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Mechanistic investigations of phase behavior in Eudragit®E blends

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Abstract

Blends of Eudragit®E (EE) and polymeric excipients using thermal analysis and FTIR spectroscopy were examined. The interactions amongst the blend components were quantified in terms of parameters K_1 and K_2 in Schneider equation and were explained on the basis of interactions between the functional groups of the blend constituents investigated by FTIR spectroscopy. EE formed miscible blends with EC and polyelectrolyte complexes increasing in strength in the order: ES < HPMCP < CAP < EL. From the T_g data the weight fraction of EE in the polyelectrolyte complex was determined. The importance of formulating polyelectrolyte complexes in stoichiometric ratios has been highlighted. The duration over which the release can be sustained by polyelectrolyte complexes has been correlated with equilibrium swelling of the polyelectrolyte complex and parameter K_1 for the first time. This would help in the choice of blend constituents and composition to tailor drug release.

Keywords: Polymer blends; Polymer–polymer interactions; Glass transition temperature; Polyelectrolyte complex; Miscibility; Degree of swelling

1. Introduction

Use of polymers as carriers in drug delivery has been well established. The development of drug delivery systems for newer drugs and design of new dosage forms for existing drugs poses newer challenges in terms of formulation needs and release profiles desired. While the design of new polymers for meeting these needs is being continuously explored, their applications would be delayed because of the time, effort and cost involved in seeking regulatory approvals. Blends of currently approved polymers are used to modulate drug release profiles not otherwise achievable with either of the polymers (Yamada et al., 2001; Sanchez-Lafuente et al., 2002; Lecomte et al., 2003, 2004; Gibaud et al., 2004).

The release profiles from polymer blends depend on the interactions between the constituents at molecular levels, which govern the blend morphology (Kumar et al., 1999). Polymer blends in general are immiscible, since entropy of mixing is small and does not compensate for unfavorable endothermic heat of mixing. The polymer blends become partially miscible, miscible and eventually form polyelectrolyte complexes with increasing degree of interaction. The importance of the phase morphology of polymer blends in controlling the release has been stressed in the past (Edlund and Albertsson, 2000). Pitt et al. (1992) reported that only in miscible blends, composition variation could be used to manipulate drug release. However, this approach was not effective in case of partially miscible and immiscible blends. Lyu et al. (2005) arrived at the same conclusion after a more thorough analysis of phase behavior of polymer blends based on thermal analysis. However, the factors responsible for the observed thermal behavior were not investigated. In summary, studies correlating the polymer–polymer interactions and their implications on phase behavior and drug release have not been reported to our knowledge.

We recently reported the correlation between extent of interactions in blends of a self-associated cationic polymer containing vinylpyridine with ionic and nonionic polymers and their implications for drug release (Menjoge and Kulkarni, 2007). The polymer blends exhibiting highest interactions were found to exhibit diffusion controlled release while those exhibiting weaker interactions, led to initial burst followed by sustained release in acidic medium.

Eudragit®E is used in the oral dosage forms like immediate release tablets, chewable tablets, orally disintegrating and film coated tablets (USFDA, inactive ingredient database). Further, Eudragit®E coatings are used for gastric release, taste masking and controlled release applications. In case of particulate coatings, the surface area is large and large amounts of polymer are

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needed. Daily permissible limits for polymethacrylate derivatives are 2 mg/kg body weight (Kibbe, 2000). Film coatings containing blends of Eudragit®E with other hydrophobic polymers for which daily permissible limits are higher, will enable achieve the desired release profile within permissible limits. pH sensitive hydrogels are being explored for site specific drug delivery in gastrointestinal tract (Said, 2005; Yao et al., 1993). Chitosan–Eudragit®S complexes were recently investigated for the release of diclofenac sodium in colon (Lorenzo-Lamosa et al., 1998). However, complexes based on Eudragit®E and polyacids have not been extensively investigated (Moustafine et al., 2005a).

In this communication we report the results of modulated differential scanning calorimetry (MDSC) analysis of blends of EE with pH dependent and independent polymers and establish the stoichiometry of polyelectrolyte complexes. The molecular interactions responsible for the observed behavior have been identified by FTIR spectroscopy. In the present investigation this technique has been used specifically to predict the availability of free ionizable groups and its implications on swelling response of polymer blends to pH. The results also help select blend compositions, which may contain the desired component in excess over polyelectrolyte complex, or otherwise, depending upon the pH dependent swelling response and the drug release pattern desired.

2. Materials and methods

The film forming polymers: Eudragit®EPO (EE), Eudragit®L 100 (EL), Eudragit®S 100 (ES) (Degussa/Rohm Pharma), Hydroxypropyl methylcellulose phthalate (HPMCP) (Eastman), Cellulose acetate phthalate (CAP) (Eastman) and Ethylcellulose (EC) were gift from Lupin Laboratories Ltd., India, and Zein was purchased from Sigma–Aldrich. The solvents methanol (MeOH) and chloroform ($CHCl_3$) were purchased from Qualigens.

2.1. Preparation of polymer blends

The blends of EE with EC, EL, ES, CAP, HPMCP and Zein were prepared by adding the solutions of these polymers in mixture of methanol and chloroform. The blends were prepared in the range 25–75% (w/w) of EE with other polymers and used for further physicochemical characterization.

2.2. Physicochemical characterization of polymer blends

2.2.1. FTIR spectroscopy

The neat polymers and blend samples were examined by FTIR spectroscopy using Perkin-Elmer model spectrum one in diffused reflectance mode. Two to three milligrams of samples were thoroughly mixed, triturated with potassium bromide (100 mg) and placed in the sample holder. The samples were scanned from 4000 to 450 cm^{-1}. The recording conditions were resolution, 4.0; zero fitting, 2.0; sample scan, 16; acquisition, single sided. The peak assignments for the polymers investigated are as follows:

EE: IR (KBr, cm^{-1}); 2949–2874 (methyl C–H asym/sym stretch); 2821–2770 (methylamino, N–CH_3, C–H stretch); 1728 (C=O, ester); 1454 (methyl C–H asym/sym bend); 1273–1240 (C–O stretch); 1148 (aliphatic amine C–N stretch; C–O stretch, ester). These results are similar to those reported by Lin et al. (1999) and Juppo et al. (2003).

ZEIN: IR (KBr, cm^{-1}); 1657 (amide I, C=O stretching vibrations); 1542 (amide II, N–H bending vibration). These assignments are similar to those reported by Duodu et al. (2001).

EC: IR (KBr, cm^{-1}); 3487 (broad band for OH groups); 2976, 2878 (methyl C–H asym/sym stretch); 1448, 1486 (methylene C–H bend); 1375 (C–H bending), 1131, 1064 (cyclic ether C–O stretch in C–O–C). Bugay and Findlay (1999), reported similar assignments.

EL: 2500–3500 (OH groups); 2950–2997 (methyl C–H asym/sym stretch); 2836 (methoxy (CH_3–O–), C–H stretch); 1723 (esterified carboxylic acid, C=O); 1388, 1449, 1484 (methyl C–H vibrations, asym/sym stretch), 1162, 1269 (ester vibrations). Cilurzo et al. (2003) has reported similar values.

ES: 2500–3500 (OH groups); 2950–2997 (methyl C–H asym/sym stretch); 2839 (methoxy (CH_3–O–), C–H stretch); 1728 (esterified carboxylic acid, C=O); 1388, 1449, 1484 (methyl C–H vibrations, asym/sym stretch); 1150, 1193, 1270 (ester vibrations). These values are similar to those assigned by Cilurzo et al. (2003).

CAP: 3570–3200 (OH group); 2980, 2883 (methyl C–H asym/sym stretch); 1750, 1725, 1701 (C=O ester, carboxylic acid); 1599 (C=C conjugated vinyl, aromatic ring); 1492 (methylene C–H bend); 1284 (ester bond C–O–C), 1140–1071 (cyclic ether C–O stretch in C–O–C); 746 (monosubstituted aromatic ring). Bugay and Findlay (1999) have described similar assignments.

HPMCP: 3460 (O–H groups); 2989, 2884 (methyl C–H asym/sym stretch); 2938 (methylene C–H asym/sym stretch); 2828 (methoxy O–CH_3), 1725 (C=O, ester); 1599 (C=C conjugated vinyl, aromatic ring); 1448, 1486 (methylene C–H bend); 1285 (ester bond C–O–C); 1128, 1067 (cyclic ether C–O stretch in C–O–C); 949 (aromatic C–H in plane bend), 746 (monosubstituted aromatic ring). These assignments are similar to those described by Bugay and Findlay (1999).

2.2.2. MDSC analysis

The neat polymers and polymer blends were subjected to thermal analysis using TA Instruments DSC Q100 V9.0 built 275, using MDSC heat-only method, with nitrogen as purge gas at a flow rate of 50 ml/min. The modulation amplitude was +0.53 °C every 40 s. Indium was used to calibrate the enthalpy and temperature values. The experiments were conducted in crimped sealed aluminium pans. The weight of each sample was in the range 1–2 mg and the heating rate was 5 °C/min from 10 to 200 °C.

2.2.3. Degree of swelling of polyelectrolyte complexes

The degree of swelling was investigated at two different pH conditions (a) acidic medium (pH 1.2) and (b) intestinal buffer of pH 6.8 for 5 h each. The buffers used for the study were hydrochloric acid buffer pH 1.2 (USP 26 NF 21), phosphate buffer pH 6.8 (USP 26 NF 21). The polyelectrolyte complex was exposed to 50 ml dissolution medium in 250 ml jacketed flask, equilibrated at 37 °C, with help of wire holder. The polyelectrolyte complex was removed every 1 h and blotted with tissue paper and weighed. The equilibrium swelling was determined after 24 h. The swelling was calculated as the ratio of difference between the weight of the swollen polymer film (W_s) and the dry polymer film (W_d) to that of the swollen polymer film (W_s).

$$(\%)\,\text{Eq. swelling} = \frac{W_s - W_d}{W_s} \times 100$$

2.3. Miscibility in polymers: theoretical considerations

2.3.1. Thermal analysis

The estimation of the glass transition temperature (T_g) is the most widely used tool to evaluate miscibility in polymer blends. The immiscible blends exhibit two T_gs corresponding to the individual components. In partially miscible blends, the two values shift inwards depending upon extent of miscibility (Schneider, 1996). At the other extreme, when the interactions between the blend components are strong, inter-polymer complexes are formed, which exhibit T_g values higher than the weight average values. The T_g's of individual polymers recorded by us are shown in Table 1.

