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Correlation between the molecular morphology and the biocompatibility of bioadhesive carriers prepared from spray-dried starch/Carbopol® blends

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Abstract

Spray-dried Amioca® starch/Carbopol® 974P (C 974P; cross-linked poly(acrylic acid)) blends were evaluated as bioadhesive drug carriers and compared with equivalent physical mixtures. For both mixture types, the nano-morphology was determined by means of SEM and ^{13}C-CP/MAS solid state NMR. Whereas phase separation occurs into individual starch and C 974P molecular domains for the physical mixtures, spray-drying results in homogeneous blends of Amioca® starch and C 974P.

This intimate mixing improves the bioadhesive capacity significantly as compared to equivalent physical mixtures. Up to a 20 wt% content of C 974P, the spray-dried blends did not show any sign of irritation. This makes them promising biocompatible powders for application as safe bioadhesive carriers.

Keywords: Solid state NMR; Morphology; Bioadhesion and mucosal irritation

1. Introduction

In the last decade, bioadhesive polymers have been used in the development of controlled drug delivery systems to improve buccal, nasal and oral administration of drugs and considerable attention has been focused on the development of novel bioadhesive polymers or platforms. Bioadhesive, in particular mucoadhesive, polymers increase the residence time at the (mucosal) application site. Mucoadhesive polymers are generally hydrophilic in nature, hydrate and swell in aqueous environments and contain numerous hydrogen bond forming groups [1]. Typical polymers that have been used as mucoadhesive drug carriers are poly(acrylic acid) (PAA) [2], poly(methacrylic acid) [3], cellulose derivatives [4], poly(ethylene oxide) [5], lectins [6] and chitosan [7]. Of these, PAA and its cross-linked commercial forms, Carbopol® and Polycarbophil, exhibit strong mucoadhesive properties [8].

In a previous paper, the development of a bioadhesive drug carrier containing a physical mixture of 5% cross-linked poly(acrylic acid) (Carbopol® 974P) and a thermally modified starch was reported [5]. This drug carrier was formulated as a buccal bioadhesive tablet and has been shown to be effective for local buccal delivery of miconazole nitrate [8] as well as for systemic testosterone delivery after buccal absorption [7]. The same mixture was also used as a vaginal bioadhesive tablet for the local vaginal controlled release of metronidazole [8]. A lyophilised mixture of 10% Carbopol® 974P with a thermally modified starch was used as a bioadhesive platform for nasal insulin delivery [9]. Poly(acrylic acid) based bioadhesive polymers have also been investigated as absorption

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promoting agents for the peroral delivery of peptide drugs [10]. They can prolong the residence time and increase the contact to the mucosa at the site of drug absorption.

In the present study, the preparation of a new bioadhesive polymer blend, obtained by spray-drying an aqueous mixture of Amioca® starch, an amylopectin corn starch, and Carbopol® 974P, a highly cross-linked poly(acrylic acid), is described. Spray-dried Amioca®/Carbopol® mixtures, containing different Carbopol® 974P concentrations, were evaluated as buccal bioadhesive drug carriers. The bioadhesive capacities and the mucosal irritation potency were determined and compared to equivalent physical mixtures.

We want to highlight that a second important goal of this paper is an evaluation of ^{13}C-CP/MAS solid state NMR relaxometry as an innovative tool to study the molecular morphology (on the nanometer scale) of this class of drug delivery systems. Scanning electron microscopy (SEM) was accomplished to obtain complementary pictures.

2. Experimental

2.1. Materials

Drum Dried Waxy Maize (DDWM) was supplied by Cerestar (Vilvoorde, Belgium). Carbopol® 974P (C 974P) was supplied by BF Goodrich (Cleveland, Ohio, USA). Amioca® is a National Starch product (National Starch and Chemical Company, Bridgewater, New Jersey, USA). Sodium stearyl fumarate (NaSF) was given by Edward Mendell Co. Inc. (New York, USA). Benzalkonium chloride was purchased from Sigma (Bornem, Belgium). All other chemicals used were of analytical grade.

