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Release of theophylline from polymer blend hydrogels

Jianhong Liu, Shiqi Lin, Lin Li *, Erjia Liu

School of Mechanical and Aerospace Engineering, Nanyang Technological University, 50 Nanyang Avenue, 639798 Singapore, Singapore

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Abstract

Polymer blending is a simple yet attractive method to obtain combined physical and mechanical properties of polymers. In this paper, three types of blend hydrogels were prepared, each by physically blending two different natural polymers, and a model drug, theophylline (TPH), was immobilized into these hydrogels for the studies of drug release. The release profiles of TPH from various types of hydrogels were determined by UV–vis absorption measurement at 272 nm. The experimental results show that the releases of TPH from these hydrogels are dependent upon the composition of the hydrogel, the type of component, the possible interactions between two component polymers, as well as external temperature. All the release profiles clearly demonstrate a temperature effect. Among the three blend hydrogels, the slowest release was observed from the blend hydrogel of gelatin and agar with a weight ratio of 1:1. The drug release patterns and release mechanisms have been discussed by considering the possible molecular interactions and gel network structures.

Keywords: Drug release; Hydrogel; Polymer blend; Theophylline

1. Introduction

Hydrogels are one of the most promising and versatile materials with many potential applications. In particular, controlled release systems can be prepared using hydrogels (Hoffman, 2002; Prokop et al., 2002). Hydrogels made of single polymers have been extensively used in drug delivery studies. However, in many cases a single polymer alone cannot meet divergent demands in controlled drug release in terms of both properties and performance (Changez et al., 2003). Drug release kinetics from monolithic hydrogel devices typically follows the Fickian diffusion (Peppas and Reinhart, 1983). The diffusivity of water-soluble drugs is explained by "free volume theory" (Yasuda et al., 1971; Peppas and Reinhart, 1983; Sato and Kim, 1984). When a hydrogel is used as a rate-controlling membrane in reservoir device, its relatively weak mechanical properties limit its practical application. In order to overcome these limitations, in recent years, heterogeneous hydrogels derived from polymer blends, block copolymers, or interpenetrating polymer networks (IPN), have been investigated for drug de-

* Corresponding author. Tel.: +65 67906285; fax: +65 67911859.
E-mail address: mlli@ntu.edu.sg (L. Li).

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livery (Korsmeyer et al., 1982; Mueller and Heiber, 1982; Bae et al., 1991; Pitt et al., 1992). Blending is a simple method to combine the advantages of different polymers. The resulting polymer blends may show synergistic properties (Bae and Kim, 1993). As a blend hydrogel or an IPN hydrogel has more complicated network structures than a homo-hydrogel, the practical and expected properties from these heterogeneous hydrogels for drug delivery application are illustrated as: (1) new release mechanisms for improved release kinetics; (2) biocompatibility; (3) improved mechanical properties; and (4) additional functionality (polymer–polymer interactions) (Bae and Kim, 1993).

However, the above-mentioned heterogeneous hydrogels are commonly based on synthetic polymers. Over the years, much work (Nijenhuis, 1997) has been devoted to the study of gel formation by natural polymers and biopolymers, such as polysaccharides and proteins, which includes the methods of inducing gelation in aqueous solutions. Thermal setting is probably the most widely used method for gelation of these natural polymers. Consequently, the structures and mechanisms for formation of gel networks for these individual polymers, and their mechanical properties, have been well understood.

