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Effect of Eriochrome Black T on the gelatinization of xyloglucan investigated using rheological measurement and release behavior of Eriochrome Black T from xyloglucan gel matrices

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ABSTRACT

A novel gel system was obtained by mixing aqueous solutions of tamarind seed xyloglucan (TSX) and Eriochrome Black T (EBT), an antiangiogenic compound. The shear-viscosity flow curves revealed that all the studies mixtures displayed a shear thinning behavior. Viscosity increased with increasing EBT concentrations. According to frequency sweep tests, mixtures at EBT concentration of 1.30% and 2.50% (w/v) in 1% (w/v) TSX formed a weak gel. The time sweep tests revealed that these mixtures remained as sol at room temperature (25 °C) for a long period of time but turned into gel in a short time at body temperature (37 °C). The in vitro EBT release profiles demonstrated sustained release of EBT. Loading concentration of EBT affected the gel strength and consequently the release mechanism of EBT. According to release kinetic analyses, the release profiles of 1.30% and 2.50% (w/v) EBT systems occur through an anomalous mechanism and Fickian diffusion, respectively. In conclusion, these EBT–TSX systems appear to be suitable as injectable implants for sustained delivery of EBT at a site of application, and as such they may be beneficial for the future treatment of solid malignant tumors.

1. Introduction

Tamarind seed xyloglucan (TSX), a well-known polysaccharide, finds various uses in food and pharmaceutical industries (Itoh et al., 2008). For biomedical application, xyloglucan has many advantageous properties, including no-toxicity, biocompatibility, biodegradability and non-carcinogenicity (Sano et al., 1996; Ghelardi et al., 2004; Simi and Abraham, 2010). TSX has a cellulose backbone of (1 → 4)-β-D-glucose. About 80% of this main chain is substituted with (1 → 6)–α-xylose. In addition, some xylose residues are further substituted with (1 → 2)-β-galactose (Shirakawa et al., 1998). Although cellulose is insoluble in water, TSX is a water soluble polymer due to the steric effect of its side chains. Generally, TSX alone cannot form a gel. However, modified TSX, where some of the galactose residues have been removed, can form a gel (Shirakawa et al., 1998). This modified TSX has previously been investigated for ophthalmic (Miyazaki et al., 2001), oral (Kawasaki et al., 1999; Miyazaki et al., 2003), rectal (Miyazaki et al., 1998), percutaneous and intraperitoneal (Suisha et al., 1998) administration. In addition, modified TSX has been blended with other polymers, such as pectin and alginate, for oral sustained-delivery of drugs (Itoh et al., 2008, in press).

Although several uses of this modified TSX have been reported in the literature, unmodified (natural) TSX has not been studied as a material for sustained drug delivery systems. Recently, natural TSX was reported to be able to form a gel when admixed with small molecular weight compounds, such as sugar, alcohols (Yuguchi et al., 2004), polyphenol (Nitta et al., 2004), iodine (Yuguchi et al., 2005a) and Congo red (Yuguchi et al., 2005b).

Angiogenesis is the growth of new blood vessels from existing vessels. This physiological process is essential for growth and metastasis of solid malignant tumors. Therefore, inhibition of angiogenesis would be expected to suppress tumor growth, and offer a new therapeutic possibility for cancer treatment. Therefore, research in the area of antiangiogenesis has increased considerably in the last decade (Norden et al., 2008). Eriochrome Black T (EBT), a common complexometric indicator, was recently discovered to be an antiangiogenic agent (Morris et al., 1997; Langer et al., 2000). It is an analog of suramin, a lead compound that inhibits tumor cell proliferation and angiogenesis. EBT was reported to be more potent and less toxic than suramin (Morris et al., 1997). EBT is structurally related to Congo Red, a molecule that can form a gel with TSX (Yuguchi et al., 2005b). Both compounds contain azo linkages and sulfonic acid groups. However, EBT has hydroxyl and nitro groups, rather than the amino group in Congo red. Due to

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the certain similarities and differences in the functional groups of Congo red and EBT, it was of interest to examine whether gelation of TSX can take place in the presence of EBT. This would be beneficial in understanding the type of chemical structure and/or interaction involved in gel formation with TSX. More importantly, the possibly generated gel system would be useful for sustained release of EBT. Furthermore, the EBT–TSX system may be valuable as another alternative gel-forming material. Our preliminary study shows that TSX can form gels with the addition of certain amounts of EBT. Therefore, the rheological properties of EBT–TSX gel systems were investigated in this study. These properties may also reveal the potential use of EBT–TSX systems as an injectable implant, i.e. the rapid conversion of the injected solutions into gel implants in the body. This type of administration has been demonstrated to be useful for delivering high concentration of drugs at specific tumor sites, resulting in reduced toxicity and a better outcome for the treatment of solid malignant tumor. In addition, the release and the release kinetics of EBT from the EBT–TSX gel systems were also examined.

2. Materials and methods

2.1. Materials

TSX was purchased from Megazyme international Ireland Ltd., Wicklow, Ireland. EBT was obtained from Merck, Darmstadt, Germany. All other chemicals used were of analytical grade.

2.2. Sample preparations

A stock solution of TSX was prepared at a concentration of 2% (w/v) by dispersing a required amount of TSX in distilled water. Then, the solution was slowly homogenized with a mechanical stirrer for 4 h at 50 °C. Solutions of EBT were prepared by dissolving the required amounts of EBT in distilled water. Appropriate volumes of TSX and EBT solutions were mixed to obtain 0.33%, 0.65%, 1.30% and 2.50% (w/v) of EBT in 1% (w/v) TSX.

2.3. Rheological behavior measurements

The rheological properties of samples were measured using a HAAKE RS-I rheometer, with a cone-plate sensor C20/1°, coupled to HAAKE DC 30/K 10 circulating system. The periphery of the samples was always covered by a layer of silicone oil to prevent evaporation. Raw data were analyzed using the RheoWin 4 Data Manager. Flow behaviors were evaluated to measure the viscosity as a function of shear rate. The shear rate range was from 0.1 to 100/s. Strain tests for each sample were first studied to determine the linear viscoelastic range (LVR). A constant strain was then chosen to perform other oscillatory testing at a strain of 0.1%. The gel or liquid character of samples was investigated by frequency sweep tests. For frequency sweep experiments, the samples were allowed to age for 24 h at room temperature before measurement. Freshly prepared samples were used for time sweeps tests. These tests were performed to determine the gelation time and extent of the gelation at 1 Hz and at both ambient (25 °C) and physiological temperatures (37 °C).

2.4. In vitro release of EBT from EBT–TSX gels

In vitro measurements were carried out in a shaking incubator (37 °C) at 40 rpm using a membrane-less dissolution model as previously described (Zhang et al., 2002; Yang et al., 2009). Physiological saline (0.9% (w/w) NaCl) was used as the release medium. The samples of EBT–TSX (1 mL) were placed in a flat-bottomed vial and allowed to form gel at room temperature. Subsequently, a physiological saline solution (8 mL) was gently placed on the surface of the gel samples. These samples were then placed in the shaking incubator at 37 °C. Two milliliters of the release medium were removed at predetermined time intervals and replaced with 2 mL of fresh release medium. The amount of EBT in the release medium was determined using a UV spectrometer (Hewlett-Packard 8452A diode array spectrophotometer) at the detection wavelength of 604 nm. All release experiments were performed in triplicate.

For kinetic data treatment, the cumulative release fraction was calculated and plotted as a function of time. The well-known Korsmeyer–Peppas equation or power law, which is generally used to describe drug release behavior from polysaccharide gel, was used to evaluate the release mechanism of EBT (Korsmeyer et al., 1983; Lo et al., 2003; Francois et al., 2005):

$$\frac{M_t}{M_\infty} = kt^n \quad (1)$$

where M_t and M_∞ are the cumulative amounts of drug released at time t and infinite time, respectively, k is the release constant, n is the release exponent characterizing the release mechanism. This equation is extensively used for analyzing the first 60% of a release curve. The exponent values (n) were determined from $\log(M_t/M_\infty)$ versus $\log(t)$ plots. All drug release data were fitted using SigmaPlot 10.0 software.

3. Results and discussion

The flow curves of samples are shown in Fig. 1. The samples displayed a shear thinning or a pseudoplastic behavior where viscosity decreases with the increase of shear rate. This observed behavior could therefore be used to advantage in facilitating the flow of the EBT–TSX samples during injection through the syringe for parenteral use. As shown in Fig. 1, the viscosity is also dependent on EBT concentration, and appears to increase with increasing concentration of EBT, reflecting the interaction between TSX and EBT.

For dynamic rheological measurements, strain sweep tests were performed to determine the linear viscoelastic region where the modulus is independent of the strain. As shown in Fig. 2 the limit of the LVR was observed at about 0.5% strain. Accordingly, the strain of 0.1% was used for all subsequent rheological measurements.

Due to the fact that all freshly prepared samples are sol, frequency sweep experiments cannot discriminate the difference of mechanical spectra of the samples (data not shown). After aging for 24 h, some samples at high concentrations of EBT turned into gels. Frequency sweep experiments were therefore performed on aged samples to investigate the influence of EBT concentrations

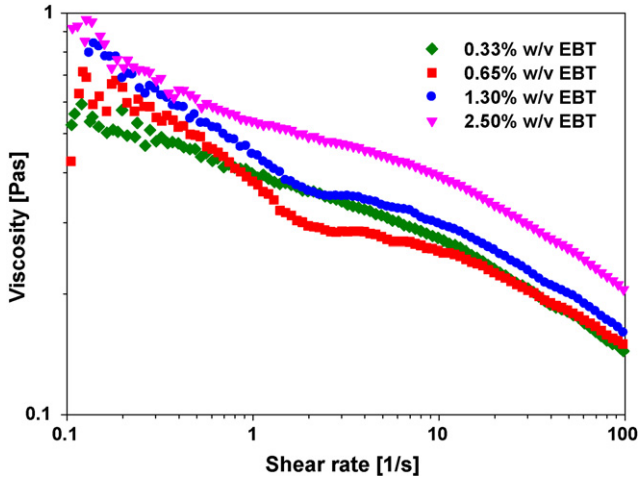

Fig. 1. Viscosity-shear rate flow curves for 1% (w/v) TSX aqueous solution containing different concentrations of EBT. Experiments carried out at 25 °C, and at 0.1% strain.

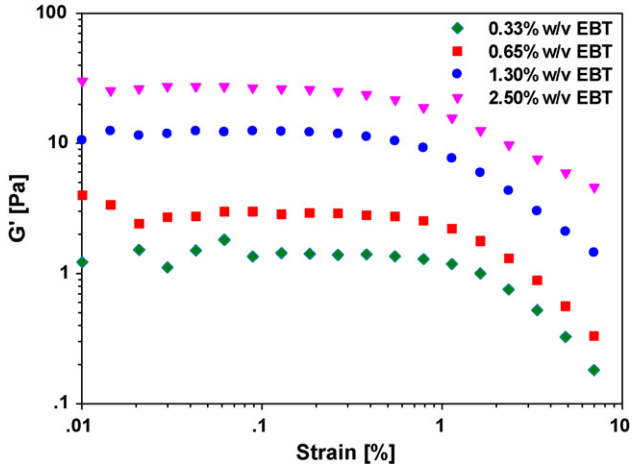

Fig. 2. The strain dependence of storage modulus at a frequency of 1 Hz for 1% (w/v) TSX aqueous solution containing different concentrations of EBT.

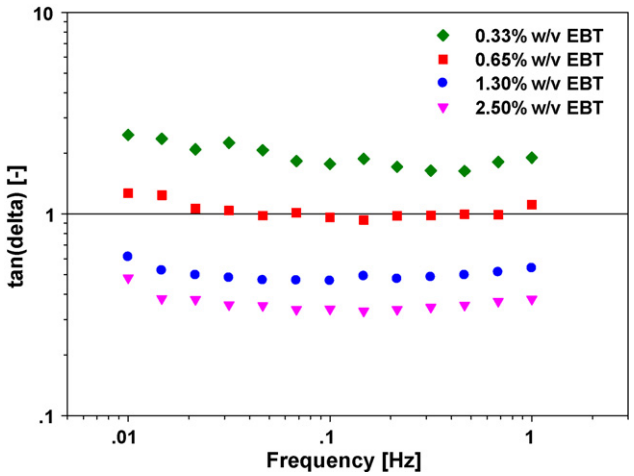

Fig. 4. Loss tangent as a function of frequency for 1% (w/v) TSX aqueous solution containing different concentrations of EBT.