The simplest framework to correlate T_gs of blends is given by Fox equation:

$$\frac{1}{T_g} = \frac{X_1}{T_{g1}} + \frac{X_2}{T_{g2}} \quad (1)$$

where T_{g1} and T_{g2} represent T_gs of polymers 1 and 2, respectively and X_1 and X_2, are weight fractions of polymers in blend. The T_g's of polymer blends may exhibit both positive and negative deviations from composition dependence predicted by Fox equation. Schneider equation (Schneider, 1997) accounts for both positive and negative deviations from the Fox equation as well as the sigmoidal T_g versus composition curves;

$$\frac{T_g - T_{g1}}{T_{g2} - T_{g1}} = (1 + K_1)W_{2c} - (K_1 + K_2)W_{2c}^2 + K_2 W_{2c}^3 \quad (2)$$

where $W_{2c} = [K'(T_{g1}/T_{g2})w_2]/[w_1 + K'(T_{g1}/T_{g2})w_2]$ is the corrected weight fraction and K_1 is related to the difference in interaction energies of hetero and homo contacts in polymer blend, K_2 accounts for the energetic perturbations in molecular surrounding of the hetero contacts in blend, w_1 and w_2 are weight fractions of component 1 and component 2 in blend, respectively.

The value K_1 is an indication of the extent of interaction between the constituents of the polymer blends. A higher value of K_1 indicates greater number of favorable interactions in polymer blends and participation of larger number of homo and hetero molecular groups in polymer blends. The rate of swelling as well as equilibrium swelling of blends in buffer medium with different pH decreased as K_1 values increased. This significantly retarded the rate of drug release (Menjoge and Kulkarni, 2007). In the present investigations we have quantified the extent of interactions between EE and other polymers in the framework of Schneider equation to predict the morphology of blend.

3. Results and discussion

Polymer blends have been used in the past to achieve release profiles that cannot be achieved using individual components. Recently we showed that the blends based on the new reverse enteric polymer NREP and a wide range of pH independent and pH dependent polymers used as excipients, exhibit increasing levels of interactions depending on the presence and disposition of functional groups involved. The degree of interactions could be quantified in terms of parameters of Schneider equation and explained on the basis of functional group interactions observed by IR spectroscopy.

Eudragit®E is the most widely used cationic polymer in pharmaceutical formulations. We therefore investigated the blends of Eudragit®E with other polymeric excipients using thermal and spectroscopic methods. Higher basicity of dimethyl amino group has been shown to result in polyelectrolyte complexes. The stoichiometric composition of the polyelectrolyte complex has been arrived at from T_g measurements. The strength of the complex which influences the swelling response has been correlated with the parameter K_1. The importance of formulating polyelectrolyte complexes devoid of free polymer and those containing a known excess of either of the constituents in tailoring drug release has been discussed.

3.1. Potential interactions with EE

EE is a terpolymer comprising methyl methacrylate (MMA), butyl methacrylate (BuMA) and dimethylamino ethylmethacry-

Table 1
Glass transition temperatures of neat polymers

Polymer	T_g observed (° C)	T_g reported (° C)	Reference
EE	55.3	44.5, 46	Lin et al. (1999), Eerikainen and Kauppinen (2003)
EL	164	157, 160, 162	Lin et al. (1995, 1999), Cilurzo et al. (2003)
ES	172.8	163, 171, 179	Lin et al. (1999), Cilurzo et al. (2003)
EC	135.8	133.4, 125	Rowe (1984)
HPMCP	137	∼150	Sertsou et al. (2002)
CAP	153.75	140, 160–170	Rao et al. (1999)
Zein	164.4	156, 164, 165	Macoshi et al. (1992), Donnell et al. (1997)

late (DMAEMA). The carbonyl groups from MMA, BuMA and DMAEMA act as proton acceptors and are capable of interacting with the proton donating groups. The nitrogen from DMAEMA group is a strong base. It acts as proton acceptor and is capable of forming hydrogen bonds. The DMAEMA group if free can undergo protonation and cause rapid dissolution of polymer at acidic pH. The hydrogen bonding of DMAEMA with other polymers in blends delays the response of EE to pH, which in turn influences the drug release pattern from the blend. The FTIR investigations were aimed at identifying changes in DMAEMA groups on blending with various polymers and are discussed in the subsequent sections.

The band for carbonyl groups of MMA, BuMA and DMAEMA in EE appears at $1725\,\mathrm{cm}^{-1}$ (Fig. 1). The hydrogen bonded carbonyls show a band at $\sim 1703\,\mathrm{cm}^{-1}$ and the non-hydrogen bonded carbonyl band appears at $\sim 1730\,\mathrm{cm}^{-1}$. The spectrum of EE does not exhibit such a feature indicating absence of self-associations. The carbonyl groups in EE are available for hydrogen bonding and would contribute to formation of miscible blends with other proton-donating polymer. The bands at 2949–2874 and $2821–2770\,\mathrm{cm}^{-1}$, respectively correspond to the basic dimethylamino group in EE. These bands are important and exhibit significant changes due to alteration in the dimethylamino structure of EE (Lin et al., 1999; Moustafine et al., 2005a,b).

EE is a strong polybase, the average $\mathrm{p}K_\mathrm{a}$ of the basic monomer DMAEMA is 8.4 (Tomme et al., 2005) and hence EE acts as a strong proton acceptor. The carbonyl and dimethylamino groups in EE can form hydrogen bonds with acid hydroxyls in polyacids. If a polymer has multiple sites capable of interacting with other polymer, the extent of interaction is enhanced and is reflected in higher K_1 values derived from Schneider equation. Hence, the carbonyl stretching, methyl and methylamino symmetric/asymmetric stretching bands in neat EE were investigated for changes arising as a result of blending with different polymers. The appearance of new bands as a result of polysalt formation was also investigated. The nature of interaction at molecular level has an influence on the ionization of the polymer in the buffer media, and the phase behavior in polymer blends, which influences the release characteristics of the blends.

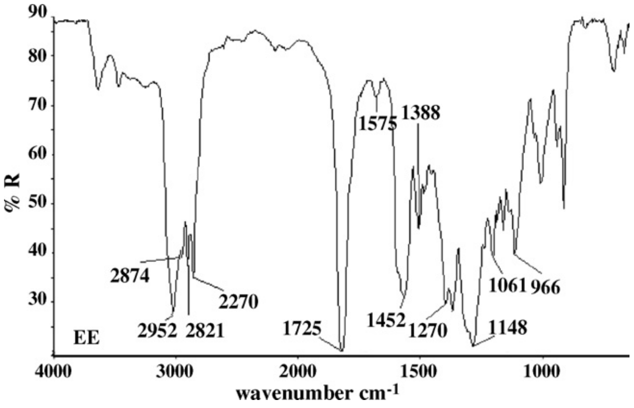

Fig. 1. FTIR spectrum of EE.

3.2. Interactions in polymer blends: quantification and elucidation

3.2.1. EE–Zein blends

The broad band at $1657\,\mathrm{cm}^{-1}$ in Zein corresponds to carbonyl groups in amide I, which are free and involved in intramolecular associations with NH groups. These intramolecular associations in Zein need to be overcome to form miscible blends on blending with EE. Blending of solutions of EE and Zein resulted in immediate phase separation at all compositions. The FTIR spectrum of EE–Zein blend is additive in nature exhibiting no shift in band frequencies corresponding to amide I and II, carbonyl and dimethylamino groups as seen from Fig. 2a and b. The FTIR analysis shows that these polymers do not interact and hence would exhibit phase separation. The FTIR spectrum shows presence of free dimethylamino groups, suggesting these are easily available for protonation resulting in rapid dissolution at acidic pH. The pH response of polymer blends can be predicted from Eqs. (3)–(6).

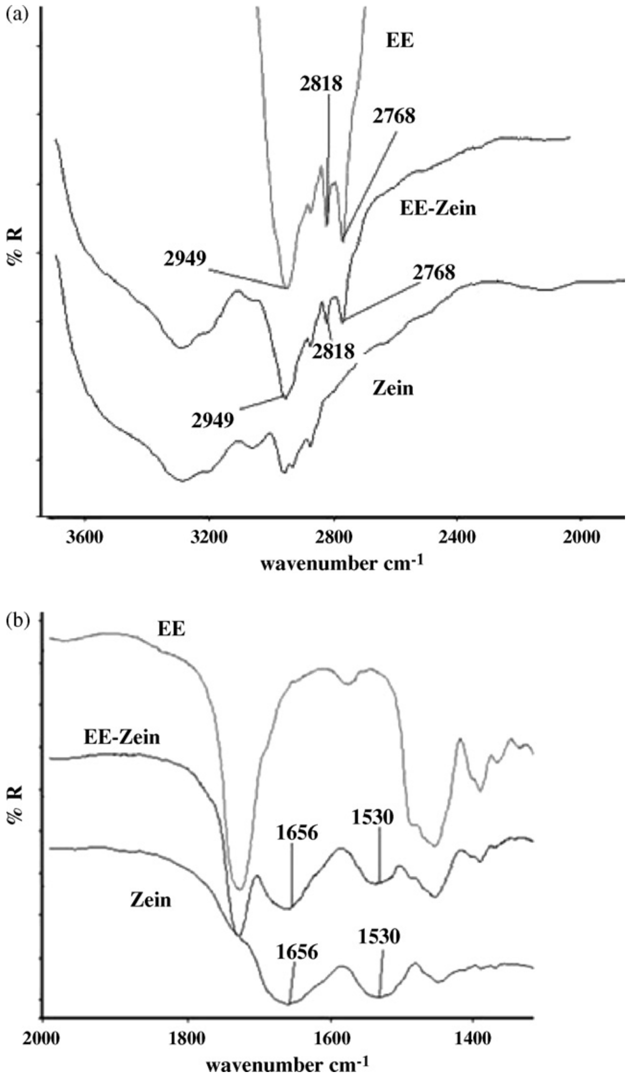

Fig. 2. Scale expanded FTIR spectrum of EE–Zein blends (a) and (b).