2.2. Preparation of the spray-dried Amioca®/Carbopol® 974P mixtures (SD)

The spray-dried Amioca® starch/Carbopol® 974P mixtures were prepared by National Starch and Chemical Company, Bridgewater, New Jersey, USA. In order to obtain pregelatinised Amioca® starch, the granular Amioca® starch, an amylopectin corn starch, was jet cooked. Phase contrast optical microscopy (Olympus BH2-UMA, Olympus America Inc., NY, USA) was used to check that the pregelatinisation was complete and no granules remained. To produce the spray-dried mixtures, an aqueous mixture of the jet cooked/pregelatinised Amioca® starch and Carbopol® 974P (C 974P), a highly cross-linked poly(acrylic acid), was spray-dried. Different ratios were spray-dried ranging from 5 to 75 wt% Carbopol® 974P [11].

2.3. Preparation of the Amioca®/Carbopol® 974P physical mixtures (PM)

The Amioca®/C 974P physical mixtures were prepared by blending granular Amioca® starch with C 974P in the required ratios using pestle and mortar.

2.4. Methods

2.4.1. Scanning electron microscopy

The powder formulation is put on an aluminium pin mount followed by coating with platinum in a JEOL JFC 1300 Auto Fine Coater during 1 min at 30 mA. The coated samples were transferred to the scanning electron microscope JEOL JSM 5600 LV (JEOL B.V. Europe, Zaventem, Belgium). Pictures were recorded at magnification 1500× (Fig. 3) and 3000× (Fig. 8).

2.4.2. Solid-state ^{13}C-CP/MAS NMR

Solid-state ^{13}C-CP/MAS NMR spectra were recorded at room temperature on an Inova 200 Varian spectrometer operating at a static magnetic field of 4.7 T. Magic angle spinning was performed at 3.1 kHz, making use of ceramic Si_3N_4 rotors. The aromatic signal of hexamethylbenzene was used to determine the Hartmann–Hahn condition ($\omega_{1H}=\gamma_H.B_{1H}=\gamma_C.B_{1C}=\omega_{1C}$) for cross-polarization and to calibrate the carbon chemical shift scale (132.1 ppm). Other spectral parameters used were a 90° pulse length of 6.1 μs, a spectral width of 50 kHz and an acquisition time of 20 ms. High power decoupling was set to 65 kHz during the acquisition time. The proton spin-lattice (T_{1H}) and spin-lattice relaxation time in the rotating frame ($T_{1\rho H}$) were measured via the chemical shift selective carbon nuclei by means of the inversion-recovery method (fixed contact time CT of 750 μs; variable evolution time between 0.01 and 15 s; 500–800 accumulations) and variable contact time method (CT varying between 1 and 11 ms; 2000 accumulations), respectively, [12]. In the latter, the proton magnetization is kept in spin lock for a variable contact time before it is cross-polarized to the carbon nuclei. The recycle time was set to five times the longest T_{1H} decay time for both pulse-sequences and a spin-lock field of 41 kHz was used for cross-polarization. The T_{1H} decay times were obtained by analysing the signal intensities according equation

$$I(t) = I_0(1 - 2\exp(-t/T_{1H}) \quad (1)$$

in which t is the variable evolution time and I_0 is the intensity of the resonance at equilibrium. The $T_{1\rho H}$ decay times were obtained by analysing the signal intensities according equation

$$I(CT) = I_0\exp(-CT/T_{1\rho H}) \quad (2)$$

in which only contact times beyond the optimal contact time (>5 times the decay time of cross-polarization T_{CH}) were used and in which CT is the variable contact time and I_0 the intensity of the signal at equilibrium. Data were analysed by non-linear least squares fitting methods employing the

Levenberg–Marquardt algorithm. The average 95% confidence limit for the T_{1H} and $T_{1\rho H}$ decay times was about 2%.

2.4.3. Determination of bioadhesion

Bioadhesion measurements were performed on 100 mg tablets. For the tablet production the powders were mixed with sodium stearyl fumarate (1 wt%), as a lubricant and compressed on a Korsch compression machine (Type EK0, Berlin, Germany) equipped with 7 mm flat punches, at a pressure of 9.8 kN. The bioadhesion of the tablets was evaluated according to a previously described ex vivo bioadhesion test method with porcine gingiva as test substrate [13]. The adhesion force (N) and the work of adhesion (mJ) were determined as the height and the area under the curve of the force vs. extension diagram. The apparatus consisted of a tensile testing machine (type L1000R, Lloyd Instruments, Segenworth, Fareham, UK), equipped with a 20 N load cell. The bioadhesion results were compared to a reference formulation, a physical mixture of 5% C 974P, 94% DDWM and 1% NaSF [14].

2.4.4. Test procedure mucosal irritation test

The mucosal irritation test using the slug *Arion lusitanicus* as model organism has been validated with reference molecules as an alternative test for screening the irritation potential of chemicals in solutions [15]. The body wall of slugs consists of a single-layered epithelium containing ciliated cells, cells with microvilli and mucus secreting cells. Slugs produce mucus to protect their skin against damage. A previous study showed that the irritation potential of bioadhesive formulations could be estimated with the mucosal irritation test using slugs [9]. Adriaens et al. [16] described that the mucosal irritation test using slugs can be used as a reliably and reproducible alternative method to study the biocompatibility of bioadhesive powder formulations. The amount of mucus, expressed as % of the body weight, produced by the slugs during a repeated contact period is a measure for irritation. Membrane damage can be estimated from the release of proteins, lactate dehydrogenase (LDH) and alkaline phosphatase (ALP) from the body wall of the slugs. Untreated slugs were used as negative controls (NC; blanks) while slugs treated with DDWM/benzalkonium chloride (DDWM/BAC 95/5) were used as positive controls (PC). Pure DDWM treated slugs were used as a reference. The slugs were placed daily on 20 mg powder during 30 min. for 5 successive days. For each powder formulation, five slugs were used. After each contact period the amount of mucus produced and LDH/ALP releases were measured. The results of the tested mucoadhesive mixtures were only accepted if the following conditions were satisfied: the mean of the total mucus production ($n=5$) after a repeated 30 min. contact period was $<2\%$ for the NC and $>10\%$ for the PC slugs. Additionally none of the NC slugs may show LDH and ALP release.

3. Results and discussion

3.1. Bioadhesion

Mucoadhesion is a complex process of forming an intimate contact between mucoadhesive and mucus and is determined by several parameters as there are the amount of hydrogen-bonds and other non-covalent interactions, the degree of swelling of the polymers and the interpenetration of the mucoadhesive polymers in the mucus (chain entanglements) [17]. The work of adhesion is, generally considered, more accurate to quantify bioadhesion [18].

To evaluate the influence of the spray-drying process on the bioadhesive capacities of Amioca® starch/Carbopol® 974P mixtures, the bioadhesive properties were compared with those of equivalent physical mixtures (all mixture compositions are expressed in wt%). The results are shown in Fig. 1. All spray-dried (SD) mixtures showed significantly higher work of adhesion values and adhesion forces as compared to their equivalent physical mixtures (PM). The physical mixtures also show a significantly weaker adhesion than the reference which contains 5% Carbopol® 974P. This can be explained by the difference in starch used. Drum dried waxy maize starch (DDWM), used in the reference formulation, and Amioca®, used in the physical mixtures, are both waxy corn starches, but DDWM is a pregelatinised starch while Amioca® is a granular starch. In water, pregelatinised starches will hydrate and swell faster than granular starches. As hydration and swelling of the polymer is an important step in the bioadhesion process, it can be expected that DDWM has improved bioadhesive properties as compared to the granular Amioca® [19]. It should be noticed that the Amioca® in the spray-dried mixtures was pregelatinised by jet cooking to obtain improved dispersions in water needed for the spray-drying process.

Fig. 2 shows the bioadhesion data for a series of spray-dried Amioca® starch/Carbopol® 974P mixtures. Up to 10% of C 974P, a comparable bioadhesive capacity is observed as for the reference formulation. Starting from 15% C 974P, all mixtures have a significantly higher bioadhesion capacity which, however, seems to be quasi independent on the C 974P concentration. Only the mixture containing 75% C 974P shows a somewhat stronger adhesion. Notice not only that a spray-dried mixture with only 5% C 974P (SD 95/5) already has comparable adhesion properties as a physical mixture with 25% C 974P (PM 75/25; see Fig. 1) but also that the adhesion for a spray-dried mixture with 15% C 974P is even improved as compared to a physical mixture with 25% C 974P (compare Figs. 1 and 2).

