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Developing hydroxypropyl methylcellulose/hydroxypropyl starch blends for use as capsule materials

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ABSTRACT

Blends of hydroxypropyl methylcellulose (HPMC) with up to 70% hydroxypropyl starch (HPS) were developed for use as hard capsule materials. Polyethylene glycol (PEG) was used as both a plasticizer and a compatibilizer in the blends. In order to prepare hard capsules for pharmaceutical application using the well-established method of dipping stainless steel mold pins into solution then drying at certain temperature, equilibrated solutions with higher solids concentration (20%) were investigated and developed. The solutions, films and capsules of the different HPMC/HPS blends were characterized by viscosity, transparency, tensile testing, water contact angle, SEM, as well as FTIR. The results showed that the blend system is immiscible but compatible in certain degree, especially after adding PEG. The hydroxypropylene groups grafted onto both cellulose and starch improved the compatibility between the HPMC and the modified starch. The higher viscosity of starch at lower temperature improved the viscosity balance of the system, which enlarged the operation window for the dipping–drying technique. The PEG increased the transparency and toughness of the various blends. By optimizing temperature and incubation time to control viscosity, capsules of various blends were successfully developed.

1. Introduction

The medicinal capsules offer better solid dosage form for drugs with low compressibility, slow dissolution and bitter tasting, and require disintegration in stomach as rapidly as possible in the most case. Gelatin has been used to produce pharmaceutical capsules since early 19th century (Jones, 2004b) and still dominates the pharmaceutical capsule materials. However, the higher price of the raw materials and well recognized shortcomings of gelatin capsules, such as animal-derived ingredients, lower soft temperature and the instability of moisture in gelatin, have led to attempts to use replacement substances, such as such as hydroxypropyl methylcellulose cellulose (Al-Tabakha, 2010; Chiwele, Jones, & Podczeck, 2000; Cole, Cadé, & Benameur, 2008; Ku et al., 2010; Ogura, Furuya, & Matsuura, 1998) and modified starch (Eith, Stepto, Wittwer, & Tomka, 1987; Gohil, Podczeck, & Turnbull, 2004; Idrissi, Dumesnil, Michel, & Traisenl, 1991; Stepto, 1997; Vilivalam, Illum, & Iqbal, 2000). Although there are many patents and publications about developing various substances capsules, only few commercial abatable products of non-gelatin capsules has recently been in the market (Jones, 2004a; Zhang, Wang, et al. 2013; Zhang, Liu, Yu, Liu, et al., 2013; Zhang, Liu, Yu, Shanks, et al., 2013). The reasons of less commercial success include higher price of these new products and requirements of establishing new processing facilities or conditions etc. So the development of non-gelatin based blends with lower price to produce capsules using conventional technology and to overcome the shortcomings of gelatin product has both scientific and commercial importance.

HPMC capsules attracted attention because of its vegetal source. The first commercial HPMC capsule was produced in later 1980s and reviewed by Al-Tabakha (Al-Tabakha, 2010) recently. Methyl cellulose (MC) was initially used to develop capsule but unsuccessful because of its poor disintegration in stomach. Several attempts were made later to improve disintegration notably by use of HPMC. HPMC can only dissolve into cold water. HPMC gelling from solution occurs when the temperature is raised (above 70 °C) while it is converted to the gelatin solution as the temperature is decreased. This means that the pins immersed in the dip pan containing the HPMC solution must be of higher temperature (70 °C) in order for the film to be formed. To avoid liquefaction of the films formed on the pins, the temperature of the pins must be further maintained post-dip

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to facilitate gelation until the films dry out in the kilns (Grosswald, Anderson, & Andrew, 2002). In order to improve processing condition and march the conventional processing procedural used for tradition gelatin-based capsule, cooling gelation agents are added into HPMC. The production of HPMC capsules is then by cooling gelation and a gelling system used to lower thermal gelation temperature of HPMC (Al-Tabakha, 2010; Chiwele et al., 2000). The higher price is still one of major hindrances for HPMC capsules, which limits its general application.

Starch is a popular low price food ingredient, and has good film-forming behavior (Arvanitoyannis, Kalichevsky, Blanshard, & Psomiadou, 1994; Arvanitoyannis, Psomiadou, & Nakayama, 1996; Arvanitoyannis, Nakayama, & Aiba, 1998; Li et al., 2011; Liu, Xie, Yu, Chen, & Li, 2009; Psomiadou, Arvanitoyannis, & Yamamoto, 1996; Xie et al., 2009; Yu & Christie, 2005). Starch-based capsules have also been reported (Bae, Cha, Whiteside, & Park, 2008; Ivan Tomka, Dieter Engel, Erich Brocker, & Rico Ménard, 2004; Vilivalam et al., 2000) recently but the small amount of products in the market are mainly soft capsules produced by extrusion with large amount of plasticizer and gelling agent.

A hypothesis made in this investigation is that the relative lower cost hydroxypropyl starch (HPS) has potential for replace certain amount of high price of HPMC since chemically they both are water soluble polysaccharide and have same chemical unite: glucose. Furthermore, both the HPMC and HPS were modified by the same function group hydroxypropylene, which is also expected to improve their compatibility. It is well known that, theoretically, total miscible blends are relatively rare because the Gibb's free energy of mixing is positive due to the negligible change in entropy, as a consequence of high molecular weight of polymers, and with enthalpy term being positive. One of the methods of enhancing the compatibility of polymer blends is to introduce specific interactions (compatiblizer). In this work, poly(ethylene glycol) (PEG) was used as both a plasticizer and a compatibilizer in the blends since it has a good compatibility with both HPMC (Illiger, Fadnis, Demappa, Jayaraju, & Keshavayya, 2009) and starch (Karakatsanis & Liakopoulou-Kyriakides, 1998).

Recently Jimenez (Jimenez, Jose Fabra, Talens, & Chiralt, 2012) used HPMC to reduce retrogradation of native starch and to improve permeability of the starch films casting from lower concentration (2%, w/w) solution. In order to prepare hard capsules for pharmaceutical applications by the well-established method of dipping mold pins into solution and then drying, solutions with higher solids concentrations (up to 20%) were investigated and developed in this work. Both HPMC and HPS have already many pharmaceutical and biomedical applications. Hydroxypropyl starch has been registered in Codex General Standard for Food Additives (1440) and has been widely used as thickness in food industries. Another important advantage expected is the opposite gelling behavior of HPMC and HPS: one is heating gelation and another is cooling gelation, which is expected to balance the gelation properties of the blending system, especially increasing the viscosity of PHMC at lower temperature.

The aim of this work is to develop the HPMC/HPS blends for use as hard capsule through overcoming the shortages of individual material and reducing price. Films with different ratios of HPMC/HPS were prepared by casting. The viscosity of various solutions was studied by viscometry at different temperatures and volubility; and the mechanical properties of the films were studied by tensile testing. The morphologies and compatibility of various HPMC-HPS blends were investigated by transparency, SEM and water contact angle, as well as FTIR. The results are anticipated to be not only used for develop the hard capsule but also explore the relationship between microstructures and performances of the HPMC/HPS blends, especially the blends containing PEG.

2. Experimental

2.1. Materials and solution preparation

A commercially available pharmaceutical-grade HPMC [HT-E15, from Hopetop Pharmaceutical Company, China: viscosity (2%) 6.3 mPa s; pH 6.0; methoxyl content on dry basis 29%; hydroxypropyl oxygen content on dry basis 8.4%.] was used in this work. A food-grade hydroxypropylated corn starch (A1081) with MS (molar substitution) 0.11 was supplied by Penford (Australia). Poly(ethylene glycol) (PEG 400) with molecular weight (NW) 400 was purchased from Sigma. A food-grade carrageenan (kappa, 8833-JCS) was supplied by Ravensw (Australia).

Solutions of 20% concentration were prepared with different ratios of HPMC/HPS (100:0, 90:10, 80:20, 70:30, 60:40, 50:50, 40:60, 70:30, 0:100). Distilled water containing 0.8% carrageenan and/or 2% PEG was used as solvent. The solvent containing carrageenan was firstly prepared by dispersing it in hot water (70 °C) to dissolve the carrageenan into water. The solutions were prepared by heating the solutions to 85 °C for 1hr to gelatinize the starch, and finally cooling the solutions to room temperature to dissolve HPMC. The solutions were then degassed by vacuum for sample preparation and characterizations.

2.2. Casting films and capsule preparation

50 mL of a solution was poured onto a polyethylene plate (15 cm × 15 cm), which was kept as same liquid level to control film thickness. The cast film was dried overnight at 37 °C, similar to capsule manufacture. The dry films were peeled from the plate, placed in a desiccator containing saturated sodium bromide (NaCl) solution, and stored at 73% RH and 23 °C until required for analysis. Separate control films of pure HPMC and pure HPS were prepared in the same way. The weight of the dry films was measured daily until no further measurable weight change was observed, and the thickness of the films was recorded using a micrometer. All films were about 0.15 mm thick with about 8% SD (standard deviation).

The solutions were added 0.8% carrageenan as gelation agent for capsule preparation. Capsules were prepared by dipping stainless steel mold pins (cylindrical, 7 mm diameter) into the solutions and then drying at 37 °C, as described in detail previously (Jones, 2004a). Drying time depended on capsule rigidity, and those containing a higher concentration of starch required a longer drying time, as starch has a stronger hydroxyl bond with water than HPMC. The drying time was increased gradually with increasing starch content. Processability was determined by evaluated the viscosity and gelation temperature of the various blends.

An infra-red heating balance (Model DHS-20) was used to measure moisture content in samples through heating samples to 110 °C for 20 min.

2.3. Viscosity measurements

A Brabender Viscograph-E viscometer (Brabender, Duisburg, Germany) was used to investigate the gel property of the solution by measuring the viscosity variation vs. temperature. Rotor speed of 75 rpm and measuring range of 700 cmg was used for this test. The temperature program was settled as a cycle: heated the solution from 25 °C to 90 °C at 1.5 °C/min firstly, and then cooled the temperature to 25 °C at the same rate.

An R/S-SST viscometer (Brookfield, America) was used to observe the flow pattern and study the effect of shear rate on the viscosity. The shear velocity was increased from 0 r/s to 1000 r/m.

2.4. Transparency measurements

A UV (WFZ UV-3802) spectrum was used to measure the transparency of the different solutions and films. 0.5% of various solutions were placed in a 10 mm × 10 mm square sample container for measurement. A wavelength of 206 nm was used to indicate transparency in this work. The transparency of different films was also measured at a wavelength of 206 nm and divided by thickness and presented as %/mm.

2.5. Mechanical properties

Dumbbell-shaped specimens (gap 50 mm, width 1 mm) were cut from cast films then equilibrated at 73% RH (controlled by NaCl solution) for 48 h before testing. The tensile properties of specimens were measured in accordance with ASTM D638 using an Instron mechanical testing apparatus (Model 3366). Young's modulus, tensile strength and elongation were measured at a crosshead speed of 10 mm/min. Each test trial per film consisted of seven replicate measurements.

2.6. Contact angles measurements

The water contact angles of the different films were measured at room temperature (20 °C) and RH (40%) using an FTA 200 goniometer (Data physics, OCA40 Micro). Measurement was carried out immediately after dropping the water (0.1 mL) onto a sample surface to avoid the effects of receding. The represented results were based on five replicate measurements.

2.7. Scanning electron microscopy

A Phillips XL-30 FEGSEM scanning electronic microscope (SEM) was used to investigate the surfaces of the different films. Specimens were first coated with iridium in a vacuum evaporator using a Sputter Coater (POLARON SC5750), and subsequently viewed in the SEM at a low accelerating voltage of 2 kV.

2.8. Fourier transform infrared spectroscopy

A Tensor 37 (Bruker) spectrophotometer was use to detect the Fourier Transform Infrared (FTIR) spectra of sample (film). In order to remove the effect of environment water, Samples (film) were measured using an ATR model with ZnSe ATR Accessory. FTIR spectra were collected with 64 scans, and the spectral range and spectral resolution were 4000–600 cm^{-1} and 4 cm^{-1} respectively by software OPUS 6.5.

3. Results and discussion

3.1. Transparency of solutions and films

The pure HPMC solution is reasonably clear; while the pure HPS solution is slightly cloudy and opaque, due to the retrogradation of starch, even which had already been significantly decreased through hydroxypropylation (Lan et al., 2010; Liu, Li, Chen, Yu, Chen, & Tong, 2010). The transparency ratios of the different solutions and films measured by UV spectrum are shown in Fig. 1. It is seen that the transparency ratios of both solutions and dried films decreased with increasing HPS content up to 70% content, then increased when the HPS content was higher than 80%. The transparencies of the pure HPS solution and film are higher than that of the solutions and films containing small amount of HPMC (<20%) respectively. This phenomenon indicates the system is immiscible since phase separation results in the low transparency. It has noticed that the decrease rate of transparency for films after additional of HPS is not same as the solutions. The decrease rate of film is higher than that of solutions, which indicates more phase separation occurred during drying processing. It is interesting to notice that addition of PEG slightly increased the transparencies of both the solutions and films, indicating compatibility between HPMC and the starch HPS has been improved by the PEG.

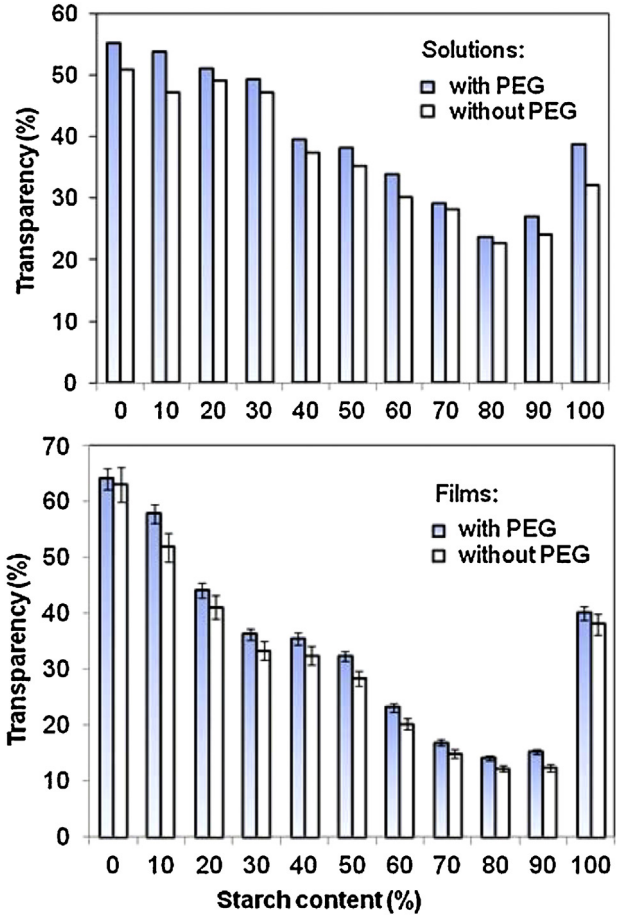

Fig. 1. Transparencies of solutions and films of different HPMC/HPS blends with and without PEG.

3.2. Viscosity of solutions

Fig. 2 shows the viscosities of the solutions with different HPMC/PHS ratios under same shear rate and at different

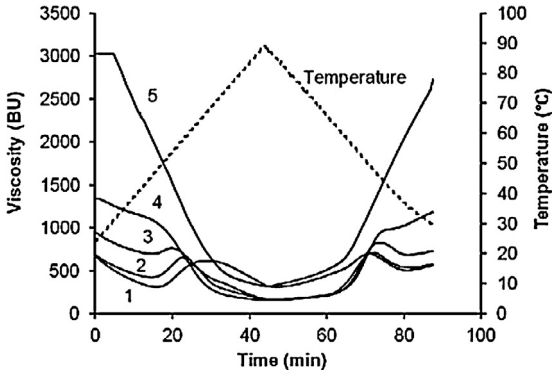

Fig. 2. Effect of temperature on the viscosity of HPMC/HPS blends: (1) 100/0; (2) 70/30; (3) 50/50; (4) 30/70; and (5) 0/100.

temperatures. It is seen that viscosity of the starch HPS is much higher that of HPMC, and the viscosity is increased gradually with increasing HPS content during both increasing and decreasing temperature. The viscosity of pure HPS decreased with increasing temperature as expected. The viscosity of pure HPMC decreased with increasing temperature at lower temperature (<50 °C) then increased in the range between 50 and 75 °C as many previous reported. The acceptable mechanism of thermal gelation of HPMC is the sufficient energy results in the outer layers of water molecules are driven from the cellulose ether chains, and the chains lock and the solution is transformed into a gel (Chen, 2007; Chen & Huang, 2008; Dziezak, 1991; Glicksman, 1969). The viscosity peak of HPMC shafted to shorter time with increasing HPS content. It has noted that the effect of HPS on the viscosity of HPMC is not linear. When the HPS content is lower than 70%, the viscosity peak of HPMC still exists and the peak temperatures are almost same, which provide an operation window for making capsule under similar conditions as pure HPMC. When the HPS is higher than 70%, there is no viscosity peak was observed but just a shoulder was detected (curve-4 in Fig. 2).

Fig. 3 shows the effect of shear velocity on the viscosity of different blends at room temperature. It is seen that the viscosity of HPS is much higher than that of HPMC under lower shear velocity, and the viscosity keeps almost constant after shear velocity is higher (>600 r/s). The viscosity of lower HPS content (<50%) solutions under different shear velocity is almost similar as pure HPMC, which provides important operation window for making capsules since the dipping processing is carried under low shear rate.

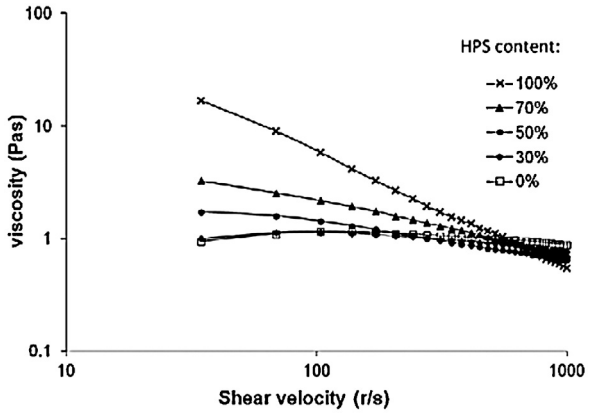

Fig. 3. Effect of shear velocity on viscosity of various blends.

3.3. Surfaces and compositions of various films

Fig. 4 shows the surfaces of various films with different HPMC/HPS contents observed under SEM. It is seen that all of the surfaces are smooth without any phase separation or heterogeneous were observed. The results indicate that the compatibility between HPMC and HPS was improved even they are still immiscible. It was considered that both PEG and hydroxypropyl groups on the modified starch contributed this result since heterogeneous morphology and phase separation were observed for the HPMC/native starch blends without PEG (Jimenez et al., 2012).

