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Drug Release Study of Systems Containing the Tragacanth and Collagen Composite: Release Characterization and Viscoelastic Measurements

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Summary: The kinetics of water penetration and pentoxifilline release from both Tragacanth gum and Tragacanth/Collagen matrices has been examined in pure deionised water. The rheological oscillatory measurements of their gel layer obtained by swelling of the imprinted pentoxifilline-filled polymer matrix with water have been performed. To qualify a polymer for application in drug formulation, appropriate gel stiffness is required. The aqueous solution of Tragacanth does not seem to acquire the actual strength that a hydrogel must retain for this purpose. Thus, along with Tragacanth, gelatin, $CaCl_2$ and 1, 8 octandiamine curing agent were individually blended in a mixture with Tragacanth gum to improve the gel behavior and drug delivery of the system. The strength of the gel at the body temperature (37 °C) was studied using a cone and plate rheometer. It was found that gelatin could enhance the gel strength of Tragacanth by forming a porous composite. The drug release to an aqueous solution at room temperature was analyzed to be slower for a composite of 1:2 Tragacanth/Collagen.

Keywords: Collagen; Composite; drug release; Tragacanth; viscoelastic

Introduction

The future application of drugs, peptides and proteins, to reach specific targets in body, mainly depends on the polymers used in the drug formulation[1,2]. Also, the application of polysaccharides has been mentioned frequently as the appropriate candidates in drug formulating to target various parts in human body such as colon[3,4]. These polymers play an important role in the controlled release purposes[2,5,6]. Unfortunately, the literature in this regard still lacks a significant amount of scientific proportions filling the gap between the rheological properties and the drug release kinetics[7]. Hydrogels are three dimensional, hydrophilic polymer networks that can imbibe large amounts of water or biological fluids. There are some literature on dynamic rheological measurements of starch gels which somehow characterizes their structural behavior[6,7]. If one understands the dynamics of the polymer molecules used in drug formulation, the problem of diseases can then be diminished to the problem of molecular science[8]. Polymers used in the formulation of drugs should be crosslinked using chemical or physical crosslinking methods or be blended with an appropriate polymer to envisage the flow properties yet to be seen in the system[7]. In the case of physical crosslinking, one uses Collagen (gelatin) with gum Tragacanth to increase the Tragacanth gel behavior. Tragacanth forms a weak gel once dissolved in water. However, the quality of crosslinking as may be expected is not as high as the chemical crosslinking. This may then produce an application that one can use to produce drugs having the controlled release properties.

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To find an appropriate drug delivering system the imprinting method is implemented. Reaction (1) schematically illustrates an equilibrium signature of imprinting a drug (L) into a network of monomer/polymers (M):

$$\begin{aligned} &M + L \xrightarrow{k_f} ML \\ &M + L \xleftarrow{k_r} ML \\ &K_{association} = \frac{k_f}{k_r} = \frac{[ML]}{[M][L]} \end{aligned} \quad (1)$$

where ''M'' stands for the macromolecular monomer or crosslinks. ''L'' stands for a ligand or template that can be drugs; peptide or protein molecules intended to be imprinted within the polymer network. To have a stable network of imprinted drug in a polymer base there is a $K_{association}$ equal to a $1/K_{dissociation}$ otherwise a stable network is not formed.

The drug formulation for the controlled release is determined and controlled by the dynamics of polymer molecules used in the pharmaceutical formulations. