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European Journal of Pharmaceutics and Biopharmaceutics 55 (2003) 47–56

European Journal of Pharmaceutics and Biopharmaceutics

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Research paper

Oral gingival delivery systems from chitosan blends with hydrophilic polymers

Cynthia G.L. Khoo[a,1,*], Sofia Frantzich[a], Adam Rosinski[a], Maria Sjöström[b], Janet Hoogstraate[c]

[a]*Pharmaceutical and Analytical R&D, Mölndal, Sweden*
[b]*Discovery, Drug Metabolism and Pharmacokinetics and Bioanalytical Chemistry, AstraZeneca, Mölndal, Sweden*
[c]*Discovery, Drug Metabolism and Pharmacokinetics, AstraZeneca, Södertalje, Sweden*

Received 11 February 2002; accepted in revised form 24 October 2002

Abstract

Chitosan blends with hydrophilic polymers including polyvinylalcohol (PVA), polyethyleneoxide (PEO) and polyvinylpyrrolidone (PVP), were investigated as candidates for oral gingival delivery systems. The bioavailabilty conferred by the chitosan blend delivery systems, as concluded from dog studies, was shown to be comparable to that based on chitosan alone, especially for those blends involving high molecular weight hydrophilic polymers. Results from differential scanning calorimetry and dynamic mechanical thermal analysis, Fourier transform infrared spectroscopy and tensile testing, indicated that the chitosan/PEO and chitosan/PVP blends showed evidence of miscibility in all blend ratios studied, while the chitosan/PVA blend only showed evidence of interaction for the (50:50) and (80:20) blends, but not for the (20:80) blend. However, even a phase separated system may show interesting and exploitable properties, as evidenced by the tensile testing data for the high molecular weight PVA blend (20:80). The study also indicated that chitosan blends were superior in other properties compared to chitosan alone. These included improved comfort and reduced irritation, ease of processing, improved film quality, improved flexibility, and enhanced dissolution. Blends of chitosan with different hydrophilic polymers could thus be promising candidates for formulation in oral mucosal delivery systems.

Keywords: Oral gingival delivery; Chitosan; Blends; Hydrophilic polymers; Blend miscibility; Bioavailability

1. Introduction

Alternative routes to peroral administration have to be considered when a candidate drug shows, for example, low peroral bioavailability, or an unacceptable plasma profile due to adverse conditions in the gastrointestinal (GI) tract. In such cases, administration via the mucosa of the oral cavity has been considered a viable route [1,2]. For the successful industrial development of a viable dosage form using this latter route, the following demands must be met; the delivery system must show that it allows significantly improved bioavailability to be achieved compared to traditional peroral administration, evokes non-irritation, is comfortable and attractive to use, is easy to manufacture, and finally, is affordable. The polymers selected must also be pharmaceutically approved, as well as demonstrate acceptable mechanical and mucoadhesive properties.

In the past two decades, a great deal of work has been done around the natural polymer, chitosan, which has shown a large variety of properties interesting for cosmetic, pharmacological, biomedical, pharmaceutical and biotechnological applications [3–7].

Recently, chitosan has been shown to enhance absorption through the epithelium; this enhancement is reported due to the interaction of chitosan through its positive charges with the cell membrane, resulting in a structural reorganization of tight junction-associated proteins resulting in enhanced transport through the paracellular pathway [8–11]. Mucus was shown to be deleterious for this enhancement but could be compensated by increasing local concentrations of chitosan and drug [9]. It has also been pointed out that chitosan, being a weak base, looses or has a weakened charge in basic and neutral environments respectively, which significantly reduces its enhancing properties in these conditions. Increasing the charge density of chitosan by quarternization of chitosan derivatives which then remain soluble and keep

* Corresponding author. Pharmaceutical and Analytical R&D, Product Development, AstraZeneca, SE-43183 Mölndal, Sweden.
E-mail address: cynthia.khoo@albihns.se (C.G.L. Khoo).
[1] Present address: Albihns Malmö AB, Box 4289, Studentgatan 4, S-203 14 Malmö, Sweden.

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doi:10.1016/S0939-6411(02)00155-8

their cationic state over a wide pH range was suggested as a solution; the concept has been tested and proven effective [12–14].

However, such derivatives are not as yet FDA-approved, and cannot be presently employed in development work.

In this work, we have attempted to formulate an oral gingival delivery system for a proprietary drug, considered a suitable candidate for this administration method, using chitosan as the main polymer excipient. An earlier in-house screening study using different homopolymers as the main excipient in patches loaded with the same drug, confirmed the superior performance of chitosan, as revealed from dog bioavailability studies [15].

Several properties of chitosan are, however, undesirable from the processing and manufacturing point of view. For example, well characterized, purified chitosan is expensive. Chitosan is also not an easy polymer to work with, with regards to solubility, film processing and film quality. We have thus chosen to work with chitosan blends with other hydrophilic polymers; this study evaluates the efficiency for absorption enhancement of a model drug using blends, compared with the homopolymers, as well as presents some relevant material properties of the blends.

2. Materials and methods

2.1. Materials

Chitosan had a reported average MW_w 400 000 g/mol; the degree of deacetylation was not determined. The poly(-vinyl alcohol) polymers used had an average MW_w 47–49 000 g/mol, hydrolysis grade 98% ('PVA 49') or an average MW_w 115–130 000 g/mol, hydrolysis grade 87–89% ('PVA 115') and were obtained from Fluka Chemie GmbH, Germany. Poly(ethylene oxide), average MW_v 100 000 g/mol ('PEO 100') and poly(ethylene oxide), average MW_v 5 million g/mol ('PEO 5M'), were obtained from Aldrich Fine Chemicals, Germany. Poly(vinyl pyrrolidone), Plasdone K90D, average MW_v 1 million g/mol ('PVP K90') and poly(vinyl pyrrolidone), Plasdone K29/32, average MW_v 50 000 g/mol ('PVP K30'), were obtained from ISP Technologies, USA. The semipermeable backing membrane used was 'Tegaderm™' were obtained from 3 M, USA. The drug used was a proprietary drug, codenamed 'AZMX', from AstraZeneca, while the enhancer used was sodium taurocholate, from Sigma-Aldrich Sweden AB.