Table 1 lists the water contact angles of the different films. As expected both HPMC and HPS are hydrophilic since all the contact angles are <90°. It is noted that the contact angle of the films increased gradually with increasing HPS, which indicates that the starch HPS is more hydrophilic than that of HPMC. Since HPS is more hydrophilic the moisture content in the film containing higher HPS content contains slight more moisture after drying under same condition. The better hydrophilic properties guarantee that the blended materials have good water solubility, which is important for capsule materials. The gradual variation of contact angle also indicates that neither PHMC nor HPS is a continuous phase in different blending contents otherwise the contact angle will

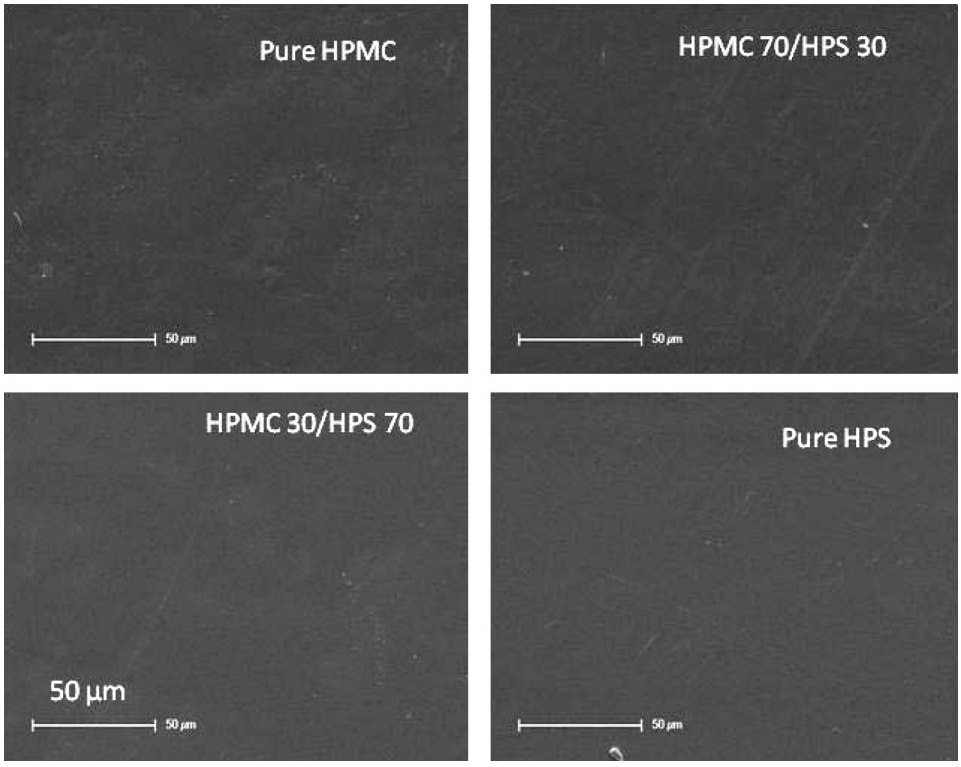

Fig. 4. Surfaces of various films observed under SEM.

Table 1
Water content and contact angles of various blends.

HPMC/HPS ratio	100:0	90:10	80:20	70:30	50:50	30:70	0:100
Water content (%)	16.3 ± 1.8	16.8 ± 1.6	17.1 ± 1.5	17.4 ± 2.1	17.8 ± 2.1	18.2 ± 2.3	18.8 ± 2.2
Contact angle (°)	32.7 ± 0.8	38.9 ± 1.6	42.7 ± 1.9	45.3 ± 2.1	56.1 ± 1.2	76.3 ± 2.4	84.3 ± 3.8

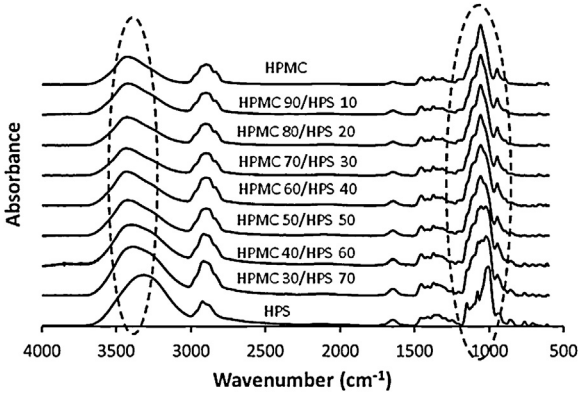

Fig. 5. FTIR spectra of various HPMC/HPS blends.

mainly represents the data of the continuous phase in certain blend contents (Zhang, Wang, et al., 2013).

