Carbohydrate Polymers 87 (2012) 1286–1294

Contents lists available at SciVerse ScienceDirect

Carbohydrate Polymers

journal homepage: www.elsevier.com/locate/carbpol

Miscibility study of chitosan/2-hydroxyethyl starch blends and evaluation of their effectiveness as drug sustained release hydrogels

Stavroula G. Nanaki[a], Ioannis A. Koutsidis[a], Ioanna Koutri[b], Evangelos Karavas[b], Dimitrios Bikiaris[a,*]

[a] Laboratory of Polymer Chemistry and Technology, Department of Chemistry, Aristotle University of Thessaloniki, GR-541 24 Thessaloniki, Greece
[b] Pharmathen S.A., Pharmaceutical Industry, Dervenakion Str 6, Pallini Attikis, GR-153 51 Attiki, Greece

ARTICLE INFO

Article history:
Received 31 January 2011
Received in revised form 13 July 2011
Accepted 6 September 2011
Available online 12 September 2011

Keywords:
Chitosan
2-Hydroxyethyl starch
Polymer blends
Solid dispersions
Ropinirole
Sustained release

ABSTRACT

Polymeric matrices of chitosan (CS), 2-hydroxyethyl starch (HES) and their blends prepared by solvent evaporation technique, have been tested as sustained release hydrogels of ropinirole drug. X-Ray diffraction (XRD), infrared spectroscopy (FT-IR) and viscometry measurements showed that the two polymers can form miscible blends. This miscibility is owed to formed hydrogen bonds taking place between the reactive groups of CS and HES and one glass transition is recorded in all blends. Neat polymers were used to prepare solid dispersion formulations with ropinirole drug. It was found that drug was released immediately within 15–30 min from HES while the release was slower from CS matrix. Completely different were the release rates from ropinirole with physical mixtures using neat polymers and their blends. Due to the different solubility and swelling behaviour of CS and HES the release rates showed a sustained profile from the blends containing high amounts of CS.

1. Introduction

Chitosan (CS), poly(beta-1,4-D-glucosamine), is a natural polyaminosacharide which is derived by alkaline N-deacetylation of chitin (Fig. 1a). It is one of the most frequently used materials for the preparation of drug delivery systems due to its biocompatibility, biodegradability and mucoadhesiveness (Sashiwa & Aiba, 2004). CS has been used in variable biomedical applications and especially for sustained-release carrier of drugs (Berger et al., 2004; Yu et al., 2008). Due to presence of amino and hydroxyl functional groups in its repeat unit, CS is soluble in dilute acidic solutions and yield a rubbery hydrogel in water. CS properties can be modified during blending with other polymers. (Fukuda, Peppas, & McGinity, 2006; Sokker, Abdel Ghaffar, Gad, & Aly, 2009; Sahoo, Sasmal, Nanda, Phani, & Nayak, 2010).

Hydroxyethyl starch (HES) is a modified natural polysaccharide and it is similar to glycogen (Fig. 1b). HES, is derived from amylopectin, a highly branched starch that is obtained from waxy maize or potatoes. It has been used in medicine for a long time as volume therapy, so that a good physiological compatibility of the hydrogels can be assumed. Furthermore, this hydrogel matrix is biodegradable and biocompatible, so a continuous release of active ingredients in the course of the erosion of the hydrogel and by diffusion is possible. Native starch may not be appropriate to prepare controlled drug delivery systems, since it is rapidly degraded in vivo and many drugs are released too quickly from such unmodified starch systems (Michailova, Titeva, Kotsilkova, Krusteva, & Minkova, 2001). In contrast, hydroxyethyl starch is a less quickly degraded than starch derivative. Compared with chitosan, hydroxyethyl starch has higher solubility.

The aim of the present study was to prepare miscible polymer blends composed by CS and HES. These blends are investigated in order to create an adjustable system, based on the high solubility of HES and the respective low one of CS. This is because in similar polymer blends, adjusting the composition of the used polymers and the polymer drug interactions, the release profile of a drug formulation can be adequate controlled (De la Torre, Enobakhare, Torrado, & Torrado, 2003; Karavas, Georgarakis, & Bikiaris, 2006a; Nanaki, Karavas, Kalantzi, & Bikiaris, 2010; Papageorgiou et al., 2008). In the present study as an active agent, Ropinirole hydrochloride (Ropi) was used, which is a very soluble drug and sustained release formulations are needed in order to provide a more efficient therapeutic method. Ropinirole hydrochloride, 4-[2-(dipropylamino) ethyl]-1,3-dihydro-2Hindol-2-one (Fig. 1c), is a nonergoline dopamine agonist at dopamine D2/D3 receptors and acts both peripherally and centrally. It is used in the treatment of Parkinson's disease and also approved for the treatment of Restless Legs Syndrome.

* Corresponding author. Tel.: +30 2310 997812; fax: +30 2310 997667.
E-mail address: dbic@chem.auth.gr (D. Bikiaris).

0144-8617/$ – see front matter © 2011 Elsevier Ltd. All rights reserved.
doi:10.1016/j.carbpol.2011.09.013

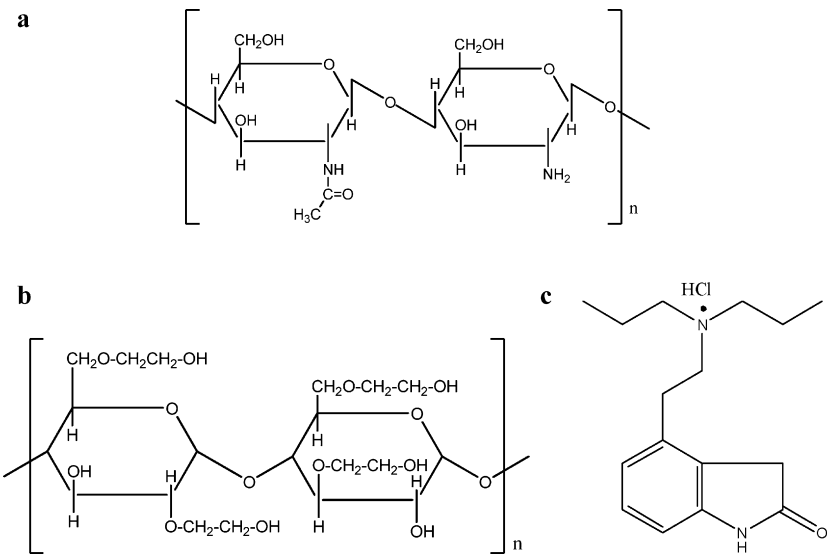

Fig. 1. Chemical structure of (a) chitosan, (b) hydroxyethyl starch and (c) ropinirole hydrochloride.

2. Experimental

2.1. Materials

Medium molecular weight chitosan (>75% deacetylation; Brookfield viscosity 200–800 cP, 1% solution in 1% acetic acid), 2-hydroxyethyl starch (FW 580; mp 268 °C; d 1.5; Viscosity 25.000 cps at 66 °C) were purchased from Aldrich. Ropinirole hydrochloride drug was purchased from Ragactives, S.L.U. (Valladolid, Spain). It is a white to pale greenish-yellow powder with a melting range of 241–245 °C, a solubility of 133 mg/mL in water and molecular weight 296.84 (260.38 as the free base). All other materials and solvents used for the analytical methods were of analytical grade.

2.2. Preparation of chitosan/hydroxylethyl starch blends

Chitosan/2-hydroxylethyl starch polymer blends (CS/HES) were prepared using the solvent evaporation technique. Chitosan was initially dissolved in distilled water containing 2% acetic acid by mechanical stirring forming solutions of 1% w/v. 2-Hydroxyethyl starch was also dissolved in distilled water at 60 °C by stirring forming solutions of 1% w/v. Proper amounts of each solution were mixed in order to prepare CS/HES blends with ratios 0/100, 10/90, 20/80, 30/70, 40/60, 50/50, 60/40, 70/30, 80/20, 90/10 and 100/0 w/w. Water was removed at 60 °C under vacuum and the blends were collected in the form of transparent cast films.