Hydrogels from gelatin (protein), agar (polysaccharide) and κ-carrageenan (polysaccharide) have received particular attention, due to their natural origin, low cost, good biocompatibility (Brown and Johnsen, 1981; Gehrke, 1993; Tabata and Ikada, 1998). Furthermore, their resemblance to human tissues is of value for these polymers to be used to study or mimic solute transport through biological media (Favre and Girard, 2001). They have been widely used in drug delivery systems (Tabata and Ikada, 1998; Sumathi and Ray, 2002; Lead et al., 2003) as well as in food industry as food additives. But there are only a few reports dealing with drug release systems based on the blends of these natural polymers (Sjöberg et al., 1999; Kuijpers et al., 2000; Kandil et al., 2004). Kuijpers et al. (2000) reported a drug delivery system based on chemical cross-linked gelatin–chondroitin sulphate hydrogels for controlled release of antibacterial proteins. The incorporation of chondroitin sulphate into gelatin gels caused a marked increase in the lysozyme loading capacity, and a slower release rate. Kandil et al. (2004) blended gelatin with synthetic materials, such as poly(vinyl alcohol) and other natural wastes, such as sugar cane bagasse and sawdust. Their results showed that the produced films had the controlled-release properties.

Recently it has been demonstrated that IPN can be formed between gelatin and some polysaccharide molecules when they are mixed together at appropriate compositions and conditions (Clark et al., 1983, 1999; Amici et al., 2000, 2002; Matsuo et al., 2002). Formation of molecularly interpenetrated network is attractive because IPN is able to avoid the problem called "phase separation". When an IPN hydrogel has been physically formed from two polymers at a given temperature, a physical phase separation between the component polymers would be nearly impossible because of the infinite zero-viscosity of the gel. IPN is also attractive in producing synergistic properties from the component polymers. For example, when a hydrophilic gelling polymer is interpenetrated with a relatively hydrophobic gelling polymer, the resultant IPN hydrogel is expected to have an improved capability of immobilizing a drug. This is actually able to open a new way for us to use IPN in designing novel drug release systems.

In the present work, an attempt has been made to prepare hydrogels from a pair of natural polymers gelatin, agar and κ-carrageenan. The effects of composition of these blend hydrogels on release of theophylline (TPH) have been studied. TPH is an effective drug used for the treatment of asthma and pulmonary disease (Yu et al., 1996), and has been widely used as a model drug in various controlled release studies (Antal et al., 1997; Shozo et al., 2000; Katime et al., 2001; Coviello et al., 2003). The possible mechanisms involved in the release results will be discussed.

2. Experimental

2.1. Materials

Agar, gelatin, κ-carrageenan, anhydrous TPH were all purchased from Sigma–Aldrich Company and used as received without further purification. Deionized water was prepared by a Millipore purification system (Alpha-Q: CPMQ004R1) and used to prepare all the hydrogels in this study.

2.2. Hydrogel preparation

The hydrogels used in this study were prepared from gelatin, agar and κ-carrageenan or their two-component blends. These hydrogels served as drug release matrices after incorporating an appropriate amount of the drug, TPH. The detailed procedure for the preparation of these hydrogels is described below.

One gram of one gelling material or a mixture of two of them was mixed with 20 ml of TPH aqueous solution (10 mM) prepared previously, so that in all the obtained gel samples, the total polymer concentration are all the same, i.e. 4.8 wt.%. For the single-polymer systems, the mixture (polymer and TPH solution) was slowly heated to around 60, 80 or 90 °C for gelatin, κ-carrageenan and agar hydrogels, respectively; for a blend hydrogel, the higher melting temperature between two component polymers was adopted as the heating temperature. Gentle stirring was needed here in order to avoid bubbles in the final gel solutions. After stirring for about one hour, the optically clear solutions were obtained. The resultant solutions were poured into an upright placed glass syringe with a top cut off (machined perpendicularly to the cylinder axis), which was kept in an oven at 60 °C before use. The warm polymer solutions in the syringe were allowed to equilibrate at the ambient temperature (about 25 °C) to form a gel.

The hydrogel samples based on the single polymers (i.e. gelatin, agar and κ-carrageenan) are designated as G-type, A-type and κ-type, respectively. These hydrogels prepared based on two-component blend are called GA, Gκ and κA hydrogels for the blends of gelatin–agar, gelatin-κ-carrageenan and κ-carrageenan-agar, respectively. Table 1 shows the sample designation and compositions for all the hydrogels prepared in this study. For example, GA55 represents the hydrogel containing a polymer blend consisting of 50 wt.% gelatin and 50 wt.% agar. These solid hydrogels were cut into the disk-shaped samples with a sharp blade for the use of following drug release experiments.