Fig. 5 shows the FTIR spectra of varicose blends. The pure HPMC film shows some absorbance peak at 3415 (OH stretching vibration), 2927, 2858 (CH stretching vibration), 1634(water in the amorphous region), 1055 cm^{-1} (C—O—C stretching) (Banks, Sammon, Melia, & Timmins, 2005; Gustafsson, Nyström, Lennholm, Bonferoni, & Caramella, 2003; Karavas, Georgarakis, & Bikiaris, 2006; Sammon, Bajwa, Timmins & Melia, 2006; Yin, Luo, Chen, & Khutoryanskiy, 2006). The applications of FTIR-ATR to monitor thermal gelation process of HPMC have been reported previously (Banks et al., 2005; Sammon et al., 2006). The changes of the ν(CO) band shows information about the onset temperature of gelation and the effect of the gel structure on the water hydrogen bonding network was elucidated. The ν(OH) at about 3400 cm^{-1} changes shows the H bonding changes during gelation process.

It has observed that some peaks of similar group in HPMC and HPS are overlapped, and there is no pure individual peak for HPMC and HPS was identified. For example, the —OH stretching of the pure HPS and pure HPMC is at 3309 cm^{-1} and 3435 cm^{-1} respectively. The peak was gradually shifted from 3309 cm^{-1} to 3435 cm^{-1} with increasing HPS content and there is no separated peak was observed. The peak migration and overlapping indicate there is certain degree formation of intermolecular hydrogen bonding. Similar shifting and overlapping phenomenon were also observed in the region between 800 and 1500 cm^{-1}. Similar phenomenons were also observed in modified starch systems (Toti, Soppimath, Mallikarjuna & Aminabhavi, 2004; Prasad, Guru, Shivakumar, Rai, 2008).

3.4. Properties of films and capsules

The mechanical properties of the films with different HPMC/HPS contents were studied by tensile testing, and the results are shown in Fig. 6. It is seen that tensile strength decreased gradually with increasing HPS content. Young's modulus gradually decreased with increasing HPS content up to 60% then increased slightly with more PHS. The lowest point of modulus indicates this is an immiscible system. The elongation of the films gradually increased with increasing HPS content. Generally, the films became softer and tougher with increasing HPS content after equilibration under the same humidity conditions. One of the reasons is that the HPS is more hydrophilic and contains more moisture.