2.2. Methods

2.2.1. Preparation of films and patches

Both homopolymer controls and blended films were made by casting onto Teflon plates from solvent, which was 0.1 M acetic acid, with the exception of PVA, which had to be dissolved in deionized water first. The solidified films used purely for polymer characterization were neutralized and washed with 0.1 NaOH and rinsed several times in water, dried in vacuum for at least 8 h at room temperature. Loaded films were not neutralized, since the charged state in chitosan was desired, and also because the drug was unstable at high pH. The films used for characterization of the polymer and polymer blend properties were placebos, so that proper interpretation of the results, for example, regarding polymer-polymer interactions, could be made without interference from other constituents. The effect of blending the polymers from the materials point of view, was, after all, an issue of equal importance in this study. The films used for the permeability and dog in vivo studies were loaded with about 50 weight % drug and 15 weight % enhancer (of total patch weight). These values were estimated from a known total weight of drug and/or enhancer added to a known volume (and weight) of polymer film/patch produced by casting.

The films used for in vitro drug release studies contained no enhancer. Although inclusion of small amounts of the enhancer was unlikely to affect the drug release results, the decision not to include enhancer was made in the course of the development work to allow adherence to the standard (internal) protocolls for the in vitro tests. Samples used for the dog (bioavailability) studies were in the form of round patches of diameter 10 mm and thickness ≈ 0.25 mm made semipermeable by attaching one side of the films to a low permeability backmembrane.

2.2.2. Polymer characterization

Thermal transitions, including melting point (T_m) and glass transition (T_g), were measured using a combination of differential scanning calorimetry (DSC), and dynamic mechanical thermal analysis (DMTA). For the DSC scans, a Perkin Elmer Pyris I instrument was used; the samples were analyzed twice between room temperature and 200°C, using a heating rate of 10°C/minute. For the DMTA scans, a DMTA IV from Rheometric Scientific was used. Temperature sweeps, at 2°C/minute, were made on the sample films held at constant tension, at a frequency of 1 Hz and strain rates varying between 0.02 and 0.1%.

Fourier transform infrared (FTIR) spectra were measured in the transmission mode using the KBr pellet method; a resolution of 4 cm^{-1} was used and about 25–50 scans were coadded for each spectrum. The equipment used was a Perkin Elmer FTS 1710, equipped with a dry air purge and a DTGS detector. Tensile tests were made using a HT Hounsfield 2000. The initial (fixed) length (l_o) of the mounted test strips was 35 mm. The strain rate applied was 10 mm/min.

2.2.3. Swelling and dissolution/erosion studies

Swelling and dissolution studies in pH 6.6 (accepted as the mean value for human saliva, which varies between pH 5.8–7.4 [1]) up to 8 h at 37°C were made using a weighing method. The degree of swelling (D.S) was calculated according to the following formula:

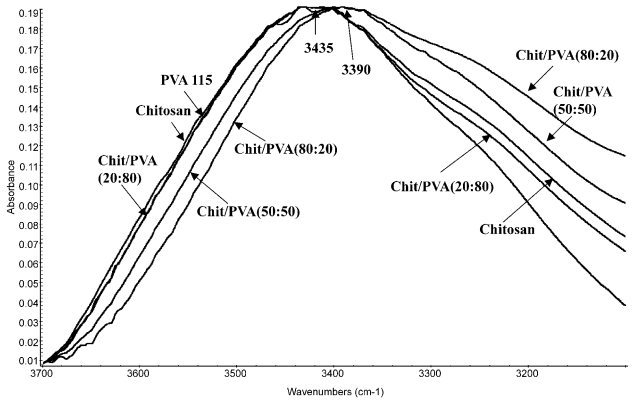

Fig. 1. FTIR spectra showing the hydroxyl (OH) stretching vibration of the chitosan and PVA 115 homopolymers, and the chitosan/PVA 115 (20:80), (50:50) and (80:20) blends.

$$\mathrm{D.S} = (W_s - W_u)/W_u \quad (1)$$

where W_s and W_u, respectively, represents the sample weight after and before swelling.

The D.S. value has not been given in % but has been interpreted simply as the number of times the original weight, and is thus unitless.

The dissolution/erosion properties were also measured using a weighing method. In this case, the samples from the swelling studies were retrieved after 30 h, dried to constant weight in a vacuum oven at room temperature, and weighed. The degree of dissolution was calculated according to the following formula:

$$\mathrm{D.D} = (Wd_o - Wd_t)/Wd_o \times 100\% \quad (2)$$

where Wd_o and Wd_t, respectively represents the *dried* sample weight before and after 30 h in buffer.

2.2.4. In vitro drug release studies

In vitro drug release studies were conducted at 37°C using a dissolution apparatus according to a standard USP paddle method coupled to liquid chromatographic analysis. A volume of 500 ml of standard phosphate buffer of pH 6.8 was used; the paddle rotation speed was 50 rpm. Each sample was placed in a basket positioned at about 1 cm over the paddle. All samples were run in duplicate. Drug release was measured at various time intervals over a 6 h period. Aliquots were withdrawn after 15, 30, 45, 60, 120, 180, 240, 300 and 360 min. The solution was immediately filtered through a membrane filter (cellulose nitrate, pore size 0.45 μm) and analyzed by HPLC. HPLC analysis was performed using a Waters 717 system with autosampler on a C8 column, d_p 5 μm, 3.9 × 150 mm from Waters symmetry with a Waters 600 controller gradient pump. Absorbance was measured at 237 nm with a Spectra 100 UV spectrometer from Spectra Physics.

2.2.5. Dog studies

The bioavailability of AZMX was studied in dogs following gingival administration of different chitosan blends. The study was carried out in four female beagle dogs, weighing

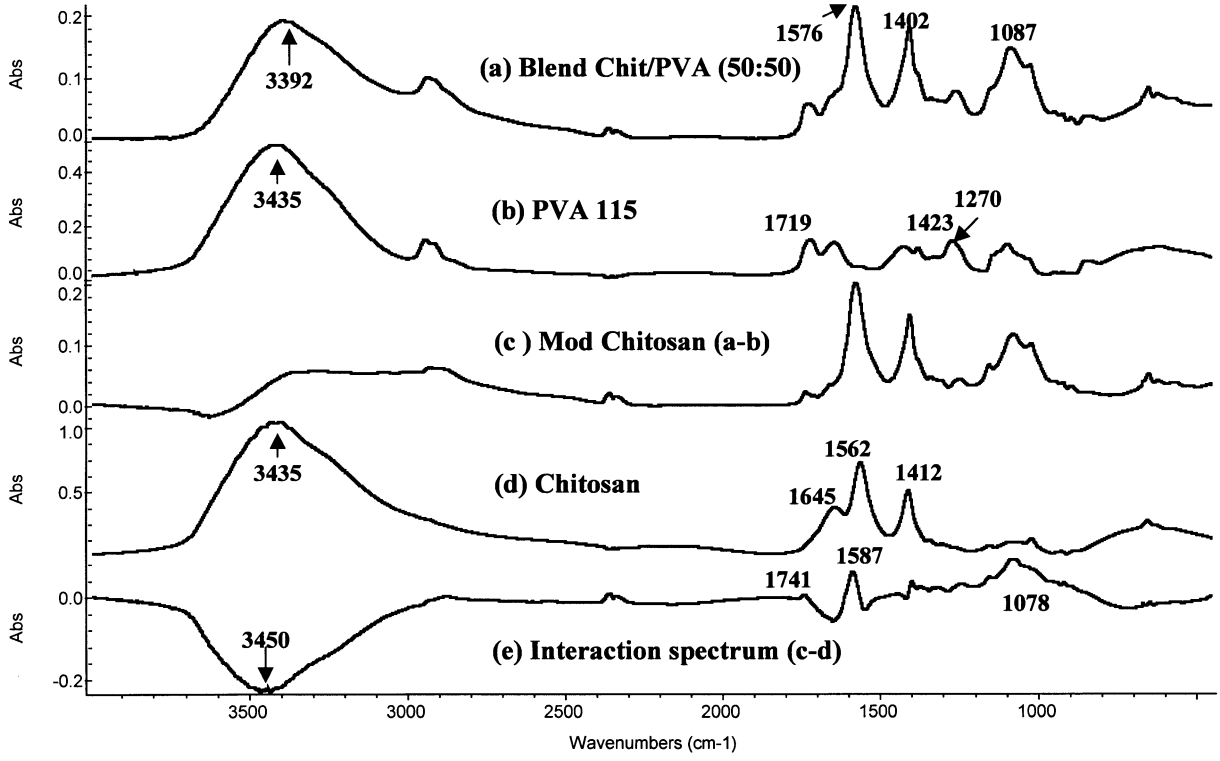

Fig. 2. FTIR spectra illustrating the spectral subtraction procedure applied to the chitosan/PVA 115 (50:50) blend.

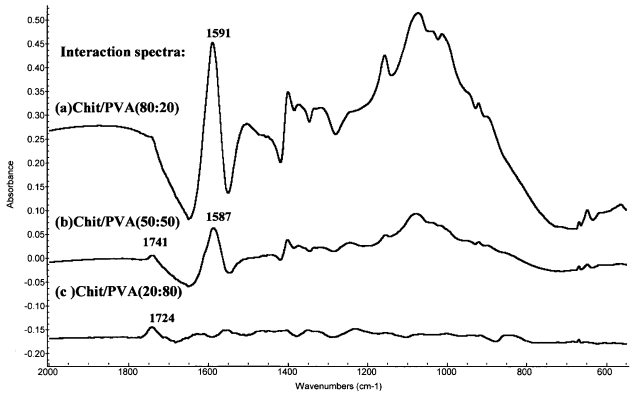

Fig. 3. FTIR spectra comparing the interaction spectra obtained for the chitosan/PVA 115 (20:80), (50:50) and (80:20) blends.

between 11 and 15 kg and aged between 1.5 and 5.5 years old. The administered dose was 2.5–4 μmol/kg. The gingival administration of the drug was started 1 h after feeding, to ensure that the measured bioavailability was mainly due to mucosal absorption. Earlier in-house control studies using the same drug had indicated a consistently negligible bioavailability when the drug was administered perorally in solution form, in the fed state [16]. Delivery systems of different chitosan (50:50) blends as well as pure chitosan and other homopolymers were tested. The patches were applied onto the upper gingiva with the backing membrane facing the inside cheek of the upper lip; drug release was thus in the direction towards the gingival mucosa. The patches were kept attached for 12 h before removal. Frequent blood samples for determination of AZMX concentration in plasma were withdrawn from a superficial leg vein predose and up to 12 h after administration. Plasma was separated by centrifugation and stored at −18°C pending analysis. The plasma concentration of AZMX was analyzed by liquid chromatography-mass spectrometry (LC-MS). The drug was isolated from plasma by solid phase extraction on octylsilica, separated by reversed

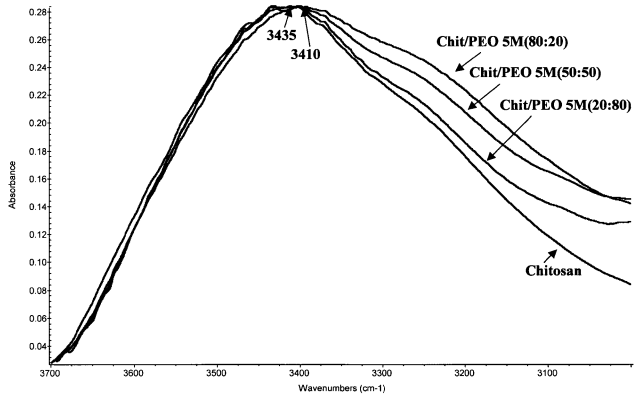

Fig. 4. FTIR spectra showing the hydroxyl (OH) stretching vibration of the chitosan homopolymer, and the chitosan/PEO 5 M (20:80), (50:50) and (80:20) blends.

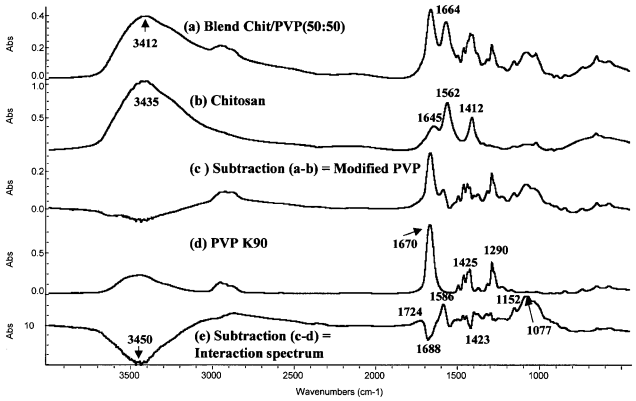

Fig. 5. FTIR spectra illustrating the spectral subtraction procedure applied to the chitosan/PVP K90 (50:50) blend.

phase liquid chromatography and measured by atmospheric pressure positive ionization mass spectrometry.

The absolute bioavailability is defined as the fraction (or percentage, as used here) of the administered dose which is absorbed intact into the systemic circulation. In practice, this is measured by comparing the total amount of intact drug reaching the systemic circulation after administration of a known dose of the dosage form via, in this case, the gingival site, with the total amount of intact drug reaching the systemic circulation after administration of an equivalent dose of the drug in the form of an intravenous bolus injection. Correction for the dosage sizes in each experiment leads to the following formula for absolute bioavailability:

$$(\text{AUC } \textit{gingival/Dose gingival}) \div (\text{AUC } \textit{intravenous/Dose intravenous}) \times 100\%$$
$$= (\text{AUC } \textit{gingival/AUC intravenous}) \times (\text{Dose } \textit{intravenous/Dose gingival}) \times 100\%$$

where AUC is defined as the area under the plasma concentration curve for the respective experiments.

3. Results and discussion

The annotations for the polymers have been simplified in Figs. 1–11; thus ‘Chit’ or ‘Ch’ represents chitosan, ‘PEO’ represents poly(ethylene oxide), ‘PVA’ represents poly

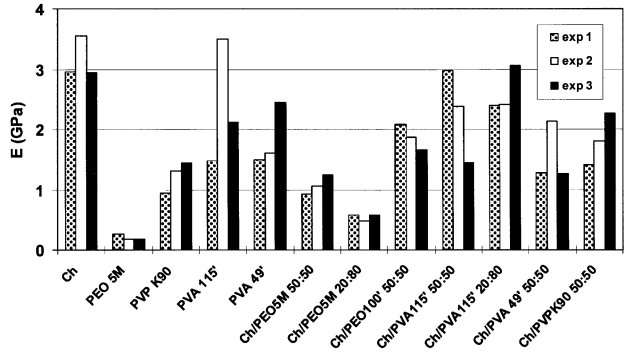

Fig. 6. Elastic moduli of the homopolymers and blends.

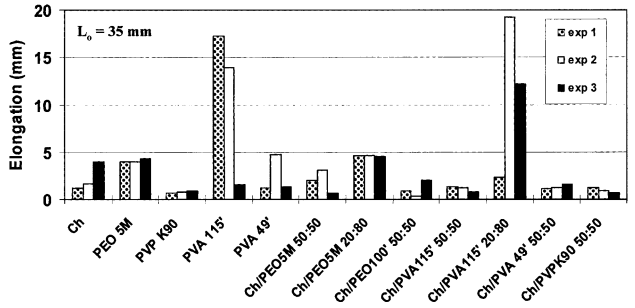

Fig. 7. Elongation at break of the homopolymers and blends ($l_o = 35$ mm).

(vinylalcohol), and 'PVP' represents poly(vinylpyrrolidone).

3.1. Observed film properties

All the polymers, except for PVP K30, could easily be moulded into apparently homogeneous films. The chitosan and PVP K90 homopolymers gave the most brittle films, whereas PVA and PEO gave the most flexible films. In general, the film quality was much improved by blending. Blends comprising a higher percentage of chitosan were, as expected, more brittle. The quality of all the films, as judged by appearance, worsened significantly after loading with drug and enhancer.

3.2. Thermal transitions

Table 1 presents a summary of the thermal transitions measured for the homopolymers and the blends. The T_g, ΔH and T_m values are based on those obtained in the second heating (DSC) cycle. Values for T_g derived from DMTA are indicated in parentheses.

3.2.1. Homopolymers

Chitosan is an amorphous polymer, and shows no T_m, but a T_g is observed at about 145°C, as detected using DMTA (maxima, log (loss modulus, E″)); DSC proved insufficiently sensitive as a method to detect this very broad transition.

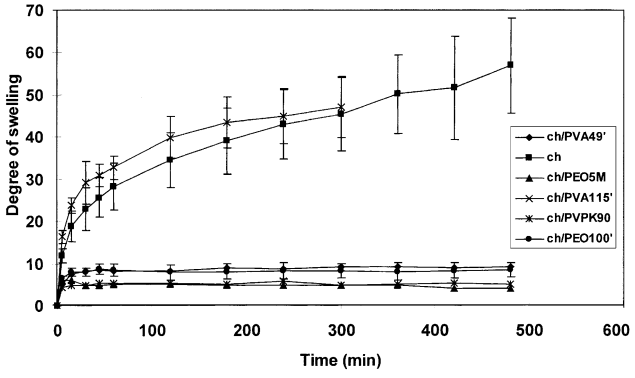

Fig. 8. D.S as a function of time, for the homopolymer chitosan and blends.

PVA 115 is a semicrystalline polymer and shows both a T_g and a T_m, which is influenced by thermal history. In the first heating curve, the sample (possessing a moisture content of about 2%), showed a sharp T_g maxima at about 50°C as well as a relatively large T_m at 185°C ($\Delta H = -32.7$ J/g). The sharp T_g may be explained by sample aging and subsequent enthalpy relaxation in the glassy state during the DSC run. From the DMTA results, a T_g of about 40°C was indicated (log E″), which is consistent with the DSC results for the first run. (All the DMTA results indicated a lower value for T_g, most probably due to the presence of moisture (usually 1–5%) in the samples.) During the cooling curve, recrystallization occurred between 62 and 113°C, but only about half the material recrystallized ($\Delta H = -16.9$ J/g). The third reheating run (essentially water-free sample) gave a higher value of T_g at 71°C and a broad T_m at a lower temperature, 142°C. The lower MW PVA 49 showed similar characteristics during the DSC scans. The third run gave a T_g at a slightly lower temperature of 68°C, and a broad T_m at 154°C.

PEO 5 M is a semicrystalline polymer possessing a large crystalline phase, as evidenced by a very sharp T_m at 60°C and about ten times the magnitude of the melting enthalpy when compared with PVA. At room temperature, it is in the rubbery state, with a T_g at about −55°C (from DMTA results). PEO 100 showed essentially the same characteristics, except that the recrystallization and remelting peaks were split at the lower temperature end, indicating a second and less ordered crystalline phase.

PVP K90 and PVP K30 are amorphous polymers showing a T_g at respectively 183 and 175°C.

3.2.2. Blends

In Table 1, additional (parenthesis*) values of ΔH for the blends have been added to depict the ΔH values calculated based on the weight fraction present of the semicrystalline polymer component within the blend, which makes it directly comparable with the values of the semicrystalline homopolymer.

Table 1 shows that all three chitosan/PVA 115 blends indicated a T_g value close to that of pure PVA but the T_g of chitosan was not clearly observed, even in the DMTA results.

While the chitosan/PVA 115 (20:80) blend exhibited the nearest value (73°C) to pure PVA (71°C), the (80:20) blend showed a shift downwards (67°C); however, the (50:50) blend showed a surprising shift upwards (76°C). Both the latter events possibly indicate the presence of some kind of interaction between the polymers, though the shift upwards should be interpreted with caution. In general, the relative closeness of the T_g values of the blend to the T_g value of pure PVA indicates that the two polymer phases are predominantly phase-separated, and that there is not any significant molecular miscibility. Increasing the chitosan component progressively in the blends from (20:80) to (80:20) decreased, as expected, the crystal perfection as well as

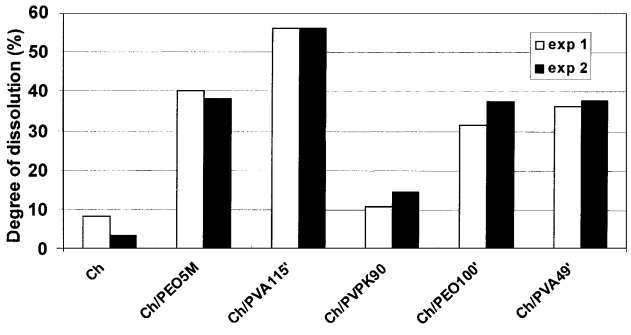

Fig. 9. Degree of dissolution (D.D (%)) as a function of time, for the homopolymer chitosan and blends.

the degree of crystallinity, as observed by the decreasing T_m and melting enthalpy (ΔH) values. However, the high absolute values of T_m and ΔH for all the blends compared with the homopolymer, were surprising.

Chitosan has been reported to impede PEO crystallization in chitosan/PEO blends [17,18]; this effect has been attributed to the effect of the stiff chitosan molecular chain on the overall mobility in the blend, which retards the rate of crystal growth [18]. This effect was seen clearly in the chitosan/PEO blends investigated here. Progressively increasing the chitosan component within the blends resulted in increasingly lower T_m values and more significantly, lower ΔH values. Comparing the blends with the homopolymer however, it was again surprising to observe blend T_m values 2–5°C higher than the homopolymer, indicating more perfect crystals within these phases. The ΔH values were lower however, reflecting a lesser % crystalline phase in the PEO component of the blend.

Some miscibility or molecular interaction may be inferred, based on the increased T_g value of the chitosan/PEO 5 M (50:50) blend, which shifted from −55°C up to −20°C in the pure PEO 5 M. Melting point depression for blends containing up to 50% chitosan, indicating interaction between the polymers, has also been reported [18].

In the chitosan/PVP blends, T_g could not be detected by DSC, but DMTA results for the (50:50) blend indicated a T_g at 150°C. Since chitosan and PVP K90 both have T_g values close to each other, it is difficult to draw conclusions about the miscibility of these blends based only on the thermal data.

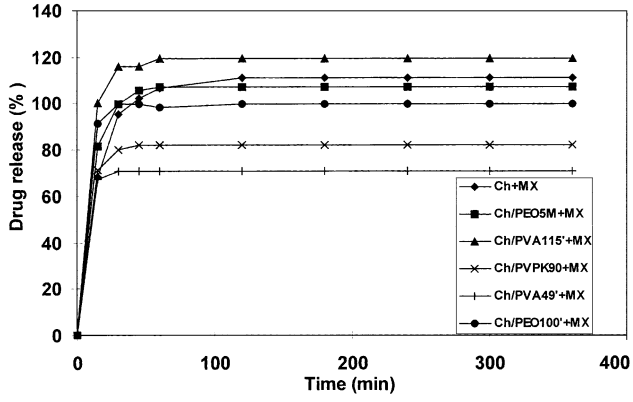

Fig. 10. Drug release (cumulative, %) as a function of time, for the homopolymer chitosan and blends.

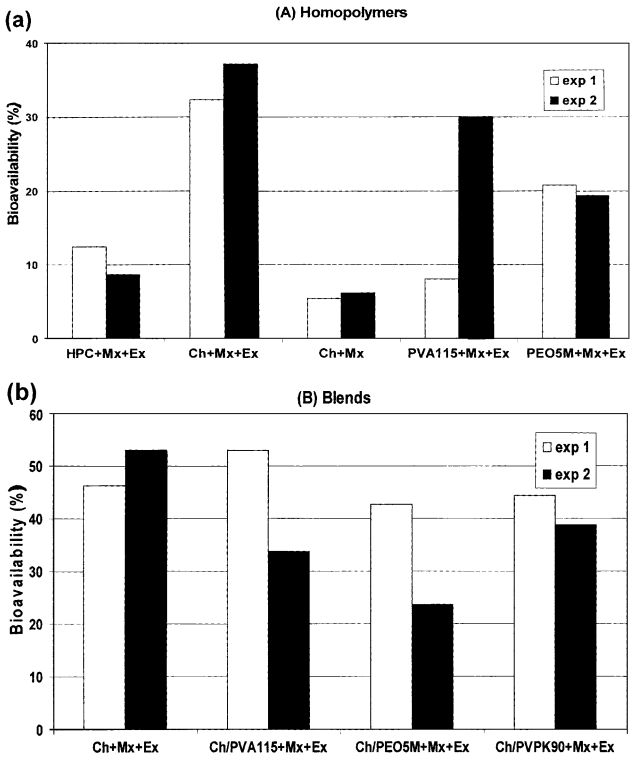

Fig. 11. (a) Bioavailability (%) shown by the homopolymer delivery systems. (b) Bioavailability (%) shown by the chitosan blend delivery systems.

3.3. Fourier transform infrared spectroscopy

3.3.1. Chitosan/PVA blends

Fig. 1 compares the hydroxyl (OH) stretching band for the two homopolymers, chitosan and PVA115, and the blends, (20:80) through (80:20). It is clearly seen that, when compared with the respective homopolymers, the OH vibration is shifted to lower frequencies, from about 3435 to 3390 cm^{-1} for two of the blends, chitosan/PVA115 (50:50) and (80:20). The OH vibration is also broadened. This is not so for the (20:80) blend, indicating that hydrogen bonding interactions involving the OH group of PVA (or chitosan) occurs to a significant extent only in the former two blends. Such an interaction between PVA and chitosan has been reported in the literature [19,20].

More information may be obtained using spectral subtraction procedures discussed by Cole and Painter, and Koenig, et al. [21,22]. In Fig. 2, the interaction spectrum (e) has been obtained, after successive subtraction of the spectra of the homopolymers PVA 115 (b), and chitosan (d), from the parent blend (50:50) spectrum, shown in (a). The internal standard bands at 1270 cm^{-1} (in PVA, assigned to

Table 1
Thermal transition values for the homopolymers and blends

Polymers	Tm (°C) (DSC)	− ΔH (J/g) (DSC)	Tg (°C) (DSC)
Homopolymers			
Chitosan (Ch)	Amorphous	–	(145, DMTA)
PVA 115	142	13.4	71 (40, DMTA)
PVA 49	155	15.9	68
PEO 5 M	60	133.4	(−55, DMTA)
PEO 100	60	118.8	Not analyzed
PVP K90	Amorphous	–	183 (148, DMTA)
PVP K30	Amorphous	–	175
Blends			
Ch/PVA 115 (20:80)	185	21.5 (26.8[a])	73
Ch/PVA 115 (50:50)	167	11.3 (22.4[a])	76 (43, DMTA)
Ch/PVA 115 (80:20)	163	2.4 (12.0[a])	67
Ch/PVA 49 (50:50)	179	8.9	72
Ch/PEO 5 M (20:80)	65	88.6 (110.8[b])	Not analyzed
Ch/PEO 5 M (50:50)	62	41.2 (82.4[b])	(−20, DMTA)
Ch/PEO 5 M (80:20)	63	13.4 (67.0[b])	Not analyzed
Ch/PEO 100 (50:50)	62	47.4	Not analyzed
Ch/PVP K90 (50:50)	Amorphous	–	(150, DMTA)
Ch/PVP K30 (50:50)	Amorphous	–	Not analyzed

[a] Values of ΔH based on wt. fraction PVA 115 in the blend.
[b] Values of ΔH based on wt. fraction PEO 5 M in the blend.