Table 1
Preparation of hydrogels: feed composition and sample designation

Gels designation	Gel composition		
	Gelatin (g)	κ-Carrageenan (g)	Agar (g)
Single hydrogels			
G-type	1.0		
A-type			1.0
κ-type		1.0	
Blend hydrogels			
GA91	0.9		0.1
GA73	0.7		0.3
GA55	0.5		0.5
Gκ73	0.7	0.3	
Gκ55	0.5	0.5	
κA91		0.9	0.1
κA73		0.7	0.3
κA55		0.5	0.5

2.3. Drug release experiments

For the drug release studies, the disc-shaped hydrogel samples (2.5 mm in thickness, 23 mm in diameter and 1 g in weight) were immersed in 20 ml water and maintained in a thermal water bath (Polyscience G20516). The releases at different temperatures (30, 37, 45 ± 0.1 °C) were investigated. The amount of TPH within the disk gel was far below its solubility in 20 ml water so that a sink condition (Ritger and Peppas, 1987) can be assured. At certain time intervals, 3 ml solution was taken out from each release system and the amount of TPH released at that time was determined by the UV–vis spectroscopic measurement at 272 nm with a HP-8453 UV–vis spectrophotometer system. After each measurement, the sample used was returned to the original medium solution in order to maintain a constant volume of surrounding release medium.

3. Results and discussion

In this study, 10 mM water solution of TPH was used to prepare all the hydrogel samples. The good water solubility of TPH plus a long-time carefully stirring during the hydrogel preparation process allowed us to obtain a homogeneous distribution of TPH in each hydrogel sample. Fig. 1 is the calibration curve of TPH based on its UV absorbance at 272 nm. The concentration range of TPH used in this study is below 0.50 mM. Therefore, in this study we do not have to worry about the solubility of TPH in the surrounding release medium, which may affect the long-term release of TPH.

The release behavior of drug molecules from a hydrogel depends on many factors, such as chemical structure of the original gelling polymer(s), hydrogel composition (if more than one polymer are used), gel

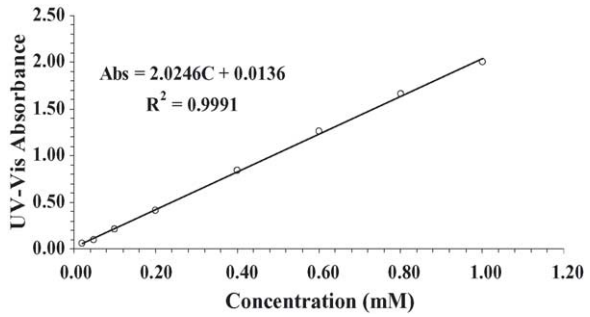

Fig. 1. Calibration curve of theophylline in aqueous solution by UV–vis absorbance at 272 nm (measured with 0.2 cm-length UV–vis cuvette).

network structure, release condition (e.g. temperature), etc. In this study, the effects of various factors on the TPH's release have been examined.

3.1. Effect of blending

Agar, gelatin, or κ-carrageenan is all good candidates to make hydrogels for controlled drug release (Tabata and Ikada, 1998; Sumathi and Ray, 2002; Lead et al., 2003). However, drug releases from these single polymer gels are often too fast, especially for release of hydrophilic drugs. This fact was explained by the negligible hydrodynamic hindrance to the movement of the drug molecules from a hydrogel network (Sjöberg et al., 1999). Thus, improvement is needed in order to achieve a sustained and prolonged release. Use of polymer blend hydrogels might be one of good solutions, as it has been reported that IPN may be formed from polymer blends, which may help to slow down the release rate (Clark et al., 1983; Amici et al., 2000, 2002; Matsuo et al., 2002). In this work, we explore the possibility of using two-component blend hydrogels as slow drug release systems.

Fig. 2a–c depict the percent cumulative release profiles of TPH from three two-component blend hydrogels: GA55, Gκ55 and κA55, compared to their corresponding single component hydrogels: G-type, κ-type and A-type, respectively. The release temperature was $37 \pm 0.1\,^{\circ}C$. The blend ratio used here was 1:1 in weight for all the three blend hydrogels. From Fig. 2, it is obvious that the significant decrease in the release rate of TPH was observed when a blend hydrogel was used.

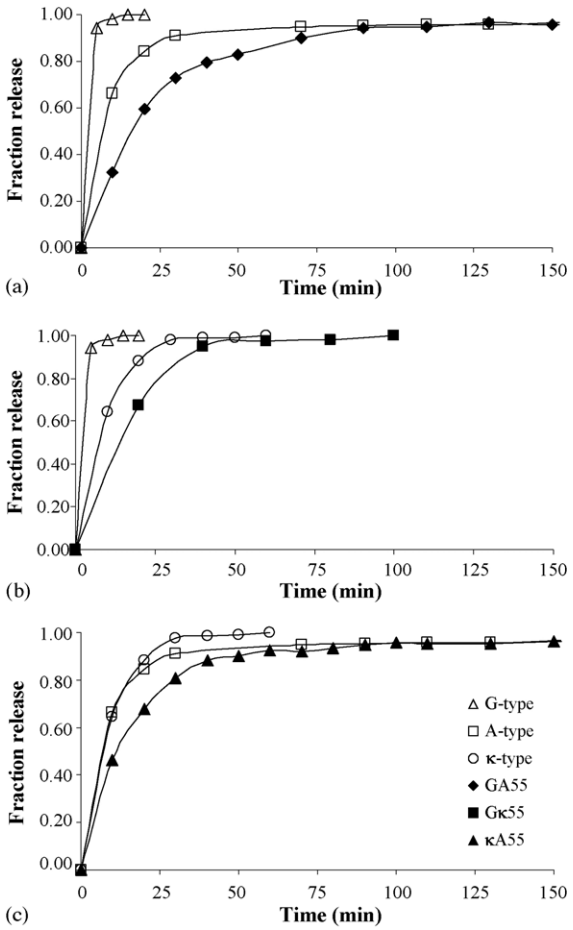

Fig. 2. Cumulative fraction releases of theophylline from hydrogels based on (a) gelatin and agar; (b) gelatin and κ-carrageenan; (c) κ-carrageenan and agar at $37 \pm 0.1\,^{\circ}C$.

In a diffusion-controlled release, the diffusion of drug molecules within a hydrogel matrix is hindered by the insoluble gel network in which drug molecules have to travel through tortuous pathways to exit the gel matrix. Here, polymer chains in the gel network act as a diffusion barrier (Uhrich et al., 1999). The slow drug release after blending suggests a prolonged pathway for the drug to travel through the polymer network. In addition, as a gel is considered as a solid whose zero-shear viscosity is infinite, the molecular diffusion of drug is also controlled by the high viscosity of a gel. Although the molecular interactions between the drug (TPH) and the individual component polymers are not considered to increase by blending to result in