on viscoelastic behavior and gel formation of the samples. The mechanical spectra, G' (storage modulus) and G'' (loss modulus) curves as a function of frequency, for all EBT–TSX mixtures are displayed in Fig. 3. According to the frequency sweep tests, the viscoelastic behavior of the samples is dependent on EBT concentrations. Samples at 0.33% (w/v) EBT in 1% (w/v) TSX exhibit the typical mechanical spectrum of viscous solutions where G' is always lower than G''. Both moduli are frequency dependent and increase as frequency increases. For sample containing 0.65% (w/v) EBT in 1% (w/v) TSX, both moduli come close and almost overlap. This is considered to be the vicinity of the sol–gel transition system. The samples at high concentrations of EBT (1.30% and 2.50% (w/v)) display typical gel-type rheological behavior. The G' values are higher than G'' values in the entire frequency range determined, and both moduli are less frequency dependent. To characterize the gel type, the experimental moduli data are also expressed as loss tangent ($\tan\delta$), which is the ratio of loss modulus to storage modulus (G''/G'). The loss tangent as a function of frequency is displayed in Fig. 4. For samples containing 1.30% and 2.50% (w/v) EBT in 1% (w/v) TSX, $\tan\delta$ values are higher than 0.1 suggesting a characteristic of weak gel (Chronakis et al., 1996; Ikeda and Nishinari, 2001). The loss tangent of 2.50% (w/v) EBT systems is lower than that of 1.30% (w/v) EBT systems indicating that the gel with higher EBT concentration displays a more solid-like character.

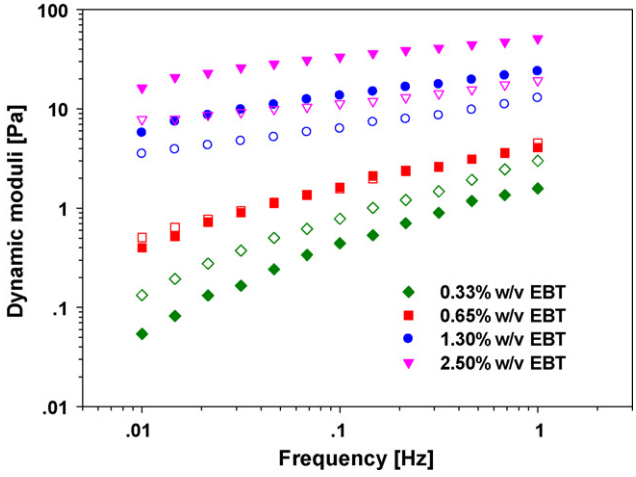

Fig. 3. Log–log plots of storage (G', closed) and loss (G'', opened) moduli versus angular frequency for 1% (w/v) TSX aqueous solution containing different concentrations of EBT.

For parenteral sustain-release or injectable implant delivery, the system should be liquid at room temperature and turn into gel at body temperature after administration to the delivery site. Thus, time sweep tests, plots of G' and G'' as functions of time, were performed at both ambient and body temperatures. The effect of temperature on the gelation process was carried out on the two samples that are capable of forming gel. According to the frequency sweep tests, these samples include the mixtures of 1.30% and 2.50% (w/v) EBT in 1% (w/v) TSX. As general utilization, the crossover of G' and G'' was used for the determination of gel point in the sol–gel transition (transition from liquid-like behavior to solid-like behavior). Time sweep experiments at both temperatures (25 and 37 °C) for the samples of 1.30% and 2.50% (w/v) in 1% (w/v) TSX are shown in Figs. 5 and 6, respectively. Both moduli of these samples are very low at the beginning and increase rapidly with time. The rate of increase of G' was faster than that of G'' and the crossover of G' and G'' was observed in these systems which were capable of forming gel. The rapid increase of G' and G'' values suggested that a strong network structure was forming. Subsequently, the increase rates of both moduli were slower until they approach the equilibrium value where the network formation came to completion. At 25 °C, G' for 1.30% (w/v) EBT sample reaches G'' at about 4.4 h. Afterwards, G' values are equal to or very slightly higher than G'' values indicating a very weak gel or just a viscous system. However, at 37 °C, the gel point for this sample was observed at 30 min (Fig. 5). After

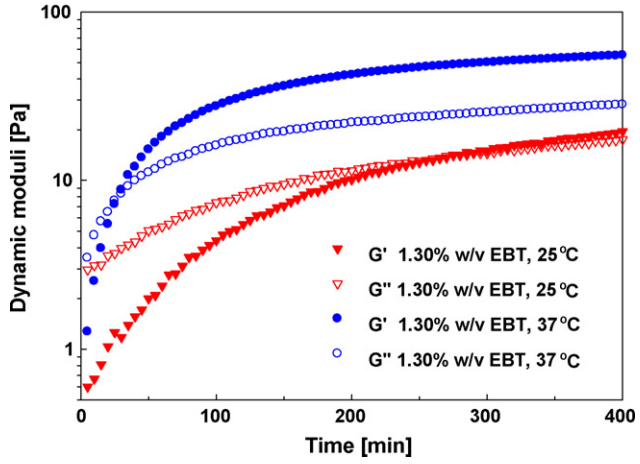

Fig. 5. Time dependence of viscoelastic moduli G' and G'' for the mixture of 1.30% (w/v) EBT and 1% (w/v) TSX at 25 and 37 °C.

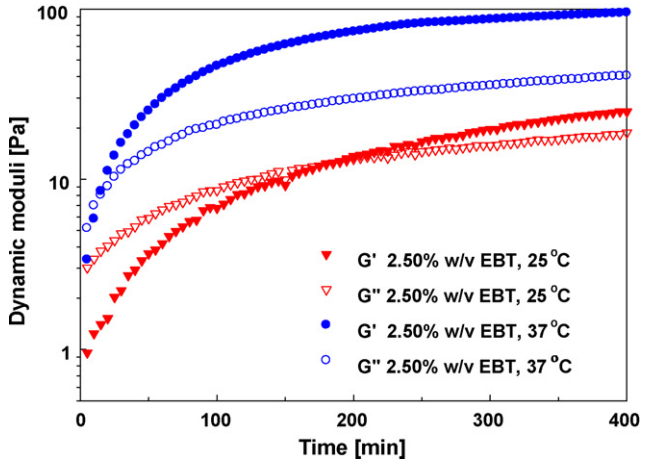

Fig. 6. Time dependence of viscoelastic moduli G' and G'' for the mixture of 2.50% (w/v) EBT and 1% (w/v) TSX at 25 and 37 °C.

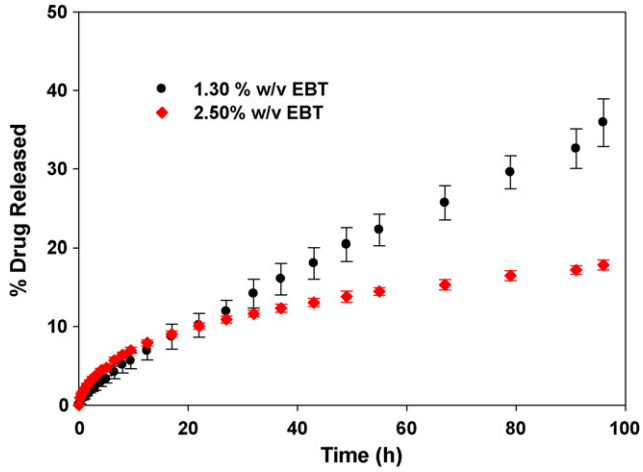

Fig. 7. In vitro release of EBT at the concentration of 1.30% and 2.50% (w/v) EBT in 1% (w/v) TSX at 37 °C.

this gelation time, the sample became a weak gel as observed from G' and G'' curves. For the sample containing 2.50% (w/v) EBT, the gel points can be detected at about 3 h and 10 min when the samples were measured at 25 and 37 °C, respectively (Fig. 6). As shown in this figure, this sample exhibits a very weak gel at 25 °C but it demonstrates a stronger gel at 37 °C.

When considering the temperature effect, the values of G' and G'' at 37 °C were higher than those at 25 °C. At 37 °C, the values of G' and G'' increased at a greater rate than those at 25 °C. Additionally, the differences between G' and G'' are also dependent on the temperature. The differences are higher at 37 °C compared to those at 25 °C. These suggest that the forming gel is stronger when it is generated at 37 °C as compared to 25 °C. With regard to the effect of EBT concentration, the differences between G' and G'' values after the gel point are higher for sample with a higher concentration of EBT. As the curves approach the plateau region, the differences between the moduli for the samples at 1.30% and 2.50% (w/v) EBT are about 28 and 55 Pa, respectively, at 37 °C (Figs. 5 and 6). Additionally, at this temperature, the G' values for 2.50% (w/v) EBT is about 3.6 times higher than those for 1.30% (w/v) EBT. These results indicate that higher concentration of EBT produces a stronger gel. Therefore the gelation time depends on both the temperature and the concentration of EBT. The gelation time decreases with increasing EBT concentration as well as with the increase in temperature from 25 to 37 °C. As indicated by the time sweep tests, the mixtures remain as a sol at room temperature for a long period of time and transform into gel in a short time period at body temperature. Thus, a mixture of EBT and TSX appears to be suitable as a parenteral implant system for possible sustained-delivery of EBT. The mixture can be administered as a solution, and subsequently it can turn into a gel with possibly sustainedly release at the desirable site of application.

The release profiles of EBT from gels containing 1.30% (w/v) and 2.50% (w/v) EBT in 1% (w/v) TSX are displayed in Fig. 7. These samples illustrate dissimilar release profiles, suggesting that the release mechanism for these two systems is different. However, these release profiles demonstrate the sustained release behavior of both systems. As EBT concentration is increased, the cumulative release fractions were decreased. In 4 days, the percentage of cumulative release from 1.30% and 2.50% (w/v) EBT in 1% (w/v) TSX

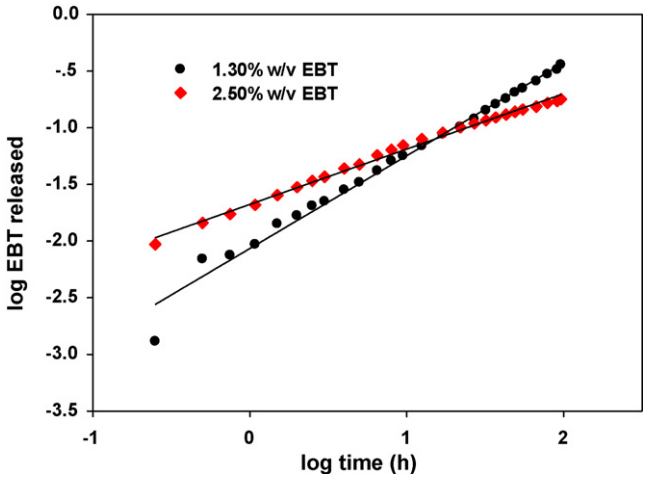

Fig. 8. The plot of log (M_t/M_∞) versus log time of 1.30% and 2.50% (w/v) EBT in 1% (w/v) TSX at 37 °C for the fitting using Korsmeyer–Peppas model.

was about 37% and 15%, respectively. According to the release profile, drug release from 1.30% (w/v) EBT system is somewhat linear, whereas that from 2.50% (w/v) EBT is almost biphasic, being relatively fast for the first 10 h followed by slow release over the next 3.5 days.

In order to determine the release kinetics of EBT, the release data were fitted to the Korsmeyer–Peppas model (Eq. (1)) as shown in Fig. 8. The n and k values determined from the slope and intercept, respectively, of the fitting straight line are presented in Table 1. The release constant k was found to increase with increased concentration of EBT. Based on the n values in Eq. (1), the drug transport may be classified as Fickian diffusion (Case I), Case II transport (zero order), and non-Fickian (anomalous) transport (Ritger and Peppas, 1987; Kaneko et al., 1998). As listed in Table 1, the n values obtained are 0.8185 for the 1.30% (w/v) EBT system. This n value is between 0.5 and 1.0 indicating that the release process is an anomalous mechanism. Thus the release of EBT was controlled by a combined mechanism of pure diffusion (Fickian diffusion) and Case

Table 1
Kinetic analyses of the release data according to Eqs. (1) and (2).

EBT in 1% (w/v) TSX	k	n	R^2	k_1	k_2	k_1/k_2	Release mechanism
1.30% (w/v) EBT	0.0086	0.8185	0.9923	0.0096	0.0027	3.5556	Anomalous
2.50% (w/v) EBT	0.0211	0.4884	0.9942				Fickian

II transport (relaxation-controlled drug release). To investigate the proportional contribution of Fickian diffusion and relaxation processes, a nonlinear regression of the release data fitted to Eq. (2) was performed (Berens and Hopfenberg, 1978; Peppas and Sahlin, 1989):

$$\frac{M_t}{M_\infty} = k_1 t^{0.5} + k_2 t \quad (2)$$

where M_t/M_∞ is the fraction of drug released in time t as specified in Eq. (1), k_1 and k_2 are kinetic constants describing diffusion and relaxation contribution, respectively. The k_1 and k_2 values obtained from the curve fitting are listed in Table 1. The k_1/k_2 ratio was 3.5556, indicating that EBT release in this system was predominantly controlled by the diffusion mechanism.

The n value for the 2.50% (w/v) EBT system was 0.4884 reflecting that the release mechanism is Fickian diffusion. This release measurement involves the release of EBT through the surface that is in direct contacts with release medium. The Higuchi model was then used to confirm whether the release occurs through Fickian diffusion. This model describes drug release by Fickian diffusion according to this equation (Higuchi, 1963; Siepmann and Peppas, 2001):

$$\frac{M_t}{M_\infty} = k_H t^{0.5} \quad (3)$$

As indicated by this equation, a straight line is assumed for the plot of M_t/M_∞ versus the square root of time. A higher correlation coefficient ($R^2 = 0.9902$) was obtained with the Higuchi model for this system, confirming that the release of EBT is based on Fickian diffusion.

According to the rheological measurements, gel formation of the 2.50% (w/v) EBT system is stronger than that of the 1.30% (w/v) EBT system. Due to the different nature of the gel structures, the release profiles of EBT from the 1.30% (w/v) and 2.50% (w/v) of EBT systems are different. For the 1.30% (w/v) EBT system, the release of EBT involves both TSX relaxation and diffusion. However, the stronger gel may decrease mobility of the polymer chain, therefore, the EBT release from the 2.50% (w/v) EBT system is a pure diffusion process without the changing or relaxing of TSX structure.

In conclusion, this study demonstrates that TSX undergoes gelation by adding EBT at concentrations of 1.30% and 2.50% (w/v). According to the shear-viscosity flow curves, all mixtures display a low viscosity and shear thinning behavior. This suggests that the mixtures might be suitable for parenteral administration. The gels formed at concentrations of 1.30% and 2.50% (w/v) EBT in 1% (w/v) TSX show characteristics of weak gels. The gelation behaviors are temperature dependent. The EBT–TSX systems remain as sol at room temperature for a long period of time and turn into a gel in a short time at body temperature. The gelation time at body temperature decreases with the increase of EBT concentrations. Furthermore, the in vitro EBT release profiles demonstrate sustained release of EBT. The concentration of EBT significantly affects the gel strength and consequently the release mechanism. According to the release kinetic analysis, the release profiles of the 1.30% and 2.50% (w/v) EBT systems occur through an anomalous mechanism and Fickian diffusion, respectively. As indicated by these investigations, the EBT–TSX system has demonstrated its potential to be a new injectable implant delivery for sustained release of EBT. This may be beneficial in the future for the treatment of solid malignant tumors. In addition, these systems may be useful as an injectable depot material for other chemotherapeutic agents.

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