C—O stretching) and 836 cm^{-1} (in chitosan) were respectively used. Note that the 'modified chitosan' spectrum (c), resembles the chitosan spectrum (d), after subtraction of the PVA component. The presence of the amide II band, which is a coupled vibration of the N—H inplane bending and the amide C—N stretching vibrations, at 1562 cm^{-1}, and the OH deformation band at 1412 cm^{-1} are clearly seen in Fig. 2c, though the amide I band at 1645 cm^{-1} is less obvious. When the interaction spectra obtained for all three blends are compared, it may be observed that both the (80:20) and the (50:50) show negative peaks at about 3450 cm^{-1}, as seen in Fig. 2e, reinforcing the conclusion that the OH band is 'used' in interactions in these two former blends; but not in the (20:80) blend. Moreover, at lower frequencies, Fig. 3 highlights the fact that the amide II band has shifted *upwards* in frequency from its original position at 1562 cm^{-1} to about 1590 cm^{-1}, possibly indicating that the undeacetylated NHCOCH3 group in chitosan is less favoured as the hydrogen bonding site than the OH group in the (80:20) and (50:50) blends.

Another interesting observation in Fig. 3 is that the interaction spectrum of the (20:80) blend shows a clear C=O peak at 1724 cm^{-1} (shifted upwards from 1719 cm^{-1} in the original PVA (see Fig. 2b), originating in the polyvinyl acetate (PVAc) dehydrolyzed component. There is a slight indication of this peak in the (50:50) blend interaction spectrum seen at 1741 cm^{-1}, but not in the (80:20) blend. The appearance of this peak in Figs. 3b,c, clearly detectable in the (20:80) blend presumably because of the higher relative concentration, and assigned to the presence of free unbonded carbonyl groups in the PVAc (dehydrolyzed) part of the homopolymer, possibly points again to the lack of hydrogen bonding interaction between the PVA and chitosan, this time through the carbonyl moiety. Alternatively, the presence of chitosan may have disturbed some of the intrachain hydrogen bonding present in this polymer, resulting thus in a shift upwards in frequency of the carbonyl vibration. This latter occurrence, together with the lack of miscibility in the (20:80) blend, has probably some relation to the interesting tensile properties of this particular blend, which will be discussed in a later section.

3.3.2. Chitosan/PEO 5 M blends

Analysis of the spectra of these blends indicates that interaction between chitosan and PEO 5 M occurs for all the blends. Fig. 4 shows that the OH absorption peak in all the Chitosan/PEO5 M blends shifts to lower frequencies (from about 3435 cm^{-1} (chitosan) to about 3400–3410 cm^{-1}), together with increasing broadening as a function of chitosan content, indicating some hydrogen bonding interaction, probably between the chitosan hydroxyl and the PEO ether groups [23]. At lower frequencies (spectra not shown), the amide II band shifts increasingly to higher frequencies for the blends (1562 cm^{-1} (chitosan) to about 1570 cm^{-1}), indicating again that the undeacetylated NHCOCH3 group in chitosan is less favoured as the hydrogen bonding site than the OH group. The chitosan/PEO100 (50:50) blend shows similar behavior to its high molecular weight counterpart.

3.3.3. Chitosan/PVP blends

Analysis of the spectra of the chitosan/PVPK90 (50:50) blend indicates that interaction exists between these poly-

mers, probably between the chitosan hydroxyl and the PVP carboxyl groups, as reported previously [24].

Comparison of the blend and homopolymer spectra in Fig. 5 shows that the OH absorption for chitosan in the blend shifts downwards in frequency from about 3435 to about 3412 cm^{-1}. At the same time the C=O absorption for PVP K90 also shifts downwards from 1670 to 1664 cm^{-1}. Both effects indicate hydrogen bonding interactions. The interaction spectrum illustrated in Fig. 5e reinforces this conclusion by indicating negative peaks at 3450 cm^{-1} (indicating 'used' OH), 1688 cm^{-1} ('used' C=O), 1423 cm^{-1} ('used' OH, deformation band). The positive band at 1586 cm^{-1} indicates an upward frequency shift for the amide II band (—CONHR) for chitosan, which could again mean that the undeacetylated NHCOCH3 group in chitosan is less favoured as the hydrogen bonding site than the OH group. The presence of the positive band at 1077 cm^{-1} (ether C—O stretching) could indicate some structural disturbances in the polymer chain.

3.4. Tensile testing

3.4.1. Chitosan/PVA blend

Figs. 6 and 7 show, respectively, the elastic modulus and the elongation at break of the homopolymers and the blends. The values obtained were based on three different sets of cast films; this procedure was found necessary to give sufficient samples for the experiments. Variation between these sets of values was found to be quite large, reflecting some inhomogeneity in the cast films. For comparison purposes however, the mean values (of the three sets of values) were used for each homopolymer or blend to describe the trends obtained for each.

Among the homopolymers, amorphous uncrosslinked chitosan showed hard and brittle properties, manifesting the highest elastic moduli, but also one of the lowest elongations at about 7%. The semicrystalline polymer, PVA 115, showed on the other hand, hard and tough properties, as observed by its high modulus, and simultaneously high elongation values at about 30%. Molecular weight plays a significant role as observed by the lower modulus and elongation values exhibited by PVA 49. PEO 5 M and PVP K90 both showed a low modulus. PEO 5 M showed a greater elongation at break due to its semicrystalline nature, while amorphous PVP K90 was observed to be a brittle polymer.

The properties of the blends generally reflected the combined properties of the parent polymers. Both the chitosan/PVA 115 blends showed high moduli values, close to the value for the parent PVA. Interestingly, although the chitosan/PVA 115 (20:80) blend showed a high average elongation value of about 30%, equal to that shown by PVA 115 itself, this was not seen in the 50:50 blend.

In the FTIR results discussed earlier, some degree of hydrogen bonding interaction was observed for the (50:50) and the (80:20) blends, but not for the (20:80) blend, neither through the hydroxyl nor carbonyl moieties. It is possible that the lack of miscibility, or presence of a clear phase-separated morphology in this (20:80) blend, allowed the tensile properties of the blend to reflect those of the PVA 115 homopolymer itself.