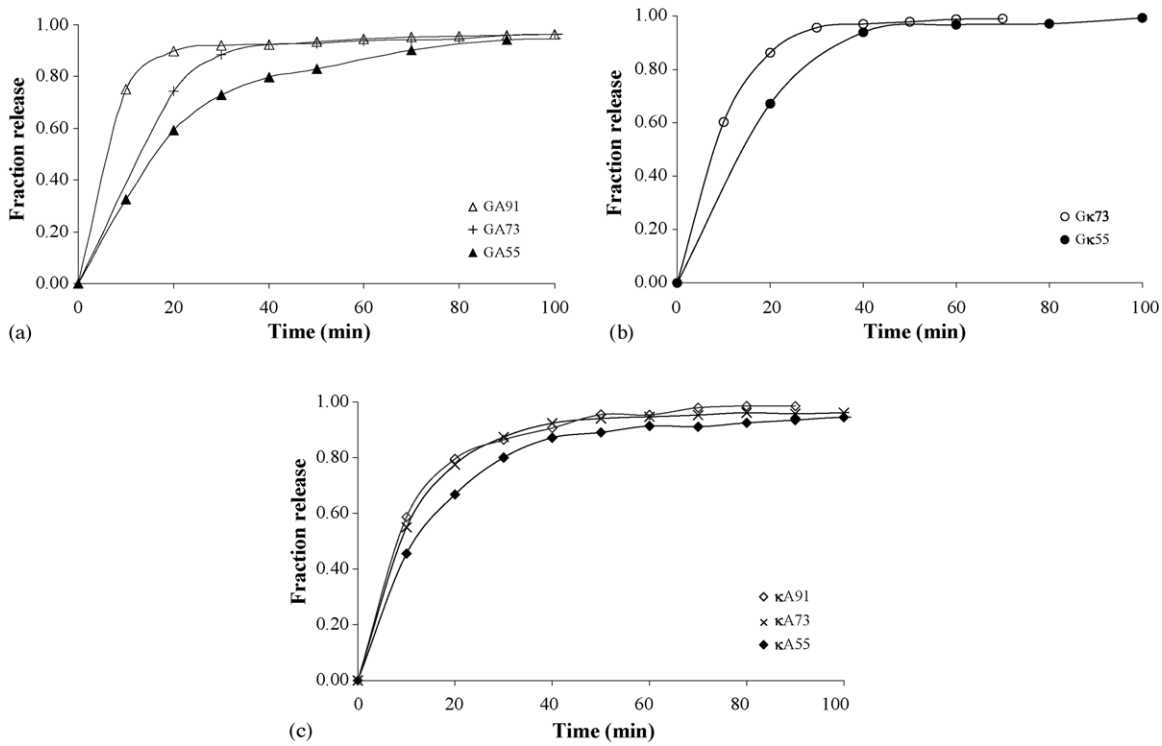

Fig. 3. Effect of blend compositions of hydrogels based on (a) gelatin and agar; (b) gelatin and κ-carrageenan; (c) κ-carrageenan and agar on the release of theophylline at $37 \pm 0.1\,^{\circ}C$.

the decrease in release rate, it would be possible for the blending to cause some changes in the gel network structure, such as polymer conformation, network density, etc. Particularly, the possibility of formation of an IPN gel from a polymer blend would be an important factor worthy to be investigated. Amici et al. (2002) reported the formation of a molecular IPN from agarose and κ-carrageenan. When an IPN hydrogel is formed from a polymer blend, the molecular diffusion of a drug immobilized in the gel may be affected if the density or the complexity of the gel network is changed by the IPN structure. However, when the total polymer content in a gel is fixed as we used in this study, it is difficult to consider a denser network formed from two-component polymers than from a single-component polymer if no additional crosslinks are formed between two networks. To make a denser network, the formation of inter-network crosslinks (i.e. crosslinks between hetero-polymer networks) would be necessary. In this case, the IPN has a different structure from a normal IPN in which there are no direct crosslinks between the two networks. It is possible that the inter-network crosslinks are formed through intermolecular hydrogen bonding, ionic bonding, or physical entanglement. In this work, we consider that all these bonds (i.e. hydrogen bond, ionic bond, and physical entanglement) could be important for the blend hydrogels formed from gelatin, agar, and κ-carrageenan. At this moment, however, we have not been able to confirm our above-mentioned hypothesis due to the technical difficulties in accurately determining the crosslinking densities of the blend hydrogels.

Another interesting finding from Fig. 2 is that adding of a polysaccharide component (agar or κ-carrageenan) to gelatin has significantly decreased the drug release rate, while this decreasing effect is smaller when two polysaccharide components (agar and κ-carrageenan) are used. This result could be explained by the different IPN structures between the former and the latter. In the case of the latter, the similarity in molecular structure between agar and κ-carrageenan would make it difficult to form the additional crosslinks (hydrogen bonds

or ionic bonds) between two networks (i.e. the agar network and the κ-carrageenan network) even though an IPN structure can be formed from the agar and the κ-carrageenan. In the blend gel formed from gelatin and agar or from gelatin and κ-carrageenan, however, it is possible to form additional crosslinks through hydrogen bonding and/or ionic bonding. For example, gelatin is a protein consisting of amino acid monomer units and it can form a helical structure due to the intramolecular hydrogen bonding. Under an acidic condition, a protein may become a cationic polyelectrolyte so that the formation of ionic bonds between gelatin and κ-carrageenan would be possible because κ-carrageenan is an anionic polyelectrolyte.

3.2. Effect of blend composition on release

In order to investigate the effect of blend composition on TPH's release, three weight ratios of blending have been employed in this study, which are 9:1, 7:3 and 5:5, where gelatin or κ-carrageenan was used as the first polymer while agar or κ-carrageenan did as the second. The percent cumulative releases of TPH to water at $37 \pm 0.1\,^{\circ}C$ from the three hydrogels based on different weight ratios were plotted as a function of time in Fig. 3a–c.

Fig. 3a shows the release profiles for the GA hydrogels consisting of gelatin and agar, while Fig. 3b and c are for the Gκ and κA hydrogels, respectively. From Fig. 3, it is observed that with increasing the content of the second polymer from 10 to 30% and further to 50%, the release profile of TPH is significantly lowered, indicating a reduced release rate. Among the three types of hydrogels, this effect is particularly dramatic in the gelatin and agar (GA) and gelatin and κ-carrageenan (Gκ) hydrogels. The κA hydrogels did not show a significant effect of blending ratio on the release. This might be due to the molecular similarity between κ-carrageenan and agar, which resulted in a similarity in the gel network structure as compared to that formed

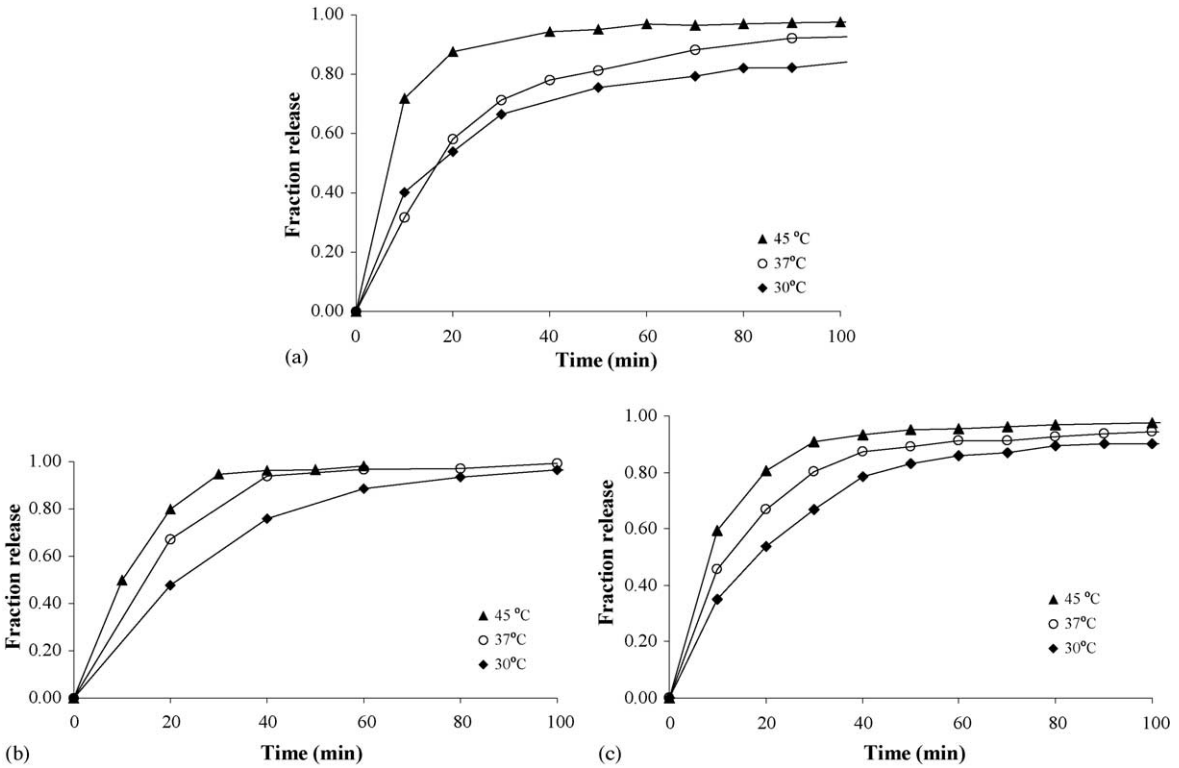

Fig. 4. Effect of temperature on the release of theophylline from hydrogels based on (a) gelatin and agar (5:5); (b) gelatin and κ-carrageenan (5:5); (c) κ-carrageenan and agar (5:5); (▲) 45 °C; (◯) 37 °C; and (♦) 30 °C.

from individual κ-carrageenan or agar. In any case, the 1:1 ratio gives the slowest release profile. The reason behind this result might be a nearly optimal formation of an IPN with a ratio of 1:1. When the second component has a fewer amount than the first one, the second one would not be able to form a complete network within the network of the first one. Secondly, the formation of inter-network crosslinks is reasonably expected to be dependent on the perfection of IPN formation. The inter-network crosslinks would be maximally formed between two complete networks that are interpenetrated physically. The only ratio that satisfies this condition is 1:1. Therefore, the ratio of 1:1 should give the densest gel network to delay the molecular diffusion of TPH through the gel matrix.

3.3. Effect of temperature on release

Thermosensitive hydrogels always show temperature dependence. Different types of hydrogels may have different thermosensitivities. When temperature changes, a gel network will expand or shrink, resulting in a denser or looser network. A looser gel network may provide more "free volume" for drug molecules to move. Also, temperature can affect mobility of a molecule, and the higher temperature the higher molecular mobility in a diffusion process. In addition, a substance may have different water-solubility at different temperatures. Thus, it can be expected that the release of TPH from a hydrogel is temperature-dependent and the effect of temperature on the release is complicated. In order to investigate the effect of temperature on the drug release, three different temperatures 30, 37 and 45 °C were used to conduct the release experiments. Fig. 4a–c show the release profiles of TPH from the three hydrogels with a blend ratio of 1:1 at 30, 37 and 45 °C, respectively. From these figures, the temperature effect on the release process can be clearly observed. For example, at 30 °C, the time for the Gκ55 release system (Fig. 4b) to reach an equilibrium release is about 200 min. This time has been reduced to 140 min at 37 °C, and further to 60 min at 45 °C. The temperature effect can be attributed to a combined effect from the three factors mentioned above, which are a looser gel network, a higher molecular mobility of TPH in the hydrogel and a higher solubility of TPH in the medium solution at enhanced temperatures. As a result, the rate of the drug molecules diffusing out of the hydrogel matrix will be increased.