3.2. Mucosal irritation

Table 1 shows that the mixing process (spray-drying vs. physical blending) has no significant effect on the irritation potency of C 974P although spray-dried mixtures, showing

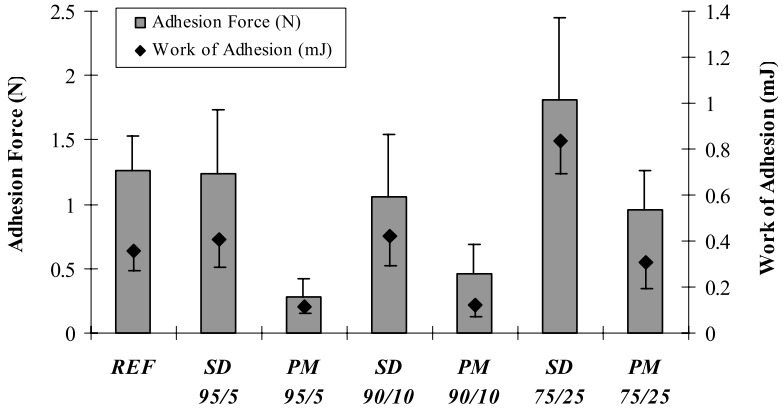

Fig. 1. Adhesion force (N) and work of adhesion (mJ) for spray-dried (SD) Amioca® starch/Carbopol® 974P mixtures (wt%) as compared to their equivalent physical mixtures (PM) and to the reference formulation (REF). (Mean ± SD, $n = 10$).

stronger adhesion characteristics, induce a slightly higher mucus production as compared to equivalent physical mixtures. On the other hand, while the mucus production of a PM 75/25 is comparable with this of a SD 85/15 mixture, the latter shows a strong improvement in adhesion properties. Even the SD 95/5 mixture has already similar adhesion characteristics as PM 75/25, even with somewhat less mucus production. The spray-dried mixtures containing up to 20% C 974P induced no irritation of the mucosal tissue of the slugs and can be considered as safe mucoadhesive carriers. Irritation studies confirm that Carbopol® is well tolerated when it is used in small amounts (< 10%). Buccal and ocular tablets containing 5% Carbopol® together with non-irritating DDWM are well accepted by volunteers [20]. A buccal erodible tablet containing 7.5% C 974P induced no irritation over a period of 6 hours in human volunteers [21].

On the other hand, Carbopol® levels of 25 and 35% induce slight irritation of the mucosa as was demonstrated by the increased mucus secretion (Table 1) but no additional effect on protein and enzyme release was detected. Spray-dried mixtures with 40% (w/w) or more C 974P induce release of proteins and LDH (lactate dehydrogenase), indicating membrane damage and severe irritation (details not reported). The irritation potential of Carbopol® was also reported in humans where bioadhesive buccal tablets consisting of 100% Carbopol® 934P and HPMC/Carbopol® 934P in a ratio of 10/90 and 50/50 resulted in small mucosal lesions [20].

3.3. Scanning electron microscopy

Fig. 3(A) is a SEM picture of an Amioca®starch/ Carbopol® 974P physical mixture (85/15) and shows a clear phase separation between the starch granules and the C 974P particles. While the dimension of most of the starch granules is in the order of 10 μm, the C 974P particles have

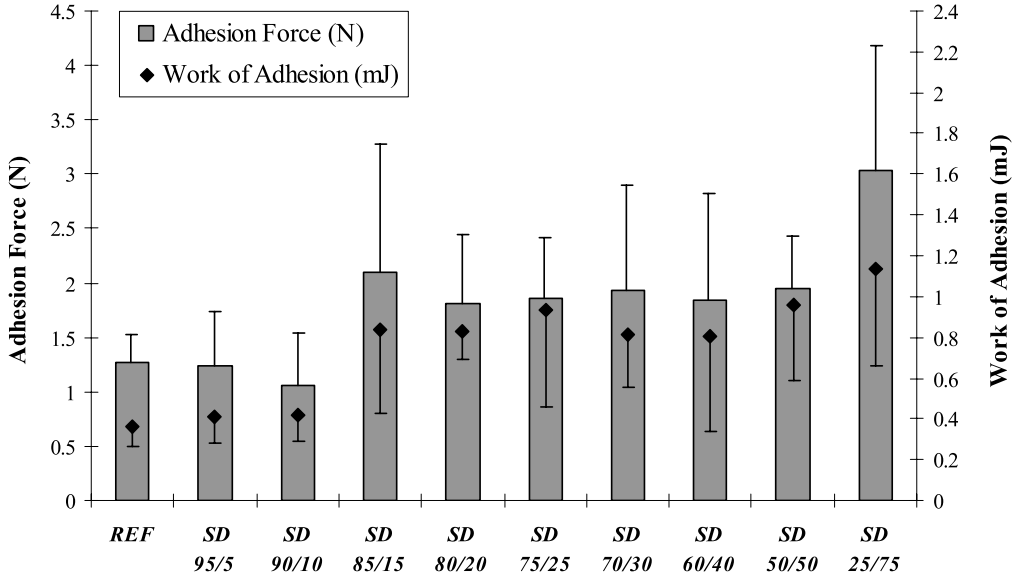

Fig. 2. Adhesion force (N) and work of adhesion (mJ) for a series of spray-dried (SD) mixtures as a function of the C 974P concentration and as compared to the reference formulation (REF). (Mean ± SD, $n = 10$).

Table 1
Influence of spray-dried (SD) and physically mixed (PM) Amioca® starch/Carbopol® 974P mixtures on the mucosal irritation (Mean ± SD for *n* trials)

Specimen	Total MP (%)	*n*
Blank (NC)	−0.3 ± 1.4	30
DDWM	3.6 ± 1.3	20
DDWM/BAC 95/5 (PC)	18.7 ± 4.8	30
PM 95/5	1.7 ± 1.8	5
SD 95/5	3.7 ± 0.8	5
PM 90/10	2.8 ± 1.0	5
SD 90/10	4.8 ± 2.5	10
SD 85/15	5.9 ± 1.7	5
SD 80/20	5.3 ± 1.7	15
PM 75/25	6.9 ± 2.5	5
SD 75/25	12.0 ± 3.2	5
SD 70/30	12.4 ± 2.0	5
SD 60/40	17.0 ± 2.2	5
SD 50/50	18.5 ± 8.3	5
Carbopol® 974P	21.4 ± 3.7	5

MP, mucus production in wt% of the body weight. *n*, number of trials to calculate the mean ± SD.

dimensions situated between 1 and 10 μm. This in contrast to the spray-dried mixture with the same composition (Fig. 3(B)) in which no phase separated C 974P particles are observed. In order to study the miscibility of the mixture components in the bulk and to explain the bioadhesive properties and irritation behaviour from a molecular point of view, physical and spray-dried mixtures were studied by ^{13}C-CP/MAS relaxometry.

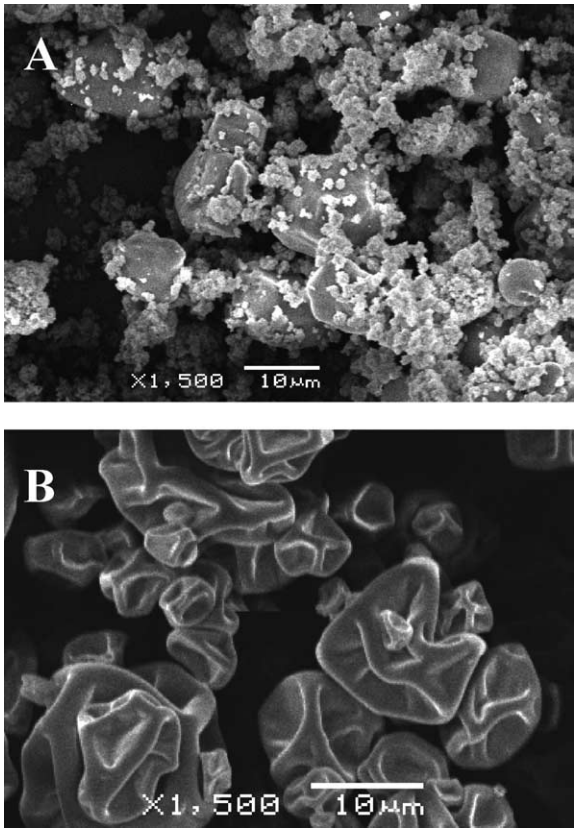

Fig. 3. SEM picture of a physical (A) and a spray-dried (B) mixture of Amioca® and Carbopol® 974P (85/15).

3.4. Solid state ^{13}C-CP/MAS NMR spectroscopy and relaxometry

Solid state NMR spectroscopy and relaxometry is a powerful non-invasive and non-destructive technique to investigate the segmental chain dynamics and molecular miscibility of polymer blends and copolymers on the nanometer level [22–25]. The proton relaxation decay times T_{1H} and $T_{1\rho H}$ provide information about the level of heterogeneity (phase morphology) of a polymer mixture on the nanometer scale due to the process of proton spin diffusion. Under the condition of spin diffusion, both proton decay times can be directly related to the dimensions of the molecular domains. The proton $T_{1\rho H}$ decay time (spin-lattice relaxation time in the rotating frame), in the order of milliseconds, will be averaged out over a short distance (in the order of 1–2 nm), making it a local property. Since the $T_{1\rho H}$ decay time is sensitive to molecular frequency motions of several 10s of kilohertz, it reflects the motion of short segments in the polymer backbone. The T_{1H} decay time (spin-lattice relaxation time) on the other hand, in the order of seconds, is sensitive to the spectral density of Larmor frequency motions (here 200 MHz) and is averaged out over a larger distance (in the order of 10 s of nanometers), making it a more large-scale molecular property. The maximum path length L, over which proton-proton spin diffusion can occur, is approximately given by

$$L \approx (6DT_{iH})^{1/2} \quad (3)$$

where D is the spin diffusion coefficient ($\sim$4-6$\times10^{-16}$m^2/s for rigid solids) and T_{iH} the decay time T_{1H} or $T_{1\rho H}$ [26]. Measuring the proton decay times via the chemical shift selective carbon signals by means of the ^{13}C-CP/MAS (Cross Polarisation/Magic Angle Spinning) technique, allows to obtain information about the degree of phase separation in polymer mixtures. The T_{iH} decay time, as measured via the carbon resonances of Amioca® will only be different from this measured via the carbon resonances of Carbopol® 974P if molecular domains larger than L appear in the mixture.

Fig. 4 presents a typical ^{13}C-CP/MAS spectrum of a spray-dried and physical mixture (SD and PM 75/25). The signals of Amioca® can be assigned as follows: the glycosidic carbon C1 (100 ppm), C6 (60 ppm), C2 (79 ppm) and C3-C5 (71 ppm) [27]. The signals of Carbopol® appear around 22–50 ppm (backbone carbons) and 178 ppm (carbonyl carbon). Notice that, independently of the composition, the C2 resonance (79 ppm) is more resolved in the spray-dried mixtures as compared to the physical mixtures. This is a first spectroscopic indication of a different interaction between Amioca® and Carbopol® in the spray-dried and physical mixtures.

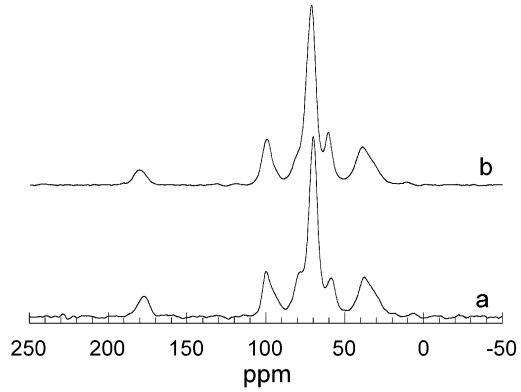

Fig. 4. ^{13}C-CP/MAS spectrum of a 75/25 mixture of Amioca® and Carbopol® 974P prepared by (A) spray-drying and (B) physical mixing.

3.4.1. Molecular miscibility of physical mixtures

Fig. 5 shows a plot of the T_{1H} decay times as a function of the composition for the physical mixtures. Independently on the composition, the T_{1H} decay time obtained via the C 974P carbon resonances is different as compared to the one observed via the Amioca® starch resonances. This means that in the bulk both mixture components are phase separated into molecular domains of which the length scale exceeds several 10s of nm. Based on the Carbopol® T_{1H} decay time and Eq. (3), the average size of the Carbopol® domains can be estimated to exceed 65 nm for the low Carbopol® content (15%) mixture and 80 nm for the high Carbopol® content (75%) mixture. This is in agreement with large-scale phase separation as observed by SEM and can be ascribed to the granular character of the Amioca® starch. It can explain the lower adhesion capacity of these blends (Fig. 1) and the absence of irritation for the blends studied (C 974P up to 25%) (Table 1).