3.4.2. Chitosan/PEO blend

All the chitosan/PEO blends exhibited somewhat higher moduli compared with PEO alone, but also lower or equivalent (for the (20:80) blend) elongation at break, due to the presence of chitosan. Surprisingly, the 50:50 chitosan blend with the lower molecular weight PEO 100 000 showed almost twice as large an elastic modulus (and correspondingly lower elongation) than its higher molecular weight counterpart. The possibility that chitosan is able to mix more intimately with the lower molecular weight PEO was considered, though a greater level of molecular interaction was not indicated in the FTIR results.

3.4.3. Chitosan/PVP blend

In the chitosan/PVP K90 (50:50) blend, the addition of chitosan increased the modulus somewhat compared to PVP K90 alone, though the enhancement was not remarkable. Apparently, the molecular interaction between the polymers in this blend clearly observed in the FTIR data did not lead to any significant improvement in the tensile properties of this blend.

3.5. Swelling and dissolution

Fig. 8 compares the degree of swelling shown by the (50:50) blends with the chitosan homopolymer in two different sets of experiments. As indicated in the figure, chitosan possesses highly swelling properties; initial swelling takes place very quickly, after which swelling continues more gradually over a relatively long time period. The chitosan/PVA 115 blend was also observed to swell greatly, and to the same level as chitosan. In most of the other blends, swelling appeared to taper off to a constant value after only about 15 min. It should be noted that for many of these blends, dissolution took place rapidly, resulting thus in a constant swelling weight after only a short time. Both chitosan itself and high molecular weight PVA showed slower dissolution properties.

Fig. 9 compares the degree of dissolution shown by the (50:50) blends with the chitosan homopolymer in two different sets of experiments. In all cases, blending with hydrophilic polymers clearly increased the dissolution properties of chitosan. Interestingly, the two materials which exhibited the highest swelling properties, chitosan and the chitosan/PVA115 blends, showed opposite trends with respect to dissolution. Less than 10% of chitosan was dissolved after 30 h, while almost 60% of the chitosan/PVA 115 (50:50) blend was dissolved. With regards to the homopolymers (figure not shown), dissolution speed proceeded in the order: PVP K90 > PVA49 > PVA115 > PEO 5 M. All

these homopolymer samples were completely dissolved already after about 1 h.

3.6. In vitro drug release

Fig. 10 shows that drug release for chitosan and all the blends occurred very quickly; plateaus were reached within 30 min. The final total drug release varied between 70 and 100% (±15%) for the different blends. The drug release, which followed the trends for swelling ability, was greatest for chitosan/PVA 115, and comparable to chitosan itself. For the blends chitosan/PVP 90 and chitosan/PVA 49, drug release appeared already to taper off at 70–80%, suggesting some entrapment of the drug within these systems.

3.7. Dog studies

Plasma concentration-time profiles (not shown here) indicated that absorption through the gingiva was fast and that the maximum plasma concentrations were reached within 100 min.

Figs. 11a,b compares the bioavailability (%) of the studied drug in the homopolymer controls and blend delivery systems respectively. Hydroxylpropylcellulose was included among the homopolymers studied to make comparisons possible with an earlier internal study [15]. It is interesting to note in Fig. 11a that the chitosan control, i.e. chitosan without enhancer, showed rather low bioavailability, but that this was greatly increased with addition of enhancer. The intrinsic enhancing properties of chitosan itself, which have been demonstrated mainly via in vitro studies [8–13] might thus be questioned. On the other hand, some neutralization of chitosan at higher pH values or interaction with the drug, might be considered to account for this observation. Fig. 11b shows that although there was some decrease in bioavailability in the duplicate experiments, the mean values for the blends were comparable with those shown by chitosan (plus enhancer) alone.

3.8. Compliance and mucoadhesive properties in dogs

The chitosan blends with PEO and PVA were most 'comfortable', as indicated by the absence or only mild indication of red irritation rashes, noted during the course of the dog studies. A qualitative scaling of the redness observed was performed. The highest irritation and discomfort were experienced with the pure chitosan films. Rashes could also be observed for several of the patches, which were in the first instance attributed mainly to the inclusion of the enhancer. The worst irritation appeared to be experienced with the chitosan (including enhancer) patch. The redness disappeared only after several hours after the patch was removed.

Mucoadhesive properties were acceptable in all cases, except the blend with low MW PEO, which fell off after a short while. All other patches stayed in place.

4. Conclusions

The study indicated that PEO and PVP gave the most miscible blends with chitosan; PVA was significantly less miscible. However, the film properties of phase-separated chitosan/PVA blends appeared to be interesting and exploitable.

The bioavailability of the drug AZMX conferred by patches made from chitosan blends were shown to be comparable to using chitosan itself as the drug delivery system. In addition, chitosan blends gave superior properties in many ways compared to chitosan alone. These include improved comfort and reduced irritation, ease of processing, improved film quality, improved flexibility, and enhanced dissolution. Blends of chitosan with different hydrophilic polymers are thus promising candidates for formulation in oral mucosal delivery systems.

Acknowledgements

We wish to thank the following people for help and useful discussions: (AstraZeneca): H. Douglasson and A.-L. Ungell for help with the dog studies, A. Dahl, R. Sundberg, S. Wendsjö, for help with the drug release experiments. (Other institutes): M. Wennerbäck (Swedish Institute of Fibre and Polymer Technology) for help with the DMTA measurements. We also thank G. Ragnarsson, J.-E. Löfroth (AZ), and Prof. F. Maurer (Lund University of Technology), for constructive comments. Finally, the general support and help of colleagues in departments Formulation I(BTS) and II(BTR) is gratefully acknowledged.

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