As predicted from the FTIR analysis, the EE–Zein blends exhibited complete phase separation at all compositions and this was reflected by appearance of two T_gs at all compositions (Fig. 3). Fig. 3a and b shows the DSC thermograms and T_g versus composition plots for EE–Zein blends. Each T_g corresponds to the phase rich in the constituent polymer. The T_g of neat Zein shifted from 164 to 169–173 °C in blends, while for the EE rich phase the T_g shifted from 55.4 to 45–48 °C. The conformational change from random coil to α and β form in Zein causes partial crystallization and is associated with shift in T_g to higher values. Presence of moisture cleaves the intra and/or intermolecular bonding in Zein, contributing to these effects (Macoshi et al., 1992). The fall in T_g of EE is due to the presence of Zein molecules in between the EE polymer chains. This was confirmed by determining the polymer fractions in each phase. The weight fraction of the two polymers in each phase was calculated from Eqs. (3)–(6) (Kim and Burns, 1990; Chang and Woo, 2003). The fraction of polymer in each phase can be determined from Fox equation (Eq. (1)), which can be rearranged to

$$w'_1 = \frac{T_{g1b} - T_{g2}}{T_{g1} - T_{g2}} \tag{3}$$

and

$$w''_1 = \frac{T_{g2b} - T_{g2}}{T_{g1} - T_{g2}} \tag{4}$$

where w'_1 and w''_1 are the apparent weight fractions of EE in the first T_g transition phase and second T_g phase, respectively. T_{g1b} and T_{g2b} are the observed T_gs of the first and second T_g phase in blends, respectively and T_{g1} and T_{g2} are the T_g's for neat polymers 1 and 2. The overall weight fraction of each phase in blends of EE with Zein was estimated using the following equations:

$$W_{1T} = w'_1 W' + w'_1 W'' \tag{5}$$

and

$$W_{2T} = w'_2 W' + w''_2 W'' \tag{6}$$

where W' is the overall weight fraction of phase rich in polymer component having higher T_g and W'' is the overall weight fraction of phase rich in polymer component having lower T_g. W_{1T} and W_{2T} are the overall weight fractions of EE and the other polymer used in blends, respectively and w'_1 and w''_1 are obtained from the Eqs. (3) and (4), respectively. The values w'_2 and w''_2 were obtained from $w'_2 = 1 - w'_1$ and $w''_2 = 1 - w''_1$.

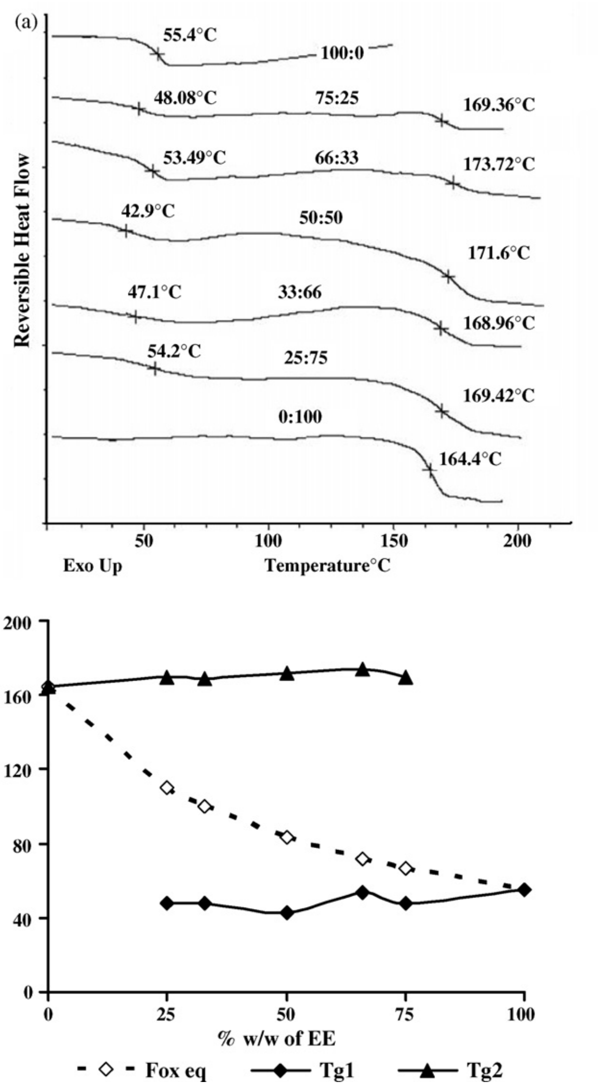

Fig. 3. Thermal analysis EE–Zein blends: (a) DSC thermograms and (b) T_g vs. composition plot.

Table 2
Weight fraction of EE in EE–EC and EE–Zein blends

EE–EC blend	Wt fraction of EE in T_{g1} phase	Wt fraction of EE in T_{g2} Phase	Total wt fraction of EE phase	Total wt fraction of EC phase
25:75	0.92	0.08	0.21	0.78
33:66	0.92	0.08	0.29	0.71
50:50	0.92	0.08	0.42	0.57
66:33	0.92	0.08	0.67	0.32
75:25	1.04	–	0.69	0.30

EE–Zein blend	Wt fraction of EE in T_{g1} phase	Wt fraction of EE in T_{g2} Phase	Total wt fraction of EE phase	Total wt fraction of Zein phase
25:75	1.0	–	0.20	0.80
33:66	1.0	–	0.26	0.73
50:50	1.0	–	0.40	0.59
66:33	1.0	–	0.61	0.38
75:25	1.0	–	0.80	0.19

The data treatment by above equation shows that T_{g1} phase shows negligible Zein and T_{g2} phase too, shows negligible presence of EE (Table 2). This confirms that the increase in T_g of Zein is due to its crystallization. Since both Zein and EE are proton-accepting polymers, they do not interact, which results in immiscibility at all compositions. Literature reveals that the blend composition has often been varied to manipulate drug release, irrespective of the blend morphology. The FTIR and thermal investigations in present work indicate that variation in blend compositions will not significantly alter the initial burst release of drug from EE–Zein blends under acidic pH conditions. Further, the study indicates that if these blends were to be investigated for sustaining the drug release, very large amounts of Zein would be required as these polymers exhibit phase separation. We demonstrated earlier that large amounts of Zein were required to sustain the drug release from immiscible blends containing Zein and polybase containing 4-vinylpyridine (Menjoge and Kulkarni, 2007).

3.2.2. EE–EC blends

EC has many cellulosic hydroxyl groups, which participate in hydrogen bonding with other polymers. EE can form miscible blends with EC via hydrogen bonding involving hydroxyl-carbonyl and hydroxyl-nitrogen groups from EC and EE, respectively. The films of EE–EC blends are translucent and indicate partial miscibility.

The free hydroxyl groups in EC exhibit a band at 3485 cm^{-1}. In EE–EC blend this band appears at the same position along with a shoulder at ∼3200 cm^{-1}, suggesting hydrogen bonding of hydroxyls from EC in intermolecular associations with EE. The hydrogen bonded hydroxyl band appears at 3200 cm^{-1} suggesting weak association between these polymers. Similar shifts were reported in the past (Lee et al., 1988). The carbonyl band in EE appears at 1725 cm^{-1} without a shoulder at lower wavenumber. The EE–EC blend shows carbonyl band splitting in two regions; one corresponding to free carbonyl groups in

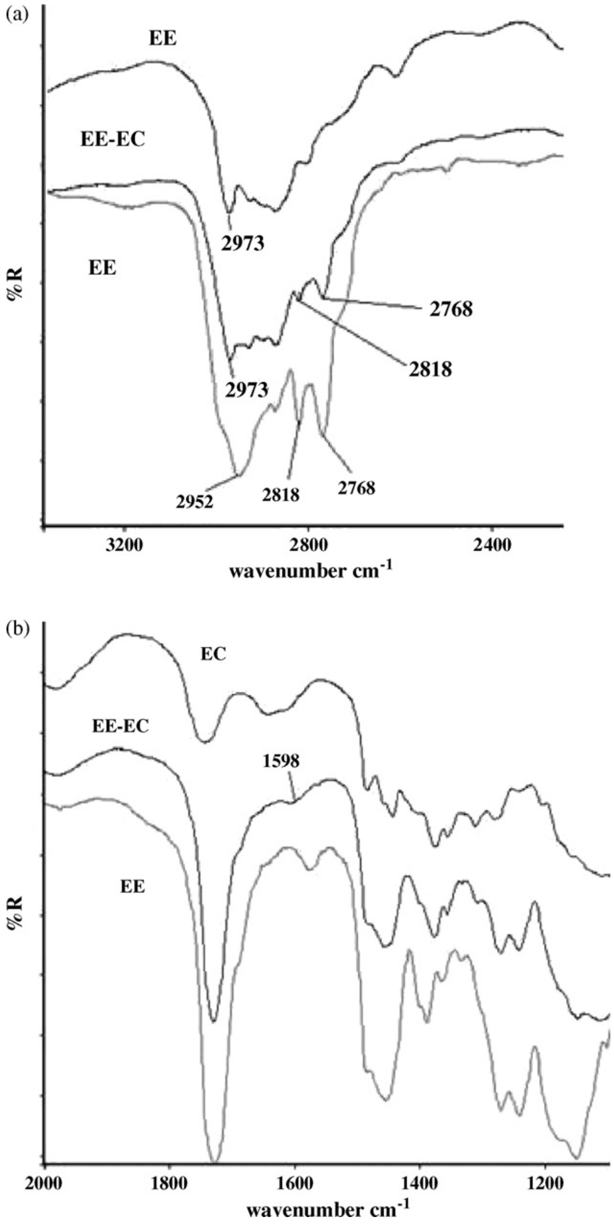

Fig. 4. Scale expanded FTIR spectrum of EE–EC blends (a) and (b).

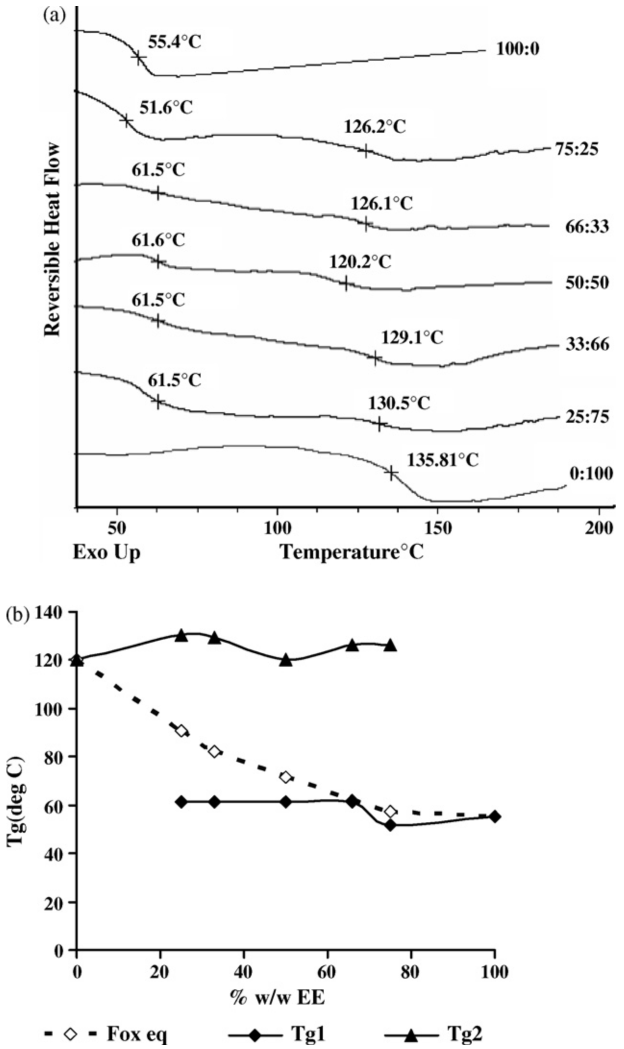

Fig. 5. Thermal analysis for EE–EC blends: (a) DSC thermograms and (b) T_g vs. composition plot.

EE (1727 cm^{-1}) and the other appearing as shoulder at lower frequency (1602 cm^{-1}). This indicates that the carbonyl groups of MMA/BuMA/DMAEMA from EE are involved in hydrogen bonding with hydroxyl groups from EC (Fig. 4a and b). The EE–EC blend spectrum shows fall in intensity of bands for dimethylamino groups at 2770 and 2820 cm^{-1}. This suggests involvement of some of the dimethylamino groups of EE in hydrogen bonding with hydroxyls from EC. The FTIR spectrum shows that these polymers do not interact strongly and so the EE–EC blends can be expected to be partially miscible.

The thermal analysis showed that EE–EC blends exhibit two T_gs (Fig. 5). The EE rich phase shows T_g in the range 51–61 °C and the EC rich phase shows T_g in the range 120–130 °C. The T_gs of EE and EC shift towards each other in blends indicating partial miscibility between the two. The presence of EE in each phase was confirmed by determining the weight fraction of EE using Eqs. (3) and (4). The overall weight fraction of each phase in EE–EC blends was studied using Eqs. (5) and (6). T_{g1} phase was rich in EE component and the T_{g2} phase has negligible EE fraction (Table 2). Small amounts of EC associated with EE raise the T_g of EE rich phase from 55.3 to 61.5 °C.

The results of thermal and FTIR analyses help predict the release pattern from EE–EC blends. The population of free methylamino groups in EE–EC, can readily protonate and cause burst release, while the hydrogen-bonded groups would have to overcome the associations between the dimethyl amino group of EE and hydroxyls in EC before protonation under acidic conditions. The partial miscibility of EE–EC blends has been validated by thermal analysis. The FTIR studies show the presence of free as well as hydrogen bonded dimethyl amino groups in EE–EC blends. Under acidic buffer conditions, the EE–EC blend compositions would show an initial burst release followed by slow release thereafter. Extending the findings for EC–NREP blends, we believe that any alteration of the EE–EC blend compositions would not be very effective in controlling the initial burst release from these blends (Menjoge and Kulkarni, 2007).

3.2.3. EE–EL and EE–ES blends

Both EL and ES are polyacids and contain acid hydroxyl groups. EL is expected to show stronger interactions with EE than ES as it has higher content of methacrylic acid than ES (Eudragit specifications). The free hydroxyl groups in neat EL

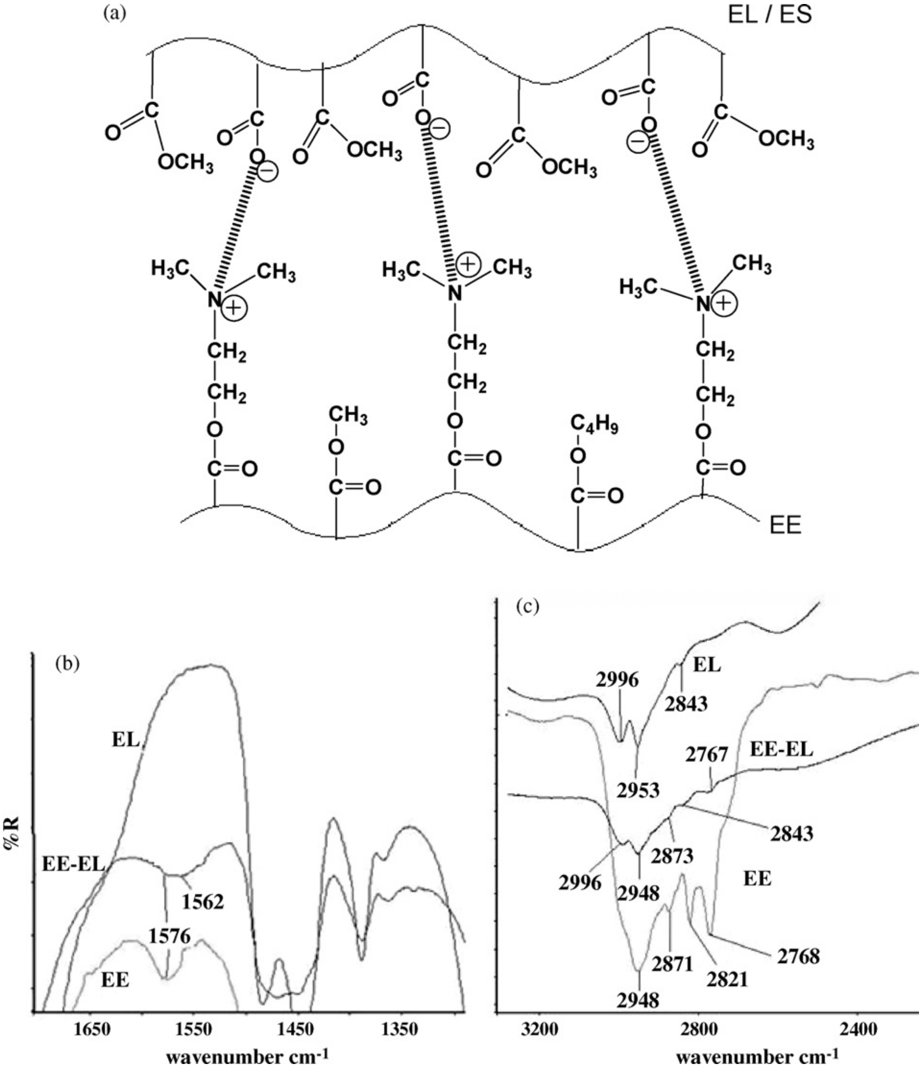

Fig. 6. Schematic representation of interactions between EE–EL (a), scale expanded FTIR spectrum of EE–EL blends (b) and (c).

and ES show a band in the region 3500–3550 cm^{-1} with a shoulder at 3200 cm^{-1}, which indicates hydrogen-bonded hydroxyls. The carbonyl stretching region in spectra of neat EL and ES shows a band at 1727 cm^{-1} corresponding to C=O and a shoulder at 1635 cm^{-1} arising from the hydrogen bonding between the acid hydroxyls (COOH) and the carbonyl from the acrylic groups. Our findings are similar to those reported by Lin et al. (1995).

Blending non-aqueous solutions of EE with EL and ES, respectively, in the composition range investigated, resulted in polyelectrolyte complexes. The spectra for EE–EL and EE–ES blends are shown in Figs. 6 and 7 and the schematic representation shows the nature of hetero contacts in these blends (Fig. 6a). Blending of EE with EL and ES is expected to show changes in the hydroxyl, carbonyl, methyl and methyl amino stretching region. The hydroxyls from the carboxylic acid of EL can form hydrogen bonds with the dimethylamino groups of DMAEMA or the carbonyl from MMA, BuMA and DMAEMA of EE, respectively.

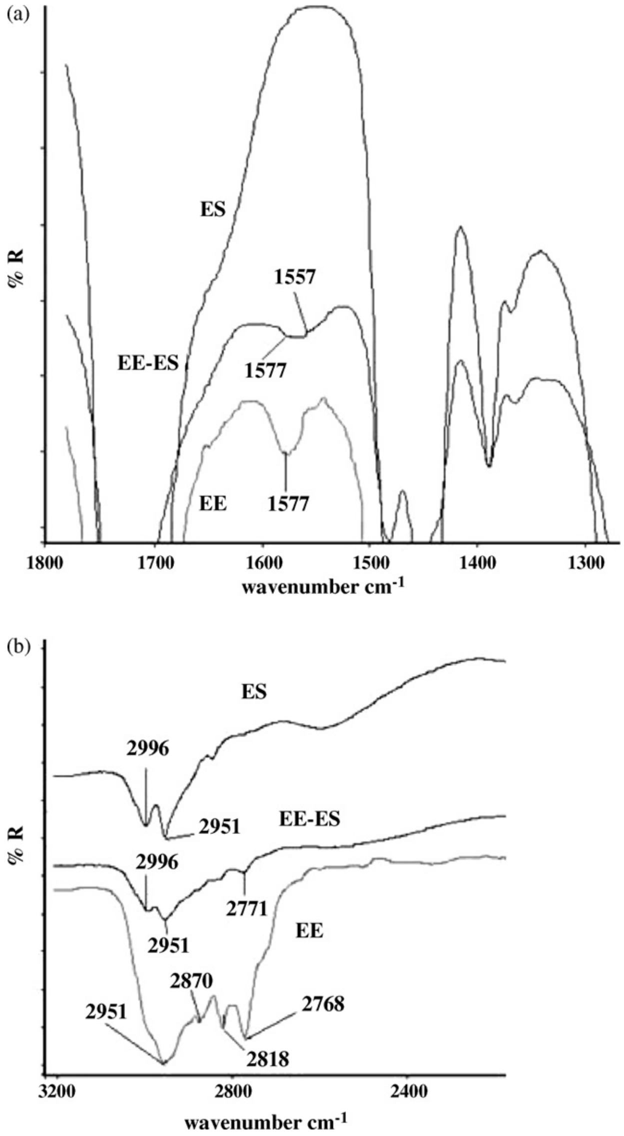

Fig. 7. Scale expanded FTIR spectrum of EE–ES blends (b) and (c).

The band for free hydroxyl group in neat EL shifts to +74 cm^{-1} from 3591 cm^{-1} in the EE–EL blend. Further, this band shows a shoulder at 3210 cm^{-1} confirming the presence of hydrogen bonded hydroxyls. Similar results were

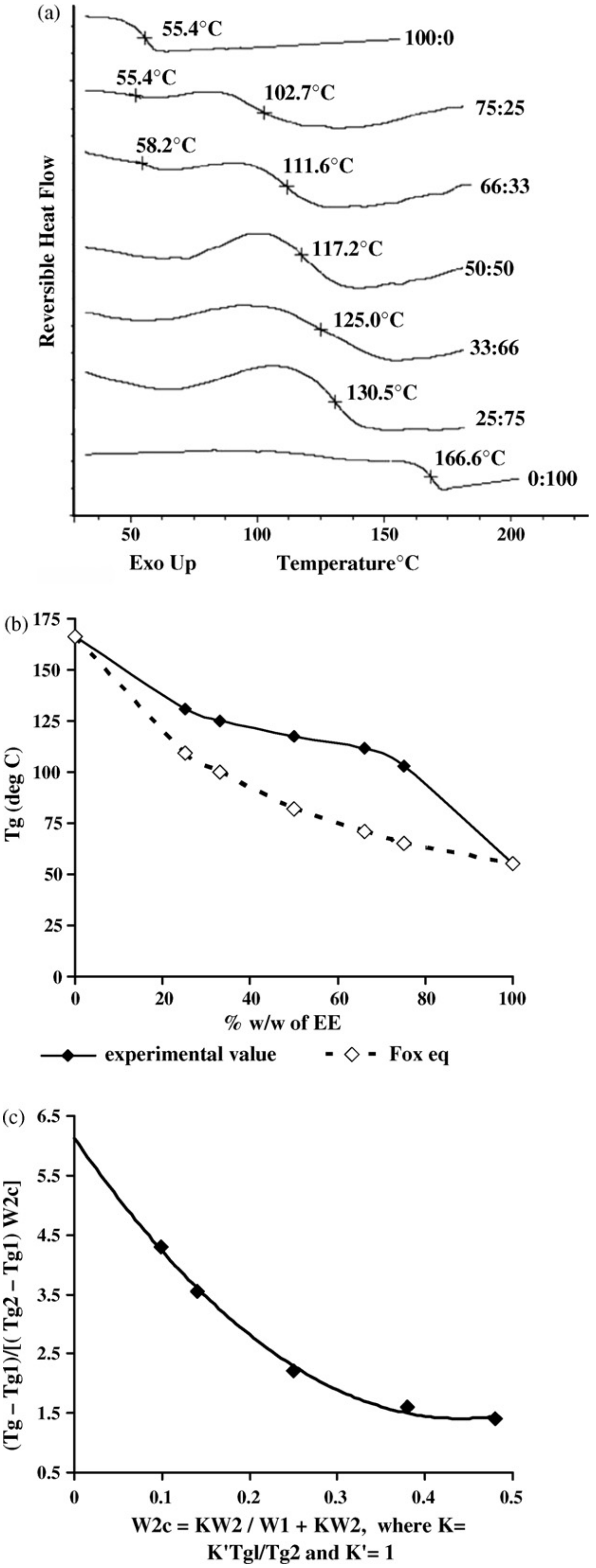

Fig. 8. Thermal analysis of EE–EL blends: (a) DSC thermograms, (b) T_g vs. composition plot and (c) plots for Schneider equation.

obtained for the EE–ES blends, which showed a shift of +61 cm^{-1} (3609 cm^{-1}) for free hydroxyl groups and a shoulder at 3224 cm^{-1} for hydrogen bonded hydroxyls. The shift is lower in EE–ES (+61 cm^{-1}) as compared to EE–EL (+74 cm^{-1}) blends suggesting lower extent of interaction between EE–ES.

The carbonyl bandwidth in EE–EL blend (1725 cm^{-1}) appears narrower than that seen in neat EL. The self-association between the carboxylic carbonyls and hydroxyls within EL is overcome on blending with EE and the carboxylic hydroxyl now participates in interpolymer association with EE. This liberation of carboxylic carbonyl from self-association is reflected in the appearance of band at 1725 cm^{-1} and another new band at 1562 cm^{-1} (Fig. 6b). The new band at 1562 cm^{-1} is for the carboxylate salt formed due to the charge transfer between EE and EL. Similar shifts were reported by Moustafine et al. (2005a,b). The carbonyl stretching region of EE−ES shows similar feature as seen for EE–EL (Fig. 7a) and a new band for carboxylate salt appears at 1559 cm^{-1}.

The scale expanded spectrum of EE–EL and EE–ES blends shows disappearance of the bands for methyl (sym/asym) and methylamino (sym/asym) stretch at 2949–2874 and 2821–2770 cm^{-1}, respectively (Figs. 6c and 7b). This change is associated with proton transfer to the methylamino group in EE, resulting in carboxylate salt formation. Similar findings were reported by Lin et al. (1999) and Moustafine et al. (2005a,b). The intermolecular associations between EE–EL and EE–ES are strong. The charge transfer results in polyelectrolyte salt formation. From the FTIR results it is expected that EE–EL and EE–ES blends should exhibit single, composition dependent T_g values and large positive deviations from Fox equation.

The T_g versus composition curves for polyacid–polybase systems involving charge transfer result in large positive deviations from additivity, and exhibit either convex or sigmoidal behavior (Schneider, 1997; Jiang et al., 1999). Fig. 8a shows DSC thermograms for EE–EL and Fig. 8b shows T_g versus composition plots. The experimentally obtained T_g values for EE–EL blends show large positive deviations from the weight average values of T_gs calculated from Fox equation. The T_g values of the EE–EL polyelectrolyte complexes are in the range 102–130 °C and are greater than the weight average T_g value by 20–30 °C. Strong intermolecular hydrogen bonding restricts the motion of polymer segments leading to increase in T_g. The data treatment by Schneider equation (Fig. 8c) for EE–EL blends resulted in $K_1 = 5.13$ and $K_2 = 24.35$, respectively (Table 3). The higher values of K_1 indicate that interaction energy of the hetero contacts exceeds that of average homo molecular contact.

From the FTIR spectrum for EE–EL blend it was concluded that the hetero contact between the acid hydroxyl of EL and tertiary nitrogen of methylamino group was accompanied by charge transfer. The local chain orientations between the blend components, contribute to favorable hetero contacts, which results in a closer packing of the polymer blend yielding higher T_g values than predicted from additivity. The local interchain orientation contributes to conformational redistributions. The large K_1 values are also associated with large K_2 values. Schneider (1997) cited similar observations. K_2 (24.35) > 0 indicates more conformational change in EE environment than in EL. As a result of charge transfer, the stiffening of the donor chain takes place contributing to higher T_g values. Schneider (1997) reported that for absolute values of $[K_2] > [K_1]$ the T_g versus composition curves were S shaped. Our findings are similar as seen from the sigmoidal curves obtained for EE–EL blends.

At blend compositions 25–50% (w/w) of EE, single composition dependent T_g was observed. However, beyond this range, two T_gs are observed. Compositions containing 66 and 75% EE, exhibited a weak transition at 58 and 55 °C along with the major transition corresponding to the polyelectrolyte complex at 102 and 111.6 °C, respectively. This indicates that the phase rich in EE is not miscible with the polyelectrolyte complex. At higher concentrations of EE, all the carboxylic hydroxyls of EL are consumed in interaction with methylamino groups and a large number of dimethyl aminoethyl groups are present in free form. Fig. 9a shows DSC thermograms for EE–ES blends and Fig. 9b shows T_g versus composition plots. As seen in case of EE–EL blends, the EE–ES blends show positive deviations from the weight average values of T_gs calculated from Fox equation. The T_g values of the EE–ES polyelectrolyte complex are lower than those seen in EE–EL blends because of lower extent of interaction between the two. The K_1 and K_2 values obtained for EE–ES blends are 2.11 and 6.58, respectively (Fig. 9c and Table 3). The lower content of methacrylic acid in ES reduces the extent of interaction between EE–ES ($K_1 = 2.11$, $K_2 = 6.58$) as compared to EE–EL ($K_1 = 5.13$, $K_2 = 24.35$).

The T_g versus composition plots (Fig. 9b) of EE–ES are convex, characteristic of hydrogen-bonded blends. The blends containing 25–66% (w/w) of EE exhibit single composition dependent T_g. At higher concentrations the T_g is comparable to the weight average value. Increase in EE content to 75:25% (w/w), results in appearance of two T_gs. A weak transition around 58 °C along with the major transition corresponding to the polyelectrolyte complex at 82 °C is seen. This indicates that the phase rich in EE is not miscible with the polyelectrolyte complex. At higher concentrations of EE, all the carboxylic hydroxyls of ES are consumed in interaction with methylamino groups in EE forming polyelectrolyte complex and excess dimethyl aminoethyl groups appear in free from. Similar behavior was observed in EE–EL blends.

The weight fractions of EE in EE–EL and EE–ES blends containing EE in excess over the polyelectrolyte complex formed were calculated from Eqs. (3) and (4). The EE–EL blend containing 66% (w/w) of EE had an EE rich phase containing 97% EE and the polyelectrolyte complex contained 57.1% EE. The EE–EL blend containing 75% (w/w) of EE had only EE in the EE rich phase and 48.3% EE in the complex. The EE–ES blend

Table 3
Parameters of the Schneider equation

Blend	$K = T_{g1}/T_{g2}$	K_1	K_2	$K_1 - K_2$
EE–EL	0.33	5.13	24.35	−19.22
EE–CAP	0.36	5.10	22.15	−17.05
EE–HPMCP	0.40	2.76	7.45	−4.69
EE–ES	0.32	2.11	6.58	−4.47

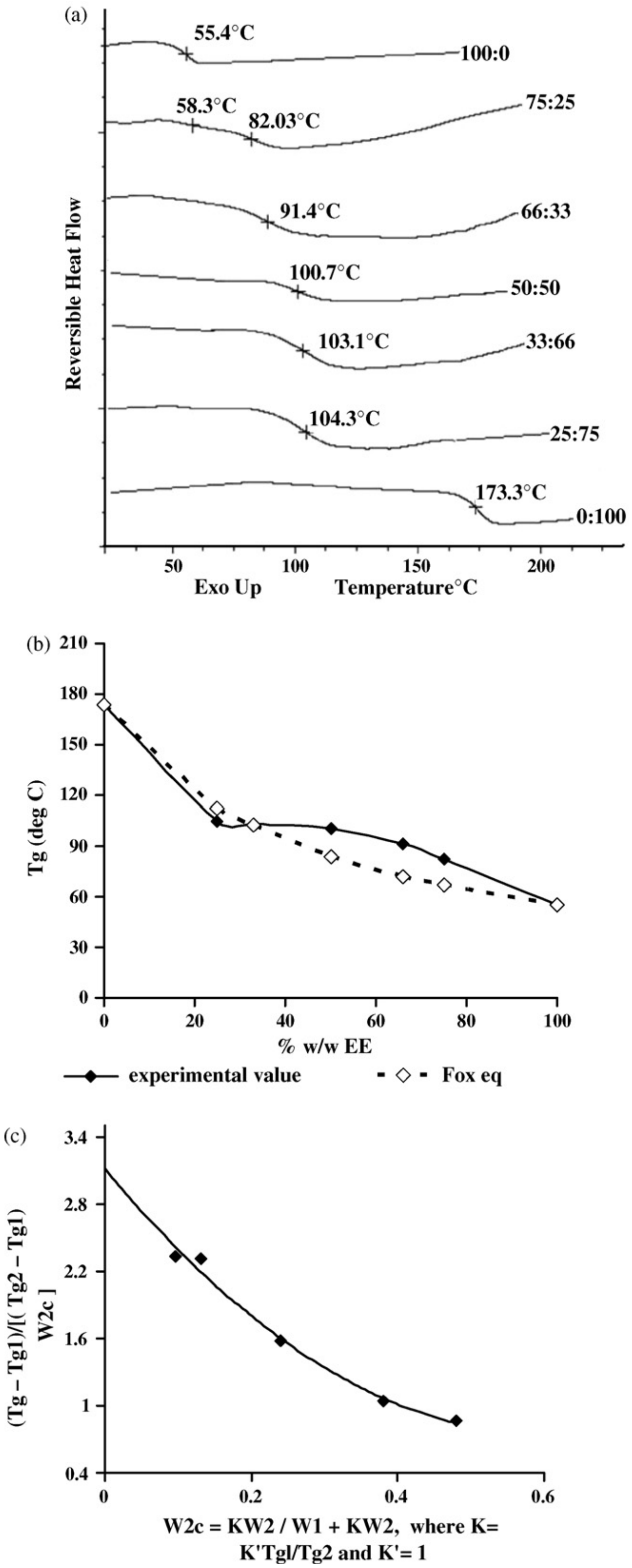

Fig. 9. . Thermal analysis EE–ES blends: (a) DSC thermograms, (b) T_g vs. composition plot and (c) plots for Schneider equation.

containing 75% (w/w) of EE had 97.7% EE in EE rich phase and 77.4% EE in the complex.

The release behavior of the polymeric carriers is predicted from their swelling characteristics (Moustafine et al., 2005a). The swelling characteristics of the pH sensitive hydrogels depend on the ionizable groups available and also the presence of defects or loops containing free ionic groups (Moustafine et al., 2005b). Once the polyelectrolyte complexes are formed, they are insoluble in most aqueous and non-aqueous solvents (Olabisi et al., 1979). The polymer not involved in complexation but entrapped within the complex is difficult to extract. The estimation of stoichiometry of polyelectrolyte complexes in EE–EL and EE–ES blends helps formulate polyelectrolyte complexes devoid of free polymer, which will sustain drug release over extended time periods. By deliberately using a known excess of either polymer, the swelling of the blend in either acidic or basic pH can be enhanced and the drug release expedited. The pH response of hydrogels based on acrylamide and crotonic acid varied with composition (Karadag et al., 2005). The hydrogels containing carboxymethyl cellulose and polyvinylamine exhibited minimum swelling at 1:1 ratio as compared to the gels containing excess of each phase (Feng and Pelton, 2007). Kokufuta et al. (1998) reported that swelling response of the gels varied with distribution of acrylic acid groups in gels. Thus, the knowledge of polyelectrolyte complex stoichiometry and phase distribution helps formulate blends to elicit desired release profile.

3.2.4. EE–CAP and EE–HPMCP blends

Blending of EE with HPMCP and CAP resulted in complex formation almost immediately as a result of strong interaction. Both CAP and HPMCP contain cellulosic hydroxyls in addition to acid hydroxyls. The carboxylic groups in CAP and HPMCP are attached to the aromatic ring and are therefore more amenable to dissociation due to stabilization effect of the ring. The schematic representation of interactions between EE–CAP and EE–HPMCP is shown in Figs. 10a and 11a. Propyl and methyl groups in HPMCP contribute to steric hindrance, limiting its interaction with EE. We believe that CAP with only acetate groups attached to cellulose structure, would exhibit stronger interactions with EE than HPMCP.

The FTIR spectra of EE–HPMCP and EE–CAP complexes are shown in Figs. 10 and 11, respectively. Both spectra show overall band broadening and fall in intensity as a result of strong interactions. FTIR spectra of CAP and HPMCP show bands for free hydroxyl groups at 3483 and 3473 cm^{-1}, respectively. The carbonyl band appears at 1725 cm^{-1} for both CAP and HPMCP and shows a shoulder at lower frequency (~1635 cm^{-1}). This indicates self-association in these polymers arising out of hydrogen-bonded carbonyl with acid hydroxyls or cellulosic hydroxyls. The spectra of EE–HPMCP and EE–CAP blends show band broadening in hydroxyl stretching region 2500–3000 cm^{-1}. The band for free hydroxyl group of HPMCP shifts from 3473 to 3477 cm^{-1} and a broad structureless shoulder appears at ~3200 cm^{-1}. Similarly, the EE–CAP blends show a band corresponding to free hydroxyl at 3550 cm^{-1}, which when compared to that of neat CAP shows a shift of +67 cm^{-1} from

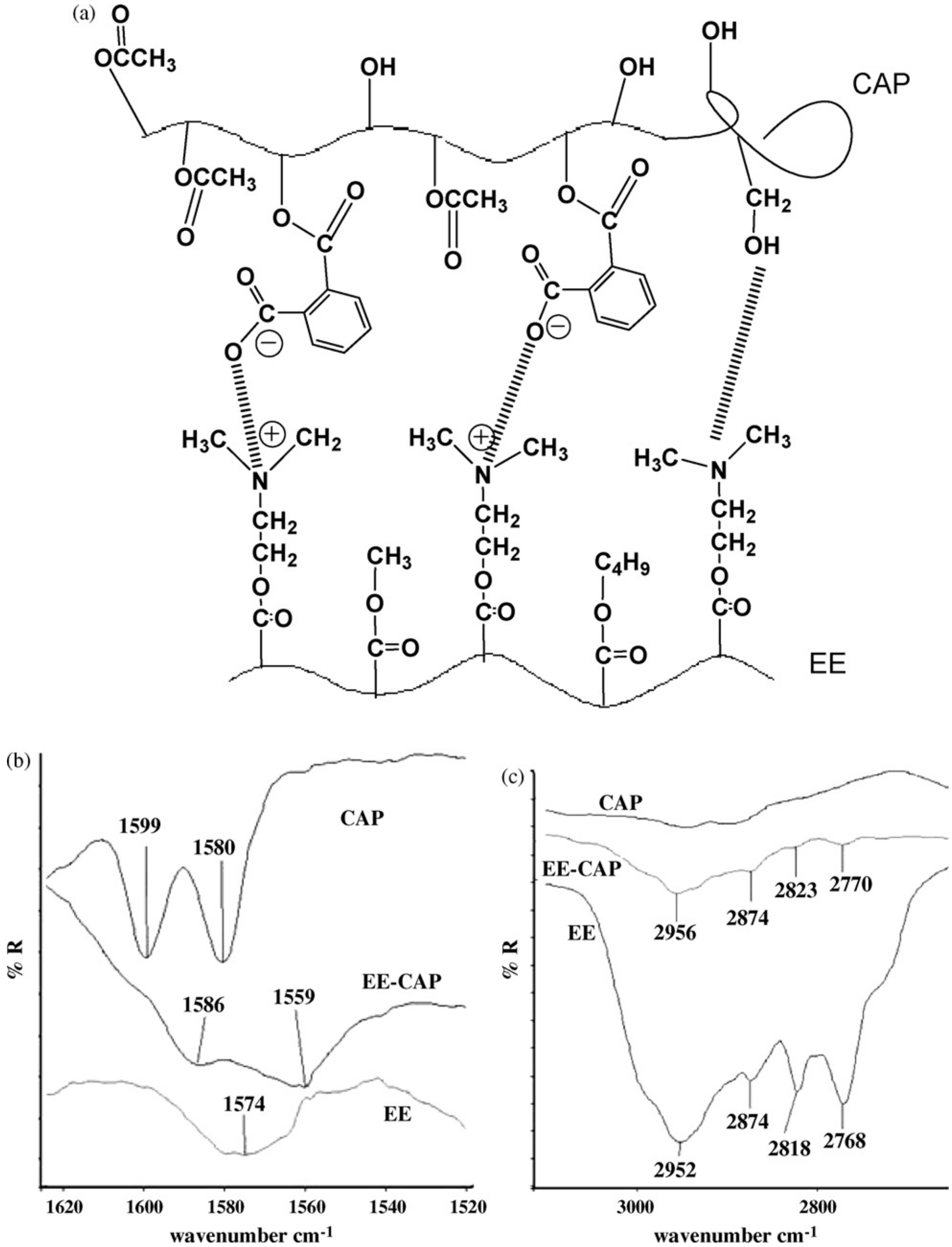

Fig. 10. Schematic representation of nature of interactions in EE–CAP blends (a) and the scale expanded FTIR spectrum of EE–CAP blends (b) and (c).

3483 cm^{-1}. The band for free hydroxyl in EE–CAP blend shows a prominent shoulder at 3331 cm^{-1} corresponding to hydrogen-bonded hydroxyl. This feature is more prominent in EE–CAP blend than in EE–HPMCP blend indicating stronger interaction in EE–CAP blends. These changes indicate contribution of hydroxyls from HPMCP and CAP in hydrogen bonding with carbonyl or methylamino groups in EE.

The carbonyl band in EE–HPMCP and EE–CAP blends appears at 1729 cm^{-1} and the band width is narrower than that seen in neat HPMCP and CAP. This indicates that self-associations between the carboxylic carbonyls and hydroxyls (either acid hydroxyls or cellulosic) in neat HPMCP and CAP is overcome on blending with EE and participation of carboxylic hydroxyl from HPMCP and CAP in interpolymer association with EE liberating the carboxylic carbonyl from self-association. This results in appearance of band at 1729 cm^{-1}. The carboxylate salt formed due to the charge transfer between EE–HPMCP and EE–CAP blends results in new bands at 1559 and 1560 cm^{-1} as seen in Figs. 10b and 11b. The scale expanded spectra of EE–HPMCP and EE–CAP blends in the region 3200–2500 cm^{-1} show that the bands corresponding to methyl (sym/asym) and methylamino (sym/asym) stretch at 2949–2874 and 2821–2770 cm^{-1}, respectively, have disappeared (Figs. 10c and 11c). This change is associated with proton transfer from acid hydroxyl of HPMCP and CAP to the methylamino group in EE resulting in carboxylate salt formation.

Figs. 12a and 13a show the DSC thermograms for EE–CAP and EE–HPMCP blends, respectively. The plots of T_g versus composition for these systems are shown in Figs. 12b and 13b. Large positive deviations (+20–30 °C) from additivity and sig-

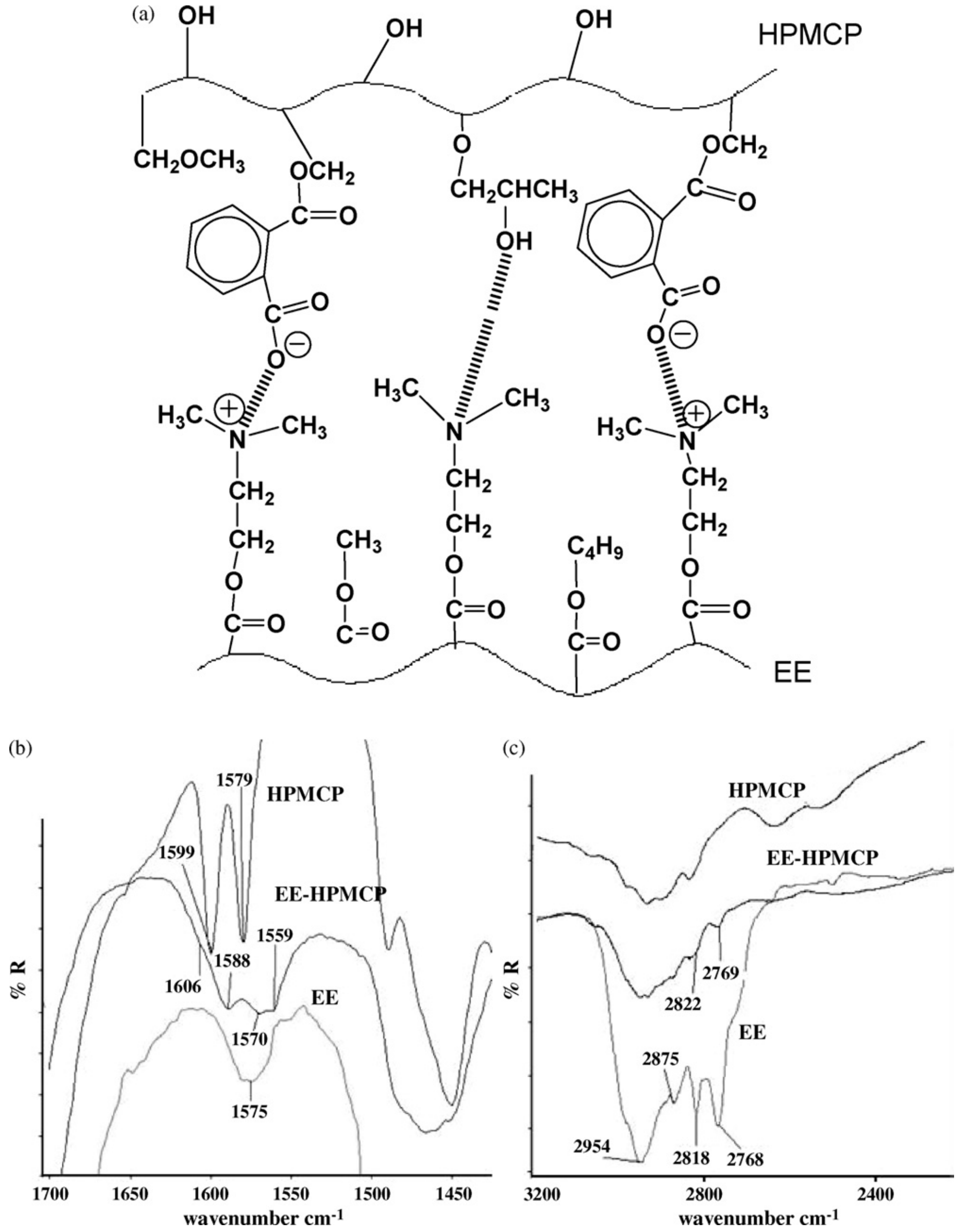

Fig. 11. Schematic representation of nature of interactions in EE–HPMCP blends (a) and the scale expanded FTIR spectrum of EE–HPMCP blends (b) and (c).

moidal curves are observed in both systems. The data treatment by Schneider equation (Fig. 12c) for EE–CAP blends yielded $K_1 = 5.1$ and $K_2 = 22.15$, respectively (Table 3). Both EL and CAP exhibit strong interactions with EE and the values of K_1 and K_2 are comparable as seen in Table 3. From the FTIR spectrum for EE–CAP blend it was concluded that the hetero contact between the acid and cellulosic hydroxyl of CAP and tertiary nitrogen of methylamino group was accompanied with charge transfer. Both EE and CAP have high charge densities favoring the hetero contact formations which is reflected in value of K_1 (5.1) > 0 due to large contributions of energetic effects. $K_2 > 0$ reflects more conformational changes occurring in EE than in CAP. This is expected as CAP has a bulky cellulosic structure and exhibits stronger self-associations than EE imparting rigidity to the polymer chains.

In EE–CAP blends containing 50–75% (w/w) EE, single composition dependent T_g is observed. The blends showing single T_g indicate formation of polyelectrolyte complex in stoichiometric proportions. However, at 33% (w/w) EE, two T_gs appear. A major transition corresponds to the T_g of complex (115.6 °C) and the second to the free fraction of the CAP (178.5 °C). The shift in T_g of CAP rich phase as compared to T_g of neat CAP suggests that it is associated with the polyelectrolyte complex or EE via hydrogen bonding but does not involve charge transfer. As EE content is lowered to 25% (w/w), T_g at 126.5 °C corresponding to polyelectrolyte complex is seen and crystallization of excess CAP is seen at 178 °C.

HPMCP differs from CAP in the presence of the propyl and methyl side groups on the cellulosic structure. However, both these polymers contain phthalic acid and cellulosic hydrox-

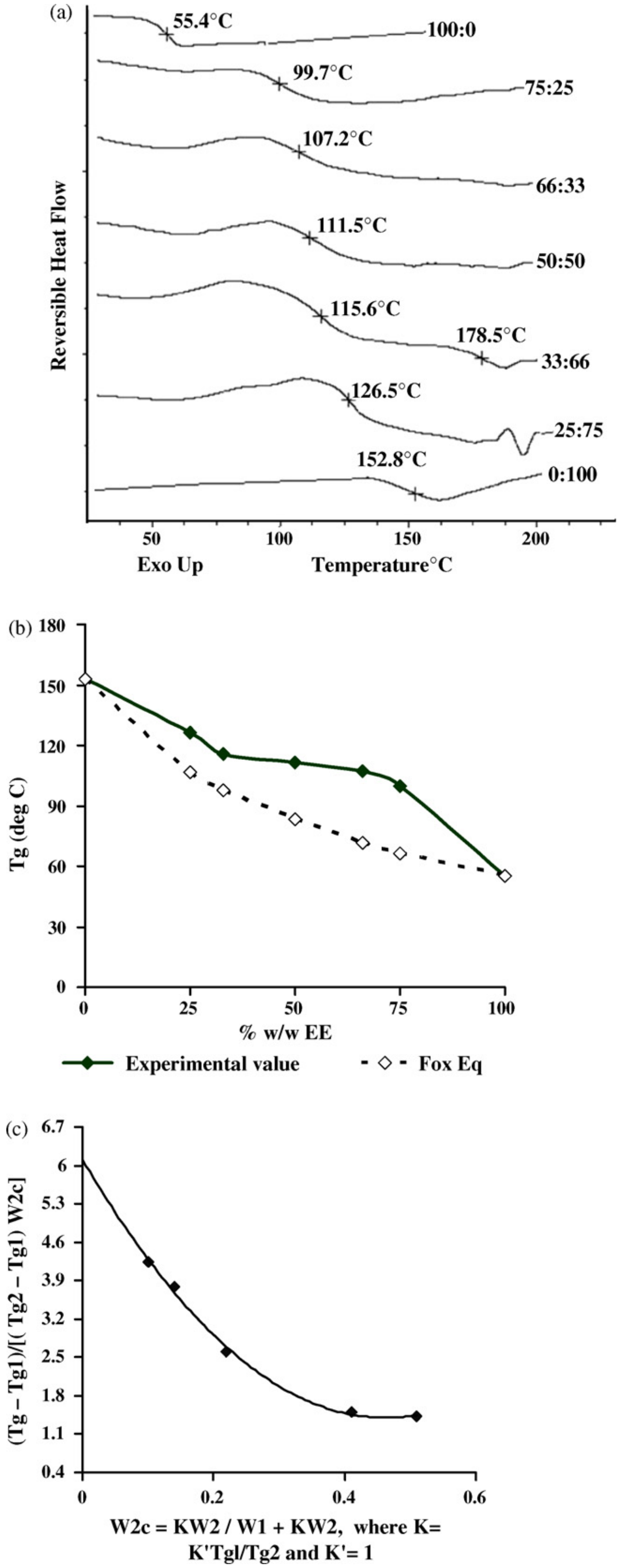

Fig. 12. Thermal analysis of EE–CAP blends: (a) DSC thermograms, (b) T_g vs. composition plot and (c) plots for Schneider equation.

yls, which form hydrogen bonds with EE, as seen from FTIR analysis. Hence the two polymers are expected to show similar interactions with EE. However, the extent of interaction was found to be different as revealed from the T_g data analysis using Schneider equation. The EE–HPMCP blends too,