2.3. Polymer blends characterization

2.3.1. X-ray diffraction (XRD)

XRD analysis was performed on cast films, which were scanned over the internal of 5–55° 2θ, using a Phillips PW1710 diffractometer with Bragg-Brentano geometry (θ, 2θ) and a Ni-filtered Cu Kα radiation.

2.3.2. Fourier transformation-infrared spectroscopy (FT-IR)

FTIR spectra of the prepared blends and neat polymers were obtained using a Perkin–Elmer FTIR spectrometer, model Spectrum One. From each sample thin films were used, which were prepared by solvent evaporation at 60 °C under vacuum. The IR spectra were obtained in absorbance mode in the spectral region of 450–4000 cm^{-1} using a resolution of 4 cm^{-1} and 64 co-added scans.

2.3.3. Viscosity measurements

Intrinsic viscosity [η] measurements of chitosan, 2-hydroxyethyl starch and their blends were performed using an Ubbelohde capillary viscometer IIa at 30 °C in distilled water at a solution concentration of 1 wt%.

2.3.4. Swelling ratio

Samples (0.2 g) of HES, CS and their blends were placed into vessels and weighted prior to being suspended in 30 mL phosphate buffer (pH 6.8) at 37 °C. The swelling ratio was calculated by weighing the vials after removing the entire phosphate buffer at predetermined time intervals. The swelling ratio (SR) was expressed by the following formula: $SR = (W_t - W_o)/W_o$, where W_t was the sample's weight at time t and W_o was the initial polymer's weight.

2.3.5. Dynamic mechanical analysis (DMA)

DMA tests performed on a Perkin–Elmer diamond dynamic mechanical analyzer operated in a dual cantilever mode. The heating rate was 3 °C/min and the frequency was 1 Hz. Tests were conducted over the temperature range from 25 °C to 180 °C. The samples were cut to dimensions of 15 mm × 3 mm × 1 mm prior to test and dried for 48 h at 80 °C under vacuum. The aim of the tests was to determine the Tg of neat polymers and blends.

2.4. Drug loading of chitosan, 2-hydroxyethyl starch and their blends CS/HES and tablet prepartion

Ropinirole was dissolved in distilled water alone as well as CS and HES to the way described in previous session (preparation of chitosan/hydroxylethyl starch blends) in order to prepare 3 different solid dispersion samples (CS/ropinirole, HES/ropinirole and CS/HES/ropinirole). For this reason the different solutions (ropinirole solution and CS or HES solution, one each time) were mixed under gently stirring at room temperature. The solvent was removed by setting the solutions under vacuum at 50 °C until constant weight and solid dispersions of CS/ropinirole and HES/ropinirole contained 2.5, 5.0, 7.5 and 10 wt% of ropinirole were prepared in the form of thin films. In a similar way solid dispersions of CS/HES blends (90/10, 80/20, 50/50, 30/70 and 10/90 w/w) with Ropinirole drug containing 2.5, 5.0, 7.5 and 10 wt% of ropinirole were also prepared. The solid dispersion films were milled and

after sieving particles sizes of 150–300 μm were collected and were used for the drug release studies.

Except solid dispersions, physical mixtures of ropinirole with CS and HES were also prepared for comparison reasons, containing 2.5, 5.0, 7.5 and 10 wt% of ropinirole drug.

CS/HES blends were also used after grinding their films in order to prepare physical mixtures with ropinirole. After sieving the fraction 150–300 μm of CS/HES blends (90/10, 80/20, 50/50, 30/70 and 10/90 w/w) was collected used and mixed with different amounts of ropinirole.

The solid dispersions and physical mixtures of ropinirole drug with different polymer matrices, which were prepared as described in the previous sessions, were used for tablets preparations for the in vitro release studies. For this reason hundred milligrams of each formulation were inserted into an adequate matrix and compressed for 5 min under pressure 10 MPa using 10 mm standard round concave punches on a Bonapace CPR 6 single punch automatic tablet press (DOTT. BONAPACE & C. s.r.l, IT). The physical state of all formulations containing different amounts of Ropinirole was characterized by using XRD and FTIR spectroscopy as described in our previous sections.

2.5. Characterization and in vitro release of drug formulations

2.5.1. In vitro release profile

In vitro release rates of Ropinirole from the prepared formulations were generated in USP dissolution apparatus II (paddle apparatus). Dissolution tests were performed in phosphate buffer pH 6.8 at 37 ± 1 °C, the rotation speed was set at 100 rpm, and the dissolution medium was 1000 mL. All dissolution studies were performed in triplicate. The dissolution apparatus used, was a DISKTEK 2100 C with an auto sampler DISTEK EVOLUTION 4300 and a DISKTEK syringe pump.

2.5.2. HPLC quantitative analysis

Quantitative analysis was performed using a Shimadzu HPLC prominence system consisting of a degasser (DGU-20A_5), a liquid chromatograph (LC-20 AD), an auto sampler (SIL-20AC), a UV/Vis detector (SPD-20A) and a column oven (CTO-20AC). For the analysis a validated method was used (Azeem, Iobal, Ahmad, Kharand, & Talegaonkar, 2008). In details, a C_{18} reversed-phase column (250 mm × 4.6 mm i.d., 5-μm particle) was used, the mobile phase was methanol-0.05 M ammonium acetate buffer (pH 7) 80:20 (*v*/*v*) and the flow rate was 1 mL min^{-1}. UV detection was performed at 250 nm.

3. Results and discussion

3.1. Characterization of the prepared blends

Polymer blends can be miscible when only one phase appeared after mixing of neat polymers or immiscible when each one polymer retains its phase in the blend. In order to characterize the prepared CS/HES blends several techniques were used. XRD pattern of neat CS film showed that is in partially crystalline state (Fig. 2). This observation is in accordance with Nunthanid (Nunthanid, Puttipipatkhachorn, Yamamoto, & Peck, 2001) who reported a peak at approximately 10° (2θ) corresponding to hydrated crystals and one at 18° (2θ) corresponding to anhydrous crystals. XRD pattern of neat HES film showed a wide broad peak corresponding to the amorphous state. XRD patterns of their CS/HES blends showed only broad peaks indicating that the prepared films are completely amorphous after solvent evaporation, while the crystalline peaks of CS were not recorded even in the films with high CS amount (Fig. 2). This amorphization is an indication that the existence of HES prohibits CS crystallization.

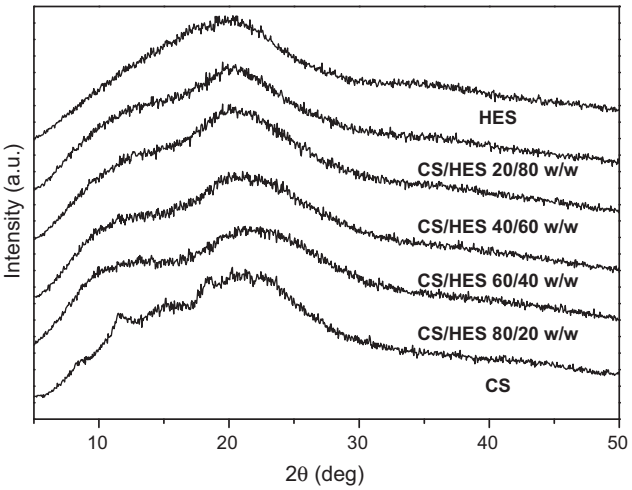

Fig. 2. XRD patterns of neat chitosan, 2-hydroxyethyl starch and their blends.