3.2.2. Molecular miscibility of spray-dried mixtures

Fig. 6 shows a plot of the T_{1H} decay time as a function of the mixture composition for the spray-dried mixtures. As compared to the physical mixtures, the relaxation behaviour

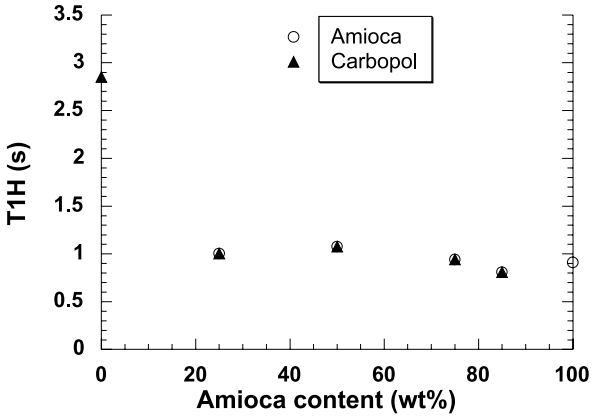

Fig. 6. The T_{1H} relaxation decay time (s) as measured via the carbon signals of Amioca® (○) and C 974P (▲) vs. the composition (wt%) of the spray-dried mixture.

is clearly different. Independently on the composition, all signals of the carbon spectrum, these of Amioca® as well as those of Carbopol®, show the same T_{1H} decay time of which the value equals this of pure spray-dried Amioca® within experimental error. This means that the process of spin diffusion transfers the C 974P magnetisation efficiently toward Amioca® where it decays with the same time constant as the Amioca® magnetisation. It can be concluded that if molecular domains of C 974P are present in the mixtures, their dimension can be estimated to be smaller than 55 nm (Eq. (3)). This can already explain the difference in adhesion properties between the physical and spray-dried mixtures from a molecular point of view: in contrast to the spray-dried mixtures, the physical mixtures are clearly phase separated on this distance scale.

In order to study, the miscibility in the spray-dried mixtures on the nanometer length scale, also the $T_{1\rho H}$ decay times were determined. Fig. 7 shows a plot of the $T_{1\rho H}$ decay times as a function of the composition. The same situation as for T_{1H} holds for high ($\geq$50%) Amioca® contents: a single $T_{1\rho H}$ decay time is observed. This means

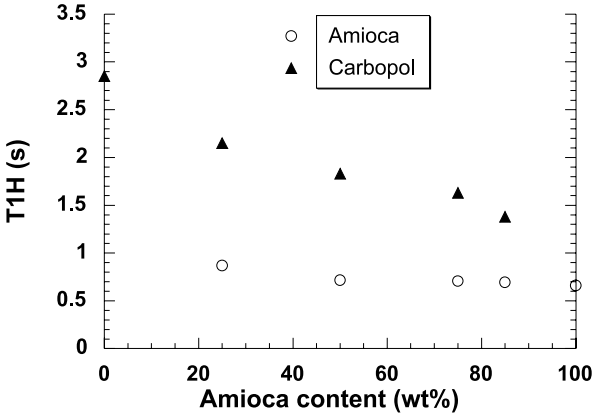

Fig. 5. The T_{1H} relaxation decay time (s) as measured via the Amioca® carbon signals (○) and C 974P signals (▲) vs. the composition (wt%) of the physical mixture.

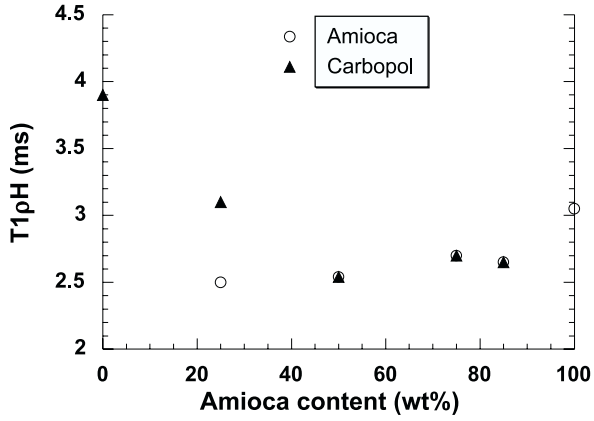

Fig. 7. The $T_{1\rho H}$ relaxation decay time (ms) as measured via the Amioca® carbon signals (○) and C 974P signals (▲) vs. the composition (wt%) of the spray-dried mixture.