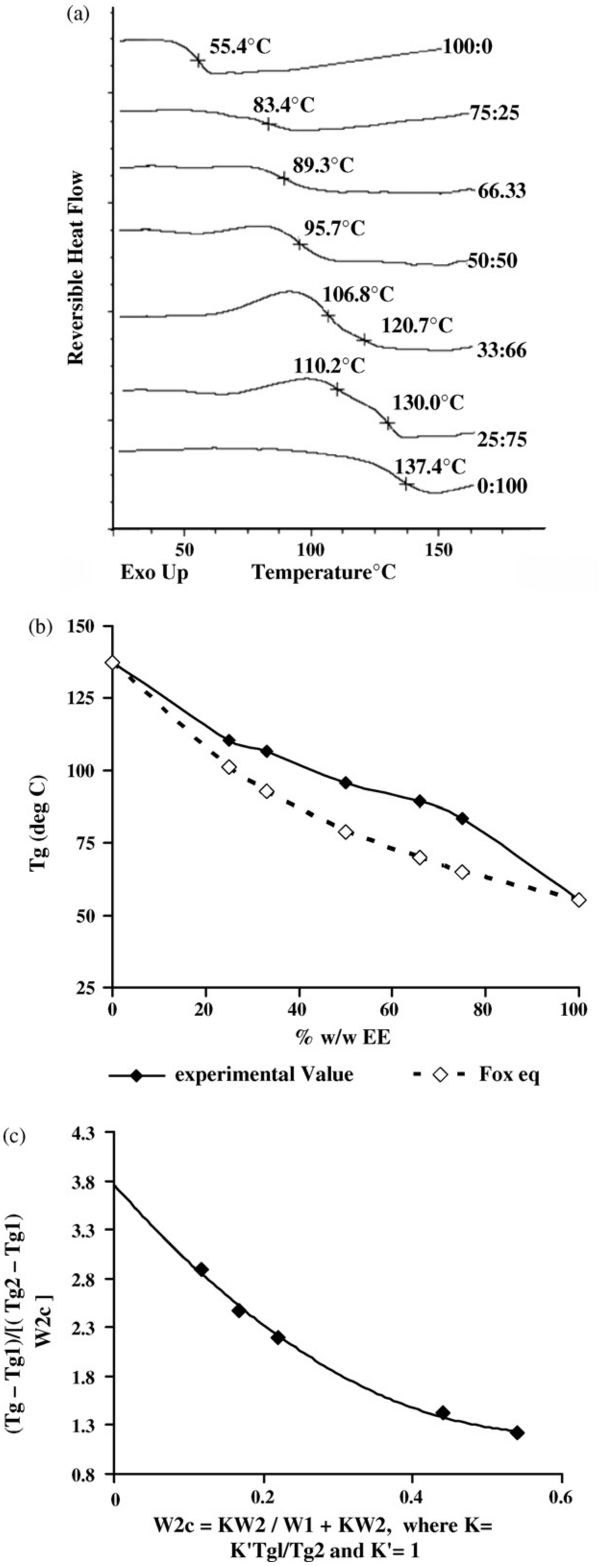

Fig. 13. Thermal analysis of EE HPMCP blends: (a) DSC thermograms, (b) T_g vs. composition plot and (c) plots for Schneider equation.

show large positive deviations from the weight average values of T_gs calculated by Fox equation (Fig. 13b). The T_g values of the EE–HPMCP polyelectrolyte complex are lower than those seen in EE–CAP blends, which can be attributed to lower extent of interaction in the former. The presence of propyl and methyl groups in HPMCP contributes to the steric hindrance and is reflected in lower values of K_1 (2.76) and K_2 (7.45) for EE–HPMCP blends as compared to EE–CAP blends ($K_1 = 5.1$, $K_2 = 22.15$). However the nature of hetero contact in both is same.

EE–HPMCP blends containing 25 and 33% (w/w) EE and EE–CAP blends containing 33% EE, exhibited two T_gs. The weight fractions in each phase were determined using Eqs. (3) and (4). EE–HPMCP blend containing 33% (w/w) EE, the EE concentration was found to be 37 and 21% in phases exhibiting T_{g1} and T_{g2}, respectively. Corresponding values for blends containing 25% EE were 33 and 9%. The presence of 9% EE in T_{g2} phase explains the shift in T_g of HPMCP from 137.41 to 130 °C. In both HPMCP and CAP blends containing 33% (w/w) EE, the percentage of EE in T_{g1} phase was 38% and in T_{g2} phase 26%.

The extent of interactions in the polymer blend influences the drug release pattern. We reported that as the extent of interaction increased and the polymer blends turned from immiscible to miscible the release pattern changed from burst to diffusion controlled (Menjoge and Kulkarni, 2007). The blends exhibiting strong interactions show slow ionization of the functional groups leading to diffusion controlled release. Similarly, the polyelectrolyte complexes exhibiting strong interactions are expected to exhibit relatively slower ionization on exposure to the buffered media than those exhibiting weaker interactions. The comparison of K_1 values of blends of EE with polyacids reveals that the order of interaction is EE–EL > EE–CAP > EE–HPMCP > EE–ES. It is therefore expected that the extent of physical crosslinking in these blends would also be in the same order.

3.3. Origin of polyelectrolyte complex formation and implications for drug release

From the DSC and FTIR study it was inferred that all polymers containing acid hydroxyls resulted in strong interaction with EE, leading to polyelectrolyte complex formation. Based on the values of the Schneider equation parameters, the interaction between EE and the polymers investigated could be arranged in the order: EL > CAP > HPMCP > ES. This order could be rationalized on the basis of the interactions between EE and individual polymers observed using FTIR spectroscopy. The probability of charge transfer is influenced by the choice of functional group and favorable structural, and steric symmetry factors, which contribute to formation of hetero contacts. The polyacceptor/polydonor having structural symmetry show better interaction as a result of increased mobility of interacting groups imparted by the presence of spacer between acceptor group and the polymeric back bone (Schneider, 1989, 1997, 1998). The presence of spacer ethyl chain in DMAEMA imparts greater mobility to form hetero contact with polyacids resulting in complexation. An examination of the structures of polymers EE, EL, CAP and HPMCP reveals that both EE and EL have similar polymer backbone and also similar spacer groups separating the functional groups from the polymer main chain. This provides better flexibility, which favors conformational redistributions to enable hetero contacts. This is reflected in K_1 and K_2 values obtained for EE–EL systems, which were highest amongst the systems investigated. In spite of higher charge density in case of both CAP and HPMCP, the two show lower interaction with EE. This is due to the dissimilarity in the structures of EE and the lack of spacer groups separating the functional groups from polymer backbone. The cellulosic ring imparts rigidity to these polymers impeding the chain mobility.

K_1 accounts for both homo-molecular and hetero-molecular contacts in polymer blends. For all EE–polyacid blends $K_1 > 0$ indicates that the interaction within the hetero contact is purely acid–base type involving the oppositely charged groups. The polymer undergoes significant conformational changes to achieve hetero-contacts resulting in $K_2 > 0$. These changes are predominant in EE, which has a T_g of 55.3 °C. The interactions between the blend components cause physical crosslinking. If the components are structurally symmetric, strong interactions (large K_1 values) leading to fall in entropy and free volume of the system, result. In the case of EE–EL system, compact 'zipp-like' packing resulting from binding between dimethylamino groups in EE and carboxylic groups in EL results in high degree of physical crosslinking, which leads to lower swelling of the polyelectrolyte complex and sustained release of the drug. Based on K_1 values the swelling of polyelectrolyte complexes containing EE is expected to follow the order: EE–EL < EE–CAP < EE–HPMCP < EE–ES. This is borne out from Figs. 14 and 15. Thus, the correlation between K_1 and degree of swelling is established. The swelling obtained for the polyelectrolyte complexes at pH 1.2 confirms this as shown in Fig. 14. The swelling obtained for the polyelectrolye complexes at pH 6.8 is of the order: EE–EL < EE–CAP < EE–ES < EE–HPMCP as seen in Fig. 15. Since the content of methacrylic acid in ES is low, probably all the carboxylic groups in ES are consumed in complexation with EE, and the swelling is suppressed as compared to EE–HPMCP blend. From the swelling response, the release of drug from

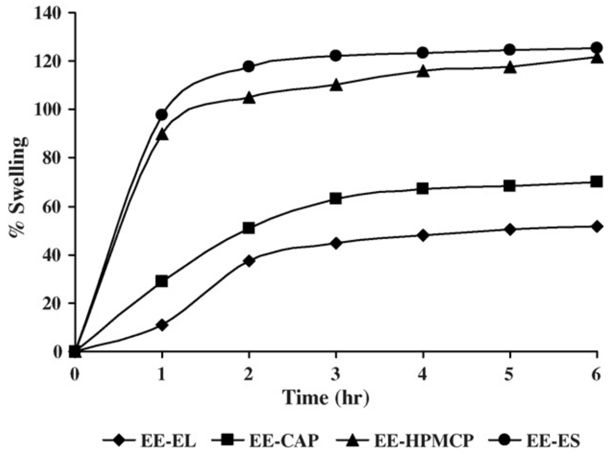

Fig. 14. Swelling response of polyelectrolyte complexes at pH 1.2.

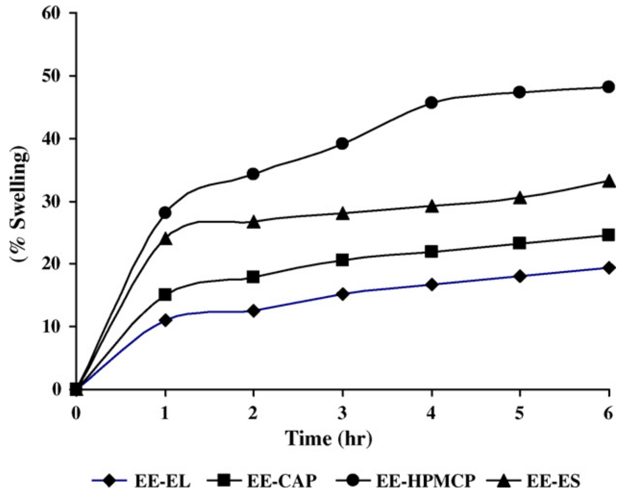

Fig. 15. Swelling response of polyelectrolyte complexes at pH 6.8.

EE–EL and EE–CAP blends is expected to be sustained over longer duration as compared to the EE–ES and EE–HPMCP blends.

Moustafine et al. (2005a,b) showed that at pH 6, EE and EL form polyelectrolyte complexes in the ratio 1:1. Since Ibuprofen has very poor solubility at gastric pH, the release of Ibuprofen was studied at pH 6.8 from matrix tablets. Little less than 20% Ibuprofen incorporated, was released at this pH in 6 h, in spite of the fact that Ibuprofen is a lower molecular weight and less bulky molecule. Significant lowering of release rate of Ibuprofen observed, could thus be attributed to highest K_1 value ($K_1 = 5.13$) observed for EE–EL blend amongst all the blend systems investigated comprising EE. By appropriate choice of drug which has right diffusivity value, the sustained release can be realized over the entire length of the GI tract.

4. Conclusions

The interactions of Eudragit$^{®}$E with Zein and ethylcellulose result in immiscible and partially miscible blends, respectively. The blends of Eudragit$^{®}$E with Eudragit$^{®}$L, Eudragit$^{®}$S, HPMCP and CAP result in polyelectrolyte complexes. The extent of interactions between blend components was quantified in terms of parameters K_1 and K_2 of Schneider equation. The extent of interactions decreased in the order: EL > CAP > HPMCP > ES. The influence of charge density and structure on extent of interactions has been established and this explains why EE forms a stronger polyelectrolyte complex with EL than CAP, HPMCP and ES. The estimation of stoichiometry of EE–polyacid complexes helps select blend compositions containing a known excess of the particular blend component as to exhibit desired pH dependent swelling and release or a blend devoid of excess of any component as to yield the lowest swelling and pH independent release of the drug. The knowledge of degree of interaction in blend components quantified in terms of Schneider equation parameters will help select blend constituents and compositions with predictable swelling behavior for sustained release over the entire length of the GI tract.

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