The prepared CS/HES films except that they are amorphous, they are also transparent in the whole composition range. This observation is an indication that the two polymers may be miscible creating a new polymer matrix constituted by one single phase. Miscible blends have only a single phase and for this reason only one glass transition temperature (T_g) should be recorded, ranged at temperatures between those corresponding to the initial polymers, or at even higher temperatures. The precise position depends on polymer ratios and the extent of interactions that take place between the reactive groups of the two polymers. On the other hand, phase separation is judged by the existence of two distinct T_g close to the T_g of the pure polymers. For this reason a detailed analysis of the T_g of the prepared polymer blends is necessary to identify blend miscibility. All films were studied with dynamic mechanical analyzer (DMA) since the glass transitions of initial polymers due to the low ΔCp variation in the case of HES were difficult to determine with DSC. Such difficulty was also mentioned in literature. Jochem (Jochem & Korber, 1987) could not identify its T_g using DSC and Chen (Chen, Bhowmick, Sputtek, Fowler, & Toner, 2002) estimated the T_g value at 44 °C by extrapolating experimental data from DSC using the Gordon–Taylor and Fox equations. From our study the T_g of HES was found at 106 °C. The recorded T_g of CS was 148 °C, as can be seen from the tan δ curve, very close to the values reported in literature (Lazaridou & Biliadelis, 2002).

Even thought the differences between the glass transition temperatures of neat polymers are very small (42 °C) it has been proved that DMA is a sensitive technique as far as the study of the miscibility of such blends is concerned (Bikiaris, Prinos, Botev, Betchev, & Panayiotou, 2004). In prepared blends it is observed that in all compositions there is only one T_g, which ranges between the glass transitions of the two initial polymers. In polymer blends with CS contents 40–90 wt% the T_g is higher than even that of neat CS. For example the blend with 20 wt% CS has a T_g = 151 °C and this with 50 wt% CS has a T_g = 157 °C, which is the highest from all the blends (Fig. 3). In the other blends containing 10–30 wt% CS the T_g is ranged between of these of the neat CS and HES, which is in accordance to the previous study in similar blends (Lazaridou & Biliadelis, 2002). This is a strong proof that the two polymers are fully miscible, creating a massive interpenetrating network.

The recorded glass transition temperatures of the CS/HES blends are presented in Fig. 3. As can be seen there is a positive variation of the recorded glass transition temperatures, compared with neat polymers. In the most blends a linear variation is expected and such a variation could be attributed to the evolved interactions taking place between the reactive groups of CS and HES. In the past,

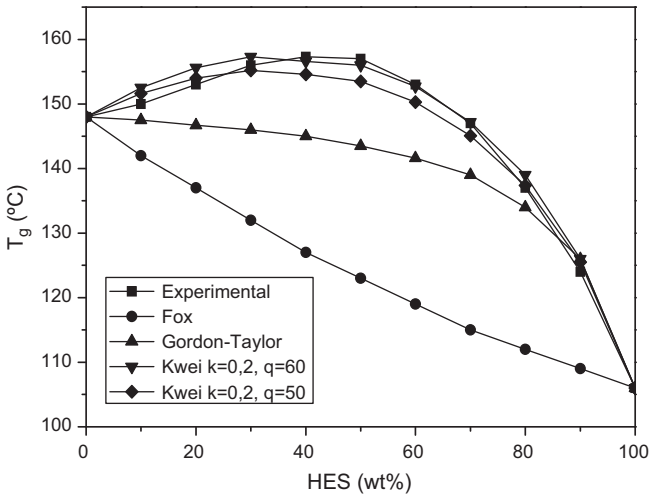

Fig. 3. Comparison of experimental T_g determined by DMA to that derived from Fox, Gordon–Taylor and Kwei equations.

several theoretical and empirical equations have been proposed to adequately describe the dependence of T_g of a miscible blend from the weight fractions and the glass transitions of the initial polymers and to estimate the extent of interactions between the different components. Among them, the Fox equation can be used to evaluate the T_g/composition relationship, which was one of the first proposed (Fox, 1956)

$$\frac{1}{T_g} = \frac{w_1}{T_{g1}} + \frac{w_2}{T_{g2}} \quad (1)$$

where T_g is the glass transition of the blend, w_1 and w_2 are the weight fractions of the initial polymers forming the blend and T_{g1}, T_{g2} are their glass transition temperatures. However, as can be seen from Fig. 3 the calculated values of glass transition temperatures are ranged between these of initial used polymers. This is because Fox equation takes into account only the weight fractions and predicts that T_g can continuously and monotonically increase with blend composition. Gordon–Taylor proposed an equation taking into account not only weight fractions but also the evolved interactions that cannot be predicted by the Fox equation (Gordon & Taylor, 1952)

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} \quad (2)$$

where k is a constant representing a semi-quantitative measure of the interaction strength between the reactive groups. If k takes values close to 1 or higher then it is suggested that strong interactions take place (Ping, Nguyen, & Néel, 1988).

Using the above equations, as can be seen in Fig. 3, only the Gordon–Taylor equation is close to the experimental data. By applying the Gordon–Taylor with $k = 0.12$, the best correlation with the experimental data is obtained. This value is inferior to 1, implying that the interactions between the reactive groups of CS and the HES hydroxyl groups are rather weak. However such a low value does not exclude the formation of completely miscible blends (Guo, Huang, & Li, 1996). Furthermore, as can be seen the correlation of experimental data with Gordon–Taylor equation is identical only for blends with concentrations 80 and 90 wt% HES. For the other blends, even though a positive variation is predicted the calculated values are much lower from the experimental. Kwei has extended the Gordon–Taylor equation by introducing a further factor (q) as a measurement of the number of specific interactions (Eq. (3)).

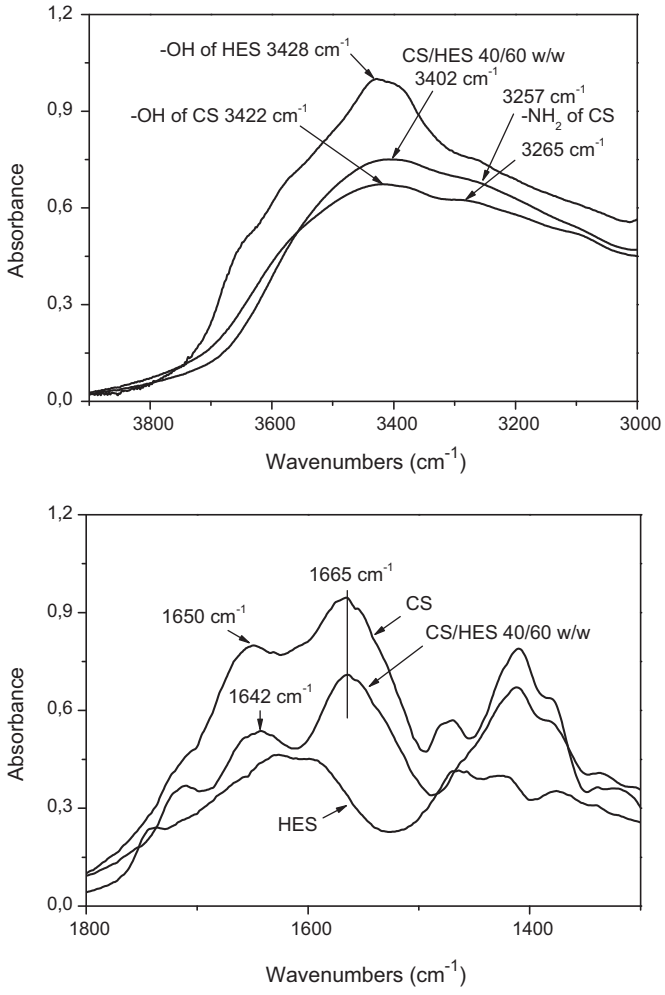

Fig. 4. FTIR Spectra of CS, HES and their CS/HES 40/60 w/w blend.