that both components of the mixtures have to be in intimate contact ($L = 2.5$ nm for a $T_{1\rho H}$ of 2.5 ms). Taking both the complete destruction of the starch granules after pregelatinisation and the formation of granule-like particles after spray-drying, as seen with SEM (Fig. 3(B)), into account, there must be a complete mixing on the nm-scale of Amioca® starch and Carbopol® 974P within these particles. This intimate mixing can explain the significant increase in adhesion properties starting from a Carbopol® concentration of 15%. For this concentration, an optimal balance between Amioca® starch and Carbopol®, in terms of surface contact between mucoadhesive and mucos, seems to be reached. This in contrast to lower C 974P contents for which no optimal surface adhesion is reached. Up to C 974P concentrations of 20% (SD 80/20), no irritation takes place (Table 1). Starting from a C 974P concentration of 25% (SD 75/25) the particle surface contains more and more C 974P and thus irritation starts (Table 1).

A completely different situation occurs for high Carbopol® 974P contents (e.g. 75%). Although the observed $T_{1\rho H}$ decay times do not coincide with those of the pure components, the $T_{1\rho H}$ decay times found via the Amioca® resonances are clearly different from those obtained via the Carbopol® signals. It can be concluded that phase separation starts to take place for these C 974P concentrations ($\geq 75\%$) resulting in molecular domains of Carbopol® that exceed 3 nm. As a matter of fact, the Carbopol® domain size is situated between 3 nm ($T_{1\rho H}$) and 55 nm (T_{1H}) for the SD 25/75 mixture. If it is assumed that mixed particles of Amioca® starch and Carbopol® are still formed, the size of the Carbopol® domains within these particles must be increased due to the high C 974P content. This can explain the further increase in adhesion capacity. On the other hand, also individual phase separated Carbopol® particles are observed by SEM in the SD 25/75 mixture (Fig. 8).

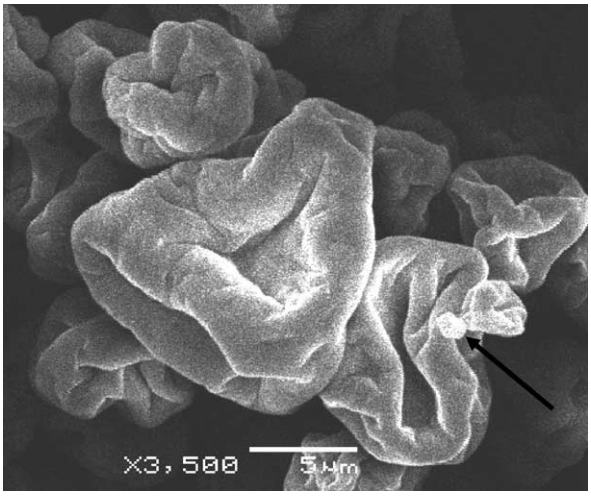

Fig. 8. SEM picture of a spray-dried mixture of Amioca® and Carbopol® 974P (25/75). A phase separated Carbopol® 974P nano-particle is indicated by the black arrow.

4. Conclusion

Scanning electron microscopy and ^{13}C-CP/MAS solid state NMR spectroscopy and relaxometry revealed that physical mixtures of Amioca® starch/Carbopol® 974P are phase separated. By spray-drying Amioca® starch/Carbopol® 974P mixtures, homogeneously mixed particles of Amioca® starch and Carbopol® 974P were formed. Only for high Carbopol® concentrations (≥ 75 wt%) phase-separated C 974P domains are formed within these particles.

In comparison with physical mixing, the spray-drying technique leads to promising bioadhesive blends since the bioadhesive capacities are significantly improved, even for lower Carbopol® contents (e.g. the adhesion properties of a SD 85/15 mixture are clearly better than these of a PM 75/25 although the mucus production is similar).

Spray-dried Amioca® starch/Carbopol® 974P mixtures are potential safe bioadhesive carriers since for up to 20% Carbopol® 974P no indications of irritation were observed.

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