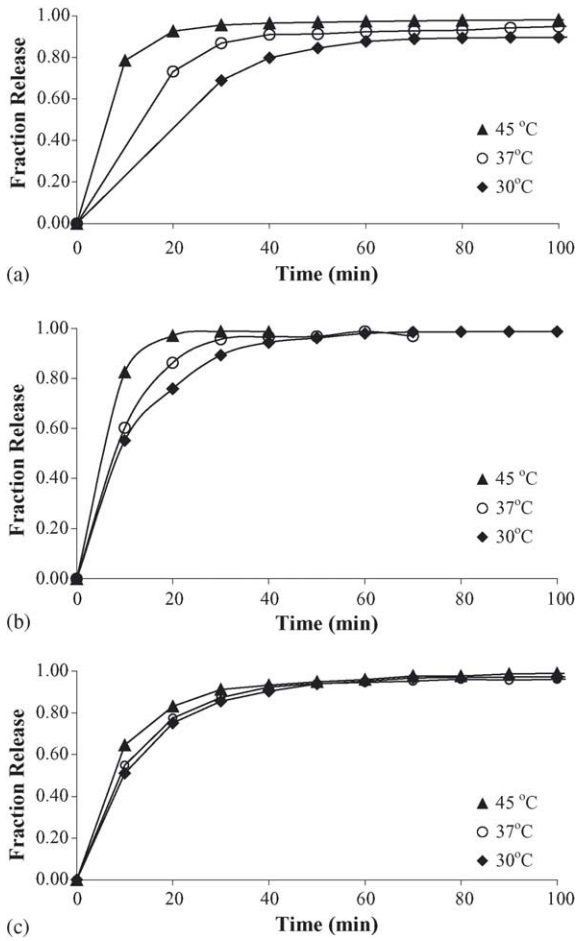

Fig. 5. Cumulative fraction releases of theophylline from hydrogels based on (a) gelatin and agar (7:3); (b) gelatin and κ-carrageenan (7:3); (c) κ-carrageenan and agar (7:3) at various temperatures: (▲) 45 °C; (◯) 37 °C; and (♦) 30 °C.

The release profiles of TPH from the three types of hydrogels with a blend ratio of 7:3 are given in Fig. 5 and a similar tendency for the temperature effect with the blend ratio of 1:1 is observed.

As shown above, the different formulations of hydrogels have resulted in different release properties, which might be due to the different gel network structures controlled by formation of IPN, inter-network crosslinks, etc. Since a gel network structure formed from a polymer blend is more complicated than that from a single polymer, the release mechanism of a drug

from a blend gel will be more complicated than that from a single polymer. In this work, we have proved that there is a clear effect of gel formulation.

4. Conclusions

Three types of hydrogels were prepared by blending two of three natural polymers: gelatin, agar and κ-carrageenan, and the blend ratios were varied. A model drug, TPH, was immobilized into each hydrogel and the release of TPH was studied. Our studies mainly focused on the effect of blend formulation on the release of TPH. The following results have been obtained: (1) blending of gelatin with a polysaccharide polymer (agar or κ-carrageenan) always results in a slower release than using gelatin itself; (2) when a 1:1 (i.e. 5:5) ratio (in weight) of gelatin to agar (or κ-carrageenan) is used, the release is much slower than using either gelatin or agar (or κ-carrageenan); (3) when the different blend ratios (9:1, 7:3, and 5:5) of gelatin to agar (or κ-carrageenan) are used, the slowest release is always obtained from the ratio of 5:5.

The possible mechanisms involved in these interesting results have been explored. The formation of IPN as confirmed by Amici et al. (2002) for the hydrogel of agarose and κ-carrageenan is considered to be a suitable explanation for the release results. However, at fixed polymer content, an IPN itself cannot be used to explain the reduction of drug release rate if the total gel network density is not increased by the formation of an IPN. Therefore, we first proposed a mechanism that the additional crosslinks called "inter-network crosslinks" should be formed between two interpenetrated gel networks through hydrogen bonding, ionic bonding, coforming of helical aggregates, or physical entangling.

The effect of temperature on the release of TPH has also been studied. The release rate was increased by increasing temperature.

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