This equation is appropriate for polymer blends for which positive values are recorded than the linear deviations.

$$T_g = \frac{w_1 T_{g1} + k w_2 T_{g2}}{w_1 + k w_2} + q w_1 w_2 \quad (3)$$

As can be seen in Fig. 3, using values of $k = 0.2$ and $q = 50$–60, an accurate prediction can be obtained, which is much better than Gordon–Taylor equation. This verifies that some interactions are taking place between CS and HES, which are responsible for the miscibility of the blends.

In order to evaluate the interactions between CS and HES, the FTIR spectra of the blends were recorded from cast films. As seen in Fig. 4 the main characteristic bands of CS are located at 3422 and 3265 cm^{-1} (O–H and –NH_2 stretching, respectively), 1650 cm^{-1} (>C=O stretching – amide I), 1413 cm^{-1} (C–H and O–H vibrations), 1148 cm^{-1} (anti-symmetric stretching of the C–O–C bridge) and 1066 cm^{-1} (skeletal vibrations involving the C–O stretching) (Ma, Yang, Kennedy, & Nie, 2009). As concerns to HES FT-IR spectra is similar to that reported from Devy (Devy, Balasse, Kaplan, Madoulet, & Andry, 2006), i.e. the characteristic peaks are located at 3428 cm^{-1} (O–H stretching), 1420–1450 cm^{-1} (C–H bending), 1050–1080 cm^{-1} (C–O–C bending), 930 cm^{-1} (C–H bending) and 850 cm^{-1} (C–H bending). By examining the wavenumbers of C–H bending peaks it can be seen that their position remained almost the same in all prepared blends, as in neat polymers. Differentiations exist at the range 3400–3300 cm^{-1} where the hydroxyl group of HES interacts with the hydroxyl group and/or amino group of

CS. Both of hydroxyl peaks of HES (3428 cm^{-1}) and CS (3422 cm^{-1}) are shifted to 3402–3416 cm^{-1} in the blends and the exact position depended from the polymer content. Furthermore, there is a shift of CS amino ($-NH_2$) groups stretching from 3265 to 3258–3260 cm^{-1} in the blends. This is an evidence for the nature of interactions that are taking place between the hydroxyl groups of HES and the amino groups of CS and are responsible for the polymer miscibility after solvent evaporation procedure. A similar shift was also observed in chitosan >C=O stretching – amide I, which in the blends was recorded in 1642 cm^{-1}. It seems that the carbonyl groups of chitosan may also participate in such interactions.

However, such intramolecular and intermolecular hydrogen bonds are possible to coexist also in neat polymers since HES has hydroxyl groups, while CS has both hydroxyl and amino groups. Furthermore, these variations can be attributed to the differentiation of CS physical state after solvent evaporation. In order to elucidate the miscibility of CS and HES two models based on viscosity measurements of the blends suggested by Chee (Chee, 1990; Sun, Wang, & Feng, 1992) were used. According to Chee model, when two polymers are mixed in different weight fractions w_1 and w_2, the interaction parameter is expressed as ΔB and can be calculated from the following equation:

$$\Delta B = \frac{b - \bar{b}}{2w_1 w_2} \tag{4}$$

where where $b = w_1 b_{11} + w_2 b_{22}$

b_{11} and b_{22} are the slopes of the viscosity curves for the pure components while b is related to Huggins' coefficient K_H and to the intrinsic viscosity $[\eta]$ as follows:

$$b = K_H[\eta]^2 \tag{5}$$

For a ternary system b is given by the equation:

$$b = w_1^2 b_{11} + w_2^2 b_{22} + 2w_1 w_2 b_{12} \tag{6}$$

b_{12} is the slope of the viscosity curve for the blend solution.

Chee has also suggested a more secure interaction parameter, μ, in case $[\eta]_1$ and $[\eta]_2$ are apart. The corresponding equation is:

$$\mu = \frac{\Delta B}{([\eta]_2 - [\eta]_1)^2} \tag{7}$$

$[\eta]_1$ and $[\eta]_2$ are the intrinsic viscosities for the pure component solutions. According to Chee, if $\mu \geq 0$ the polymers in the blend are miscible in the blend and if $\mu < 0$ the polymers are immiscible.

Sun et al. (1992) suggested a different equation than this of Chee for the definition of polymer miscibility:

$$\alpha = K_m - \frac{K_1[\eta]_1^2 w_1^2 + K_2[\eta]_2^2 w_2^2 + 2\sqrt{K_1 K_2[\eta]_1[\eta]_2 w_1 w_2}}{([\eta]_1 w_1 + [\eta]_2 w_2)^2} \tag{8}$$

K_1, K_2 and K_m are the Huggins' constants for the individual components 1 and 2 and for the blend. If $a \geq 0$, the polymers in the blend are miscible and if $a < 0$ they are not (Basavaraju, Demappa, & Rai, 2006; Jayaraju, Basavaraju, Keshavayya, & Rai, 2006; Yichun et al., 2007). In order to calculate those parameters the solution viscosities of the blends were measured using different polymer ratios. For neat CS, HES and for each polymer blend, five different concentrations were used 0.1, 0.2, 0.3, 0.4 and 0.5 wt%. The relationship between reduced viscosity (η_{red}) of neat polymers and different CS/HES blends has been plotted in order to calculate the b_{11} and b_{22} parameters (Fig. 5a). An almost linear relationship between the two factors existed for all blends and for all concentrations. The intrinsic viscosity values for all blends and for all polymer ratios were also calculated (Fig. 5b). The intrinsic viscosity values are progressively increased by increasing CS content in the blends, almost linearly for concentrations till 70 wt% CS. This blend has the highest value

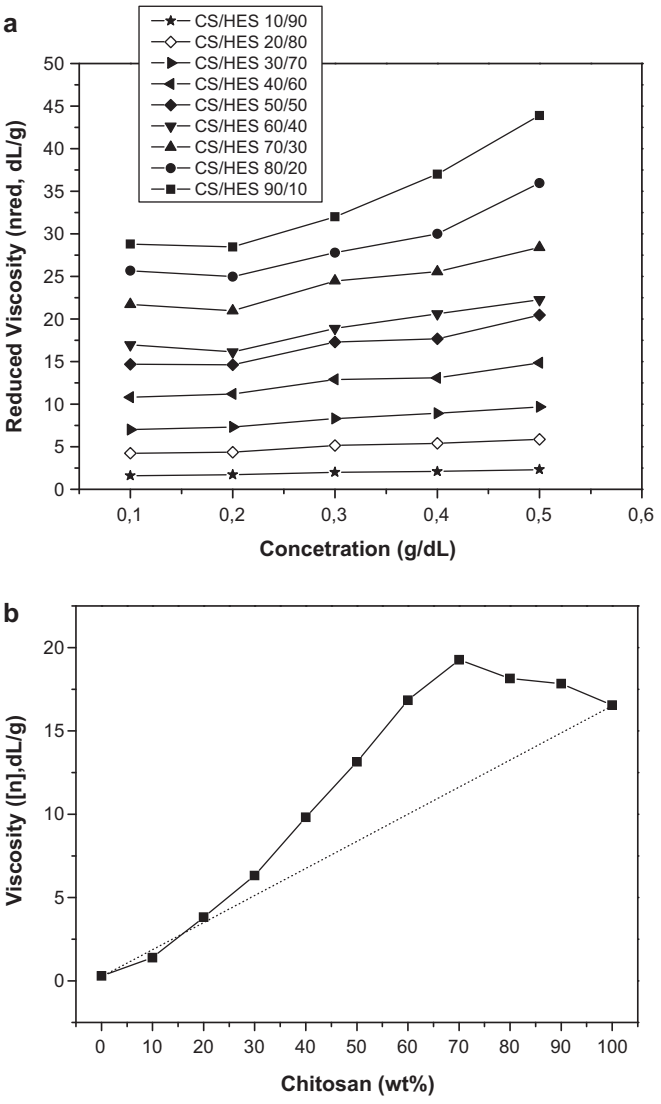

Fig. 5. (a) Plots of reduced viscosities toward blends concentration and (b) intrinsic viscosity values of various CS/HES blends.

and after that the intrinsic viscosity was slightly in the blends containing 80 and 90 wt% CS. However in all the blends the measured viscosities are higher than the linear variation between the neat polymers (dot line), which might indicate a viscous synergism. A similar positive variation was also detected in T_g measurements.

The interaction parameters μ and α were calculated from intrinsic viscosity values by using Chee and Sun equations, respectively. It was found that μ is ranged between 0.09–0.1 and α between 0.02 and 0.2 and thus both interaction parameters are higher than zero indicating that polymer blends are miscible. This is an additional proof that CS/HES are forming miscible blends, as was already verified from the above discussed techniques (SEM, DMA and FTIR).

3.2. Release profiles of ropinirole from CS and HES solid dispersions

The primary aim of the present study was to prepare sustained release formulations of ropinirole drug. Fig. 6 shows ropinirole's release profiles from solid dispersion formulations prepared with neat CS and HES. In formulations prepared with CS (Fig. 6a), the ropinirole release depends from its amount. It is very high in formulations containing 7.5 and 10 wt% ropinirole and the whole amount is released in less than 5 h. In formulations containing 5 and 2.5 wt%

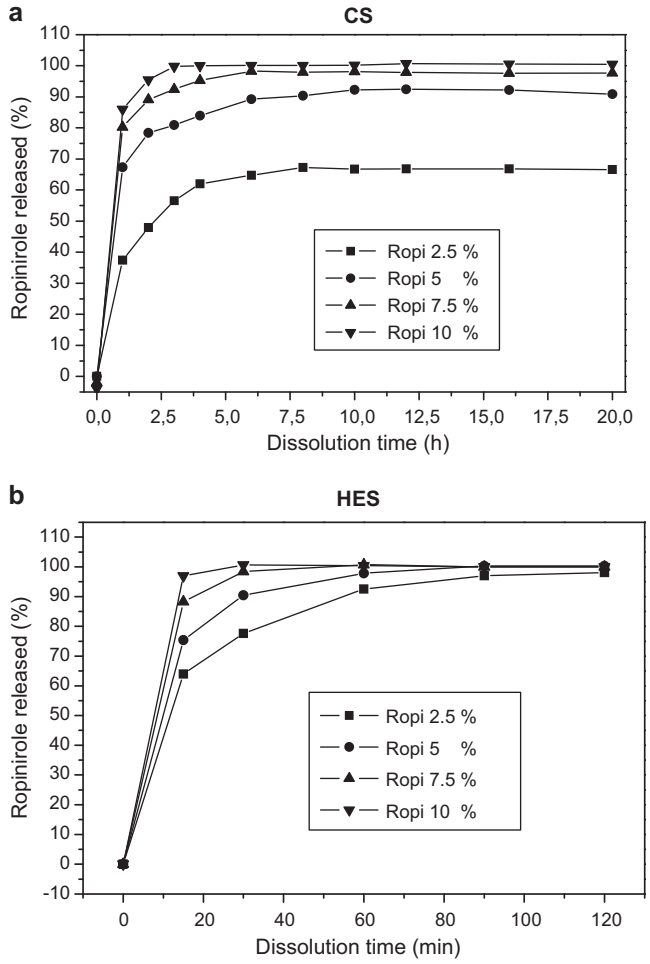

Fig. 6. Ropinirole's release from solid dispersions prepared by solvent evaporation technique (a) chitosan and (b) 2-hydroxyethyl starch.

ropinirole the release became slower. However, in these formulations it seems that a small amount of the drug is blocked within CS matrix and cannot be released any more. When HES was used as matrix the release is much faster, since the whole drug amount is completely released in less than 120 min (Fig. 6b).

The fast dissolution rate of Ropinirole from both matrices could be attributed to its high water solubility. Furthermore, in the case of HES the tablet is disintegrated due to its high solubility in about 2 h while in the case of CS the drug is mainly released through a combination of diffusion and tablet disintegration. CS creates an insoluble tablet and in contact with dissolution medium forms a surface hydrogel, which disintegrates during time. Another factor attributing to high dissolution rate of Ropinirole is the amorphization of the drug usually prepared at solid dispersions (Papageorgiou, Docoslis, Georgarakis, & Bikiaris, 2009; Karavas, Georgarakis, Sigalas, Avgoustakis, & Bikiaris, 2007). The amorphization is attributed to strong interactions taking place between the drug and the polymer carrier (Karavas, Georgarakis, & Bikiaris, 2006b). XRD patterns of Ropinirole solid dispersions (data not shown) in CS and HES showed only two broad peaks for each formulation, attributed to amorphous polymer phases, but no characteristic peak of Ropinirole was recorded.

In both CS/Ropi and HES/Ropi formulations it seems that solid dispersion is not the appropriate technique to prepare sustained release formulations. However, our research team reported in the past that similar blends can provide such formulations based to the differentiation of the blend solubility (Karavas et al., 2006a; Nanaki et al., 2010; Papageorgiou et al., 2008). For this reason formulations of Ropinirole with neat polymers as well as with their blends were prepared by simple physical mixing.

3.3. Release profiles of ropinirole from CS and HES and their blends prepared by physical mixing.

The release profiles of Ropinirole from HES physical mixtures (Fig. 7a) have some small differences to those measured from the corresponding solid dispersions. As can be seen the release is still high as in the case of solid dispersions, but it became much slower. It is characteristic that in formulation containing 10 wt% of ropinirole the drug in physical mixtures is completely released within 90 min, while in the same formulation of solid dispersion this was done in less than 30 min. This is because in the case of solid dispersions the drug was amorphous while in physical mixtures the drug is in crystalline state. However, this differentiation, due to the high solubility of ropinirole has only a small effect in release, which was slightly slower in physical mixtures than solid dispersions. This is because HES has high solubility and its tablets disintegrate completely in about 2 h. The differences are more obvious when CS was used as matrix (Fig. 7b). The release percentages are much slower compared with solid dispersions, especially in the case of formulations containing 2.5 and 5 wt% ropinirole. In all formulations there is an initial fast release attributed to the rapid dissolution of the drugs crystals located at or close to the surface of the tablets. After the burst release period, the rate of release fell as the dominant release mechanism was changed to drug diffusion through the CS matrix (Papadimitriou, Bikiaris, Avgoustakis, Karavas, & Georgarakis, 2008). As can be seen the release is extended till 15–20 h, depending from drug amount.

Hydrophilic polymers such as CS that swell in aqueous media have been widely used as excipients in controlled release tablets. One of their disadvantages is the rapid dissolution of the surface drug, followed by a period of slower release as the diffusion path length increases. This is due to the concomitant hydration and swelling of these hydrophilic and with low solubility polymers when they are in contact with dissolution medium (Gupta, Hariharan, Wheatley, & Price, 2001; Sakiyama, Chu, Fujii, & Yano, 1993). CS is not dissolved in water easily, and first it swells on contact with aqueous solutions creating a hydrocolloid gel mass on its external surface. This mass gradually dissolves or better disintegrates with time. Thus, in the present study CS/HES miscible blends were used as carriers from which the dissolution rates of ropinilore could be modified, compared with those from respective formulations of the neat polymers (HES or CS) alone, in an attempt to prepare extended release formulations. Similar miscible blends consisted from PVP/HPMC and PVP/CS were also used in our previous studies differentiating the release rates of several drugs (Karavas et al., 2006a; Papageorgiou et al., 2008).

CS/HES blends containing 90, 80, 50, 30 and 10 wt% of CS were used and mixed with ropinirole drug at concentrations 2.5 and 5 wt%, which according to the release profiles of Fig. 7b are very close to the expected sustained release. The two polymers were used in order to estimate their ability to differentiate the release behaviour of ropinirole acting as a new matrix for prolonged release formulations of ropinirole. The release percentages using CS/HES blends as matrices are presented for all blends in Fig. 7c and d.

As it is seen by Fig. 7c, compositions of CS/HES blends 10/90, 30/70 and 50/50 w/w containing 5 wt% ropinirole, the drug release is high and the ropinirole is completely released within less than 5 h. Only in compositions CS/HES 80/20 and 90/10 w/w the release was extended till 24 h but is far away from sustained release formulations. Due to the high amount of the used drug and its high solubility the release rate is very high within the first 5–10 h and became slower after that period. When 2.5 wt% of ropinirole were

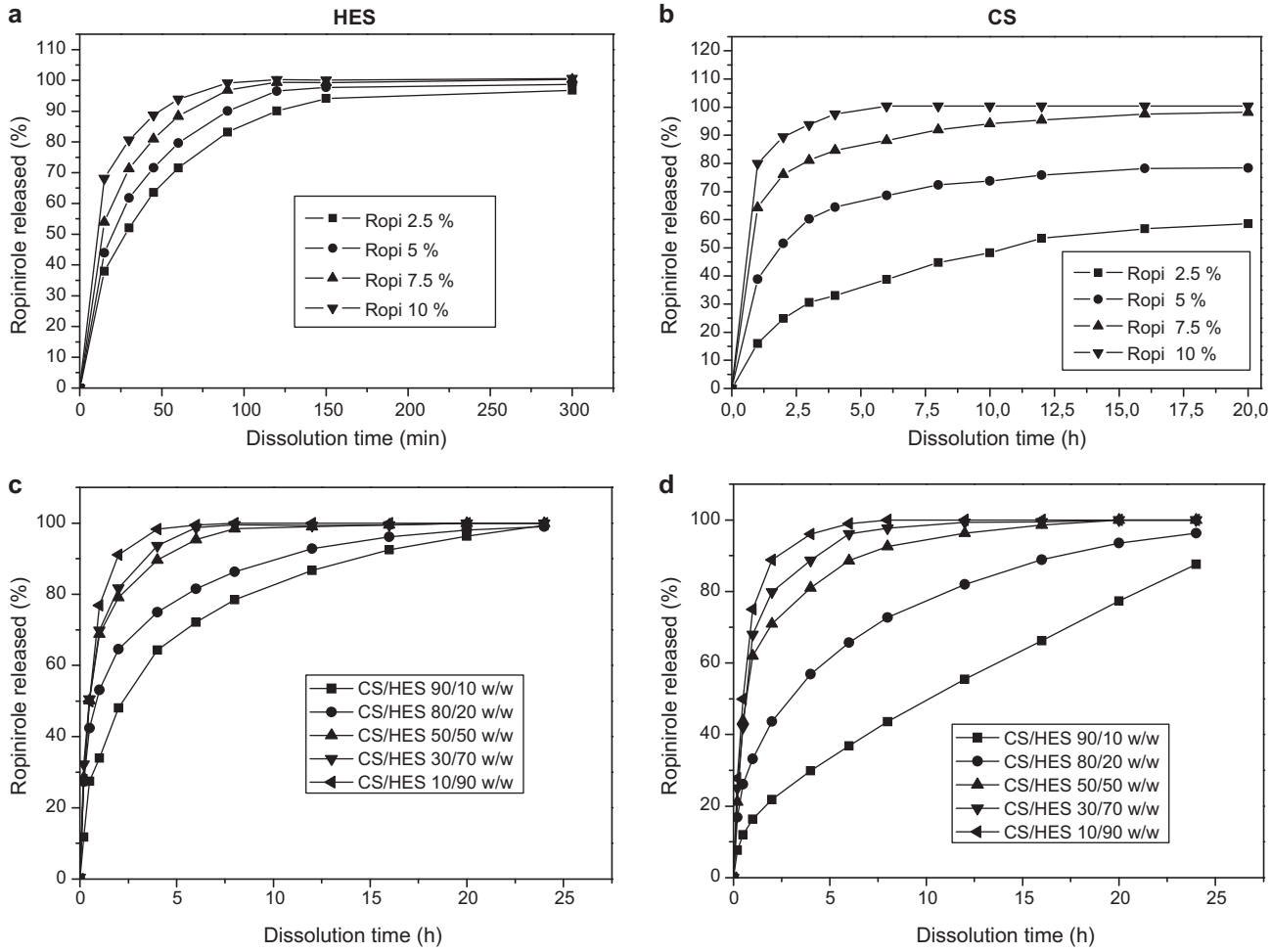

Fig. 7. Ropinirole's release from its physical mixtures with (a) HES, (b) CS and their CS/HES miscible blends with different drug content (c) 5 wt% and (d) 2.5 wt%.

used the release became lower (Fig. 7d) compared with the formulations containing 5 wt% ropinirole. This is because the diffusion rate became slower. In compositions of CS/HES blends 10/90, 30/70 and 50/50 w/w the release rate of ropinirole is high and the drug is completely dissolved within 7.5–10 h. However, in the formulations containing 80 and 90 wt% chitosan the release percentage of ropinirole was gradually reduced and the later shows almost ideal sustained release behaviour. A small burst effect is recorded at the first 2 h, where the 20% of the drug is released, and after that the rate is slower. This behaviour can be explained by the fast dissolution of the surface located drug followed from a diffusion/erosion release. The complexation of HES with CS results in an alteration of the physicochemical characteristics of the latter and the preparation of a new matrix with completely different erosion properties. According to the literature data the delay in the kinetics is strongly influenced by the presence of a gellable or expandable polymeric shell. (Conte, Maggi, Torre, Giunchedi, & La Manna, 1993; Lyu, Sparer, Hobot, & Dang, 2005; Siepmann, Siepmann, Walther, MacRae, & Bodmeier, 2005). This surface hydrogel is formed when the tablet comes in contact with the aqueous solution and water penetrates into the matrix. After that, drug is released due a combination of diffusion and matrix erosion. In our tablets swelling and erosion happen concomitantly since at the initial stages a surface gel is formed in contact with dissolution medium. CS can swell and the resulting dissolution rates through such polymer layers are slow while HES, which has higher solubility, contributes to tablets disintegration. Thus, it can be said that these blends are appropriate to control the release rate of ropinirole drug. Similar results were also mentioned in literature by using analogous gellable polymers, especially with very soluble drugs (Bonferoni, Rossi, Ferrari, Bettinetti, & Caramella, 2000; Nanaki et al., 2010).

To explain the above release behaviour in our samples swelling of CS, HES and their blends was performed at buffered pH = 6.8 and temperature 37 °C, which are the same conditions as in dissolution rates. The swelling ratio is a very important parameter because it describes the amount of water that is contained within the hydrogel at equilibrium and is a function of the network structure (Peppas & Wright, 1998). The swelling ratio and the formed surface gel affect the drug release behaviour from hydrogels (Peppas, Bures, Leobandung, & Ichikawa, 2000). As can be seen in Fig. 8, HES does not swell but a continuous decrease was recorded in its mass during time. This is because HES is very hydrophilic and has also high solubility. Thus, dissolution of HES takes place after immersion into solvent and instead swelling a mass loss was measured. On the other hand CS has the opposite behaviour and swelling ratio increases gradually during time. Furthermore, a rapid swelling stage was observed between 2 and 8 h and after that it was stabilised until 24 h.

Concerning the blends, it can be seen that at initial times (2 h) all the blends have higher swelling ratio than HES or CS. Also, it seems that as the amount of HES increases in the blend, swelling ratio also increases, which was unaccepted due to the high solubility of HES. However, an analogous observation was mentioned by Khurma et al. (Khurma, Rohindra, & Nand, 2005), who studied chitosan/PVP blends as semi-interpenetrating polymer networks. It was found that the degree of swelling increases with increasing

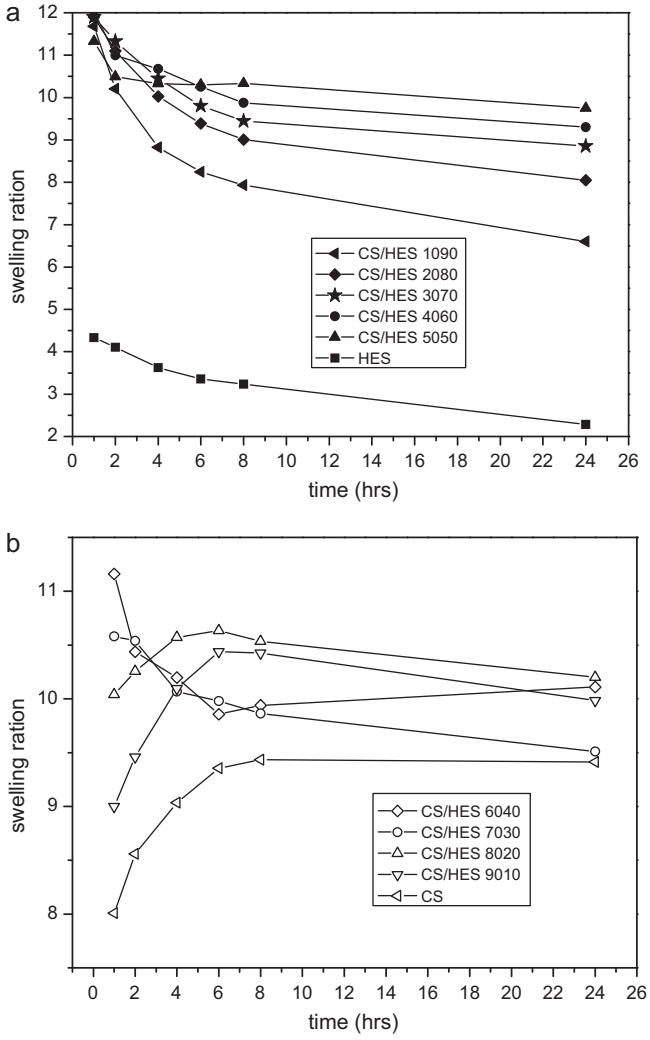

Fig. 8. Swelling ratio of CS, HES and their blends with different ratios at pH = 6.8 and temperature 37 °C.

PVP content in the hydrogel. PVP is more hydrophilic than chitosan and the presence of the ring in PVP may create void volumes within the gel structure due to the irregular arrangement of the chains in the gel. Thus, during swelling water molecules are able to diffuse in to fill up the void volumes without forming hydrogen bonds. A similar explanation could be also possible for our CS/HES blends since HES is more hydrophilic than CS and also its molecular structure is bulkier than the corresponding of CS (Fig. 1).

HES is a branched polysaccharide and thus during complexation with CS higher water molecules can be trapped inside the formed network structure. However, after that time their behaviour is completely different. The blends with high HES content start to disintegrate and thus, swelling ratio decreases rapidly after the first 2 h. The rate of course depends from HES content and thus the blend with 90 and 80 wt% HES have the highest rates. This is because HES is very soluble and can be easily dissolved in buffer solution. In the blends with HES ranged between 40 and 70 wt% the reduction in the swelling ratio after the first 2 h becomes slower and is very small in the blend containing 30 wt% HES. In this blend the swelling ratio after 2 h is 10.5 and after 24 h is just lower, 9.5. The trend is the opposite in the blends with 10 and 20 wt% HES. As can be seen in both blends there is a gradually increase during the swelling time till 6 h and only after that time the swelling rate reduces. This behaviour is almost identical to neat CS and can be explained from the fact that these samples have the highest CS content, 90 and 80 wt%, respectively. In this case it seems that even though HES has higher dissolution rates than CS the interactions taking place between the reactive groups have as result the formation of a new matrix with different properties than initial polymers. It was proved by FTIR spectroscopy (Fig. 4) that the amino group of CS can interact with the hydroxyl groups of HES. Due to this interaction, an inter-molecular hydrogel forms and functions as a retardant to drug release during dissolution testing. A similar behaviour was reported in chitosan and xanthan gum blends (Fukuda et al., 2006). For such retardants, hydrophilic polymers control drug release from tablets by hydrogelation (Peppas et al., 2000). Thus, both these blends give dissolution rates, and especially the blend containing 90 wt% CS (Fig. 7d), very close to sustained release formulations. In these blends, as was already mentioned, Ropinirole is released through a combination of diffusion and tablet disintegration. This is because, at initial times water is penetrated into the formed network and swelling increases due to the high amounts of CS. However, due to the existence of the soluble HES the interactions between CS/HES are weakened and gradually start the disintegration of the matrix. This is in accordance with the swelling of CS/HES 90/10 and 80/20 w/w blends, which after 6 h starts to reduce, since disintegration due to the existence of soluble HES is high.

4. Conclusions

Chitosan and 2-hydroxyethyl starch due to the interactions taking place between their reactive hydroxyl and amino groups can form miscible blends in the entire composition range. The formation of hydrogen bonds was verified by FTIR spectroscopy. According to the Gordon–Taylor equation these interactions are not very strong while only Kwei equation can fit very well the experimental data. Viscometry data proved that these blends are also miscible in their solutions.

Solid dispersions of neat polymers as well as their physical mixtures with ropinirole cannot be used for development of a controlled release formulation. In both cases and especially in HES immediately release formulations are prepared. This is because ropinirole is a very soluble drug and HES dissolves also immediately. However, when CS/HES blends were used containing 80 and 90 wt% CS, some controlled release formulations can be achieved. This is because the release depends on a combination of diffusion and disintegration of the formed matrix. The formulations with higher CS content disintegrate more slowly and the drug is mainly released through a combination of diffusion and matrix erosion.

References

Azeem, A., Iobal, Z., Ahmad, F. J., Kharand, R. D. & Talegaonkar, S. (2008). Development and validation of a stability-indicating method for determination of ropinirole in the bulk drug and in pharmaceutical dosage forms. *Acta Chromatographica*, *20*, 95–107.

Basavaraju, K. C., Demappa, T. & Rai, S. K. (2006). Preparation of chitosan and its miscibility studies with gelatin using viscosity, ultrasonic and refractive index. *Carbohydrate Polymers*, *66*, 357–362.

Berger, J., Reist, M., Mayer, J. M., Felt, O., Peppas, N. A. & Gurny, R. (2004). Structure and interactions in covalently and ionically crosslinked chitosan hydrogels for biomedical applications. *European Journal of Pharmaceutics and Biopharmaceutics*, *57*, 19–34.

Bikiaris, D., Prinos, J., Botev, M., Betchev, C. & Panayiotou, C. (2004). Blends of polymers with similar glass transition temperatures: A DMTA and DSC study. *Journal of Applied Polymer Science*, *93*, 726–735.

Bonferoni, M. C., Rossi, S., Ferrari, F., Bettinetti, G. P. & Caramella, C. (2000). Characterization of a diltiazem–lambda carrageenan complex. *International Journal of Pharmaceutics*, *200*, 207–216.

Chee, K. K. (1990). Determination of polymer–polymer miscibility by viscometry. *European Polymer Journal*, *26*, 423–426.

Chen, T., Bhowmick, S., Sputtek, A., Fowler, A. & Toner, M. (2002). The glass transition temperature of mixtures of trehalose and hydroxyethyl starch. *Cryobiology*, *44*, 301–306.

Conte, U., Maggi, L., Torre, M. L., Giunchedi, P. & La Manna, A. (1993). Presscoated tablets for time-programmed release of drugs. *Biomaterials*, *10*, 1017–1023.

De la Torre, P. M., Enobakhare, Y., Torrado, G. & Torrado, S. (2003). Release of amoxicillin from polyionic complexes of chitosan and poly(acrylic acid), Study of polymer/polymer and polymer/drug interactions within the network structure. *Biomaterials*, *24*, 1499–1506.

Devy, J., Balasse, E., Kaplan, H., Madoulet, C. & Andry, M.-C. (2006). Hydroxyethylstarch microcapsules: A preliminary study for tumor immunotherapy application. *International Journal of Pharmaceutics*, *307*, 194–200.

Fox, T. G. (1956). Influence of diluents and copolymer composition on the glass transition temperature of a polymer system. *Bulletin of the America Physical Society*, *1*, 123–127.

Fukuda, M., Peppas, N. A. & McGinity, J. W. (2006). Properties of sustained release hot-melt extruded tablets containing chitosan and xanthan gum. *International Journal of Pharmaceutics*, *310*, 90–100.

Gordon, M. & Taylor, J. S. (1952). Ideal copolymers and the second-order transitions of synthetic rubbers, I. Non crystalline copolymers. *Journal of Applied Chemistry*, *2*, 493–500.

Guo, Q., Huang, J. & Li, X. (1996). Miscibility of poly(N-vinyl-2-pyrrolidone) with poly(hydroxyether of phenolphthalein) and polyacrylonitrile. *European Polymer Journal*, *32*, 423–426.

Gupta, V. K., Hariharan, M., Wheatley, T. A. & Price, J. C. (2001). Controlled-release tablets from carrageenans: Effect of formulation, storage and dissolution factors. *European Journal of Pharmaceutics and Biopharmaceutics*, *51*, 241–248.

Jayaraju, J., Basavaraju, K. C., Keshavayya, J. & Rai, S. K. (2006). Viscosity, ultrasonic and refractometric studies of chitosan/polyethylene glycol blend in solution at 30, 40 and 50 °C. *Journal of Macromolecular Science, Part B: Physics*, *45*, 741–751.

Jochem, M. & Korber, C. (1987). Extended phase diagrams for the ternary solutions H_2O–NaCl–glycerol and H_2O–NaCl–hydroxyethylstarch (HES) determined by DSC. *Cryobiology*, *24*, 513–536.

Karavas, E., Georgarakis, E. & Bikiaris, D. (2006a). Adjusting drug release by using miscible polymer blends as effective drug carriers. *Journal of Thermal Analysis and Calorimetry*, *84*, 125–133.

Karavas, E., Georgarakis, E. & Bikiaris, D. (2006b). Felodipine nanodispersions as active core for predictable pulsatile chronotherapeutics using PVP/HPMC blends as coating layer. *International Journal of Pharmaceutics*, *313*, 189–197.

Karavas, E., Georgarakis, E., Sigalas, M. P., Avgoustakis, K. & Bikiaris, D. (2007). Investigation of the release mechanism of a sparingly water-soluble drug from solid dispersions in hydrophilic carriers based on physical state of drug, particle size distribution and drug–polymer interactions. *European Journal of Pharmaceutics and Biopharmaceutics*, *66*, 334–347.

Khurma, J. R., Rohindra, D. R. & Nand, A. V. (2005). Swelling and thermal characteristics of genipin crosslinked chitosan and poly(vinyl pyrrolidone) hydrogels. *Polymer Bulletin*, *54*, 195–204.

Lazaridou, A. & Biliadelis, C. G. (2002). Thermophysical properties of chitosan, chitosan–starch and chitosan–pullulan films near glass transition. *Carbohydrate Polymers*, *48*, 179–190.

Lyu, S. P., Sparer, R., Hobot, C. & Dang, K. (2005). Adjusting drug diffusivity using miscible polymer blends. *Journal of Controlled Release*, *102*, 679–687.

Ma, G., Yang, D., Kennedy, J. F. & Nie, J. (2009). Synthesize and characterization of organic-soluble acylated chitosan. *Carbohydrate Polymers*, *75*, 390–394.

Michailova, V., Titeva, St., Kotsilkova, R., Krusteva, E. & Minkova, E. (2001). Influence of hydrogel structure on the presence of water penetration and drug release from mixed hydropropylmethyl cellulose/thermally pregelatinized waxy maize starch hydrophilic matrices. *International Journal of Pharmaceutics*, *222*, 7–17.

Nanaki, S., Karavas, E., Kalantzi, L. & Bikiaris, D. (2010). Miscibility study of carrageenan blends and evaluation of their effectiveness as sustained release carriers. *Carbohydrate Polymers*, *79*, 1157–1167.

Nunthanid, J., Puttipipatkhachorn, S., Yamamoto, K. & Peck, G. E. (2001). Physical properties and molecular behavior of chitosan films. *Drug Development and Industrial Pharmacy*, *27*, 143–157.

Papadimitriou, S., Bikiaris, D., Avgoustakis, K., Karavas, E. & Georgarakis, M. (2008). Chitosan nanoparticles loaded with dorzolamide and pramipexole. *Carbohydrate Polymers*, *73*, 44–54.

Papageorgiou, G. Z., Bikiaris, D., Kanaze, F. I., Karavas, E., Stergiou, A. & Georgarakis, E. (2008). Tailoring the release rates of fluconazole using solid dispersions in polymer blends. *Drug Development and Industrial Pharmacy*, *34*, 336–346.

Papageorgiou, G. Z., Docoslis, A., Georgarakis, M. & Bikiaris, D. (2009). The effect of physical state on the drug dissolution rate. Miscibility studies of Nimodipine with PVP. *Journal of Thermal Analysis and Calorimetry*, *95*, 903–915.

Peppas, N. A. & Wright, S. L. (1998). Drug diffusion and binding in ionizable interpenetrating networks from poly(vinyl alcohol) and poly(acrylic acid). *European Journal of Pharmaceutics and Biopharmaceutics*, *46*, 15–29.

Peppas, N. A., Bures, P., Leobandung, W. & Ichikawa, H. (2000). Hydrogels in pharmaceutical formulations. *European Journal of Pharmaceutics and Biopharmaceutics*, *50*, 27–46.

Ping, Z. H., Nguyen, Q. T. & Néel, J. (1988). Investigations of poly(vinyl alcohol)/poly(n-vinyl-2-pyrrolidone) blends. *Macromolecular Chemistry and Physics*, *189*, 437–448.

Sahoo, S., Sasmal, A., Nanda, R., Phani, A. R. & Nayak, P. L. (2010). Synthesis of chitosan–polycaprolactone blend for control delivery of ofloxacin drug. *Carbohydrate Polymers*, *79*, 106–113.

Sakiyama, T., Chu, C. H., Fujii, T. & Yano, T. (1993). Preparation of polyelectrolyte complex gel from chitosan and k-carrageenan and its pH-sensitive swelling. *Journal of Applied Polymer Science*, *50*, 2021–2025.

Sashiwa, H. & Aiba, S. (2004). Chemically modified chitin and chitosan as biomaterials. *Progress in Polymers Science*, *29*, 887–908.

Siepmann, F., Siepmann, J., Walther, M., MacRae, R. J. & Bodmeier, R. (2005). Blends of aqueous polymer dispersions used for pellet coating: Importance of the particle size. *Journal of Controlled Release*, *105*, 226–239.

Sokker, H. H., Abdel Ghaffar, A. M., Gad, Y. H. & Aly, A. S. (2009). Synthesis and characterization of hydrogels based on grafted chitosan for the controlled drug release. *Carbohydrate Polymers*, *75*, 222–229.

Sun, Z., Wang, W. & Feng, Z. (1992). Criterion of polymer–polymer miscibility determined by viscometry. *European Polymer Journal*, *28*, 1259–1261.

Yichun, Y., Weihua, D., Rui, Z., Hai, L., Nianhua, D., Linbo, G., et al. (2007). Miscibility studies on the blends of collagen/chitosan by dilute solution viscometry. *European Polymer Journal*, *43*, 2066–2071.

Yu, C. Y., Zhang, X. C., Zhou, F. Z., Zhang, X. Z., Cheng, S. X. & Zhuo, R. X. (2008). Sustained release of antineoplastic drugs from chitosan-reinforced alginate microparticle drug delivery systems. *International Journal of Pharmaceutics*, *357*, 15–21.