P/ hypromellose 10	170 ± 8
Carbomer 934 P/ hypromellose 50	250 ± 13
Carbomer 934 P/ hypromellose 100	270 ± 14
Carbomer 934 P/HPC 10	230 ± 12
Carbomer 974 P/ hypromellose 10	200 ± 10
Carbomer EX55/ hypromellose 10	185 ± 8

The results suggest that an optimum ratio between the amounts of Carbomer 934 P and hypromellose exists. Hypromellose enhanced adhesion, i.e. hydration (Duchêne and Ponchel, 1989) and polymer/stay contact, but tablet integrity (absence of deformation) decreased.

4.4. Dissolution tests

Low amounts of hypromellose (10 mg) increased the release of aminophylline from Carbomer 934 P tablets ($T_{50\%} = 170$ min) (Table 6). Hypromellose absorbed and retained water, the tablets inflated and diffusion was enhanced. 50–100 mg of hypromellose decreased ($T_{50\%} = 250$ and 270 min, respectively) the dissolution rate according to Ponchel et al. (1987). Hypromellose made an excessively viscous gel around the tablet, keeping the active drug inside and limiting the release. Carbomer 934 P and EX 55 in combination with hypromellose (10 mg) have similar dissolution rates. HPC decreased the dissolution rate in accordance with its slow release properties and its low water volume absorption. The Carbomer 934 P/10 mg sodium carmellose combination gave the slowest release ($T_{50\%} = 290$ min). In summary the different dissolution rates were: sodium carmellose > Carbomer 934 P/hypromellose 10 = Carbomer 934 P = Carbomer EX55/hypromellose 10 > Carbomer 974 P/hypromellose 10 > Carbomer 934 P/HPC 10 > Carbomer 934 P/hypromellose 50 = Carbomer 934 P/hypromellose 100 > Carbomer 934P/sodium carmellose 10

5. Conclusion

This study has evaluated an original wet granulation method applied to bioadhesive tablets manufacture. The polymers studied were: Carbomer 934 P, Carbomer 974 P, Carbomer EX 55, sodium carmellose, hypromellose and HPC.

Wet granulation limited bioadhesion, because the wetting of the Carbomers and their drying was impossible when their concentrations exceeded 10%. Since the adhesion work increases with the amount of hypromellose, wet granulation did not allow the obtention of highly bioadhesive tablets. However, wetting and drying steps did not alter the polymer structure or the bioadhesive properties. Bioadhesion has been evaluated in vitro. Two parameters quantified adhesion: maximum detachment force and adhesion work. The adhesion work takes into account elongation and is thereby a more significant parameter.

Aminophylline dissolution rate over 15 h was low. It is difficult to compare the different tablet formulae, because the values recorded were low and near the sensitivity limit of the equipment. Sodium carmellose showed good bioadhesive properties. Adding high amounts of hypromellose (50 and 100 mg) to Carbomer 934 P enhanced adhesion. Carbomer 934 P/100 mg hypromellose combinations gave the best adhesion properties and a slow release dissolution. The lowest dissolution rate was obtained with the Carbomer 934 P/10 mg sodium carmellose combination.

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