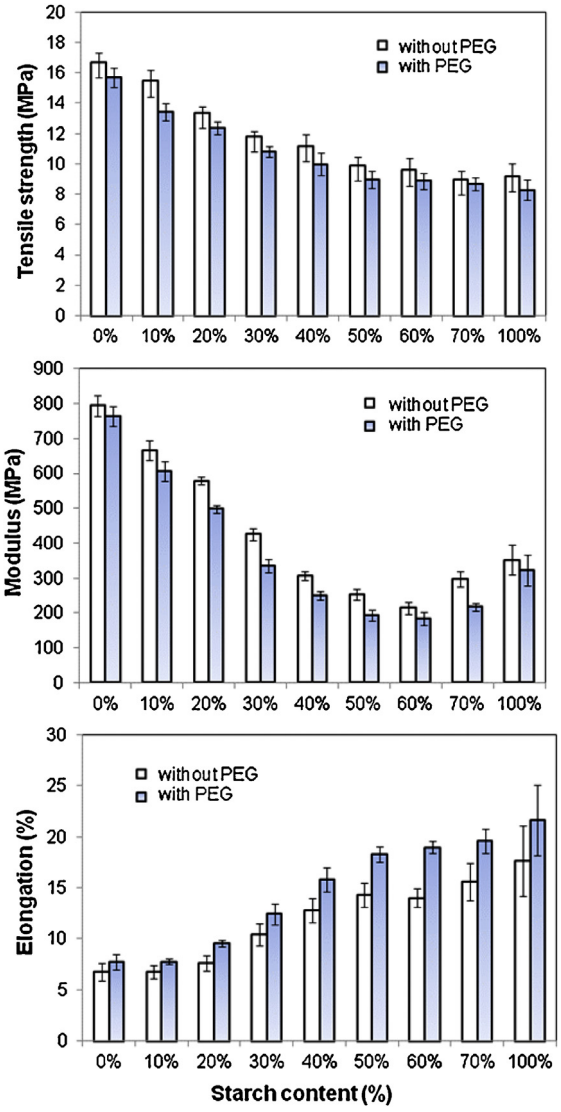

Fig. 6. Mechanical properties of the casting films of different HPMC/HPS blends.

Photographs of capsules made from the solutions with different HPMC/HPS contents are shown in Fig. 7. It is seen that the transparencies of both pure HPMC and HPS capsules are reasonable good, The transparency of the capsules decreased with increasing HPS content, which indicates there is phase separation for the blends, and the results are corresponded with the measurement of film transparencies (see Fig. 1). Capsule wall thickness increased slightly with increasing HPS content under the same dipping conditions, since the HPS increased the viscosity of the solutions. In practical terms, the total solids concentration in blended solutions should be decreased with increasing HPS concentration to reduce the viscosity.

Based on the above results, it is seen that generally the HPMC/HPS blend system is immiscible, but there is a certain degree

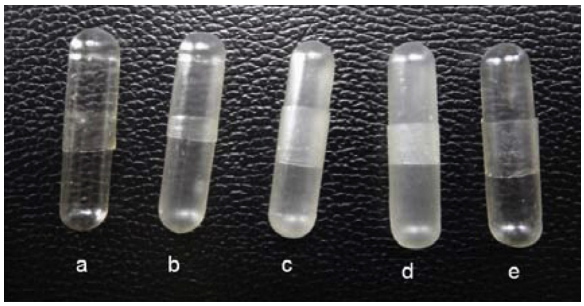

Fig. 7. Photos of capsules made from solutions with different HPMC/HPS contents: (A) 100:0; (B) 70:30; (C) 50:50; (D) 30:70; and (E) 0:100.

of compatibility, especially after addition of PEG. The miscibility and compatibility of the system will be studied in detail in a future work.

4. Conclusions

Blends of hydroxypropyl methylcellulose with hydroxypropyl starch have been developed for use as hard capsule materials. Polyethylene glycol was used as both a plasticizer and a compatibilizer in the blends. The transparencies of both solutions and dried films decrease with increasing HPS content up to 70% content, and then increase when the HPS content is higher than 80%, which indicates the system is immiscible. Adding PEG increases the transparency of the blends, indicating the compatibility between HPMC and HPS has been improved.

The viscosity of the starch HPS is much higher that of HPMC and the viscosity of the blends are increased gradually with increasing HPS content. When the HPS content is lower than 70%, the viscosity peak of HPMC still exists and the peak temperatures are almost same, which provide an operation window of making capsule under similar conditions as pure PHMC. The viscosity of HPS is much higher than that of HPMC under lower shear velocity but is similar and stable at higher shear velocity. The contact angle of the films increases gradually with increasing HPS, which indicates that the starch HPS is more hydrophilic than that of HPMC. The gradual variation of contact angle also indicates that neither PHMC nor HPS is a continuous phase. Migration and overlapping of FTIR peaks indicate there is certain degree formation of intermolecular hydrogen bonding.

In summary, the higher viscosity of the starch HPS at lower temperature improved the viscosity balance of the system, which improved the processibiliy of capsule by the well-established dipping-drying method. Other advantage of the blends include lower price of raw material. Generally, the HPMC/HPS blends show as an immiscible system, but there is certain degree of compatibility, especially after adding PEG. The miscibility and compatibility of the system should be studied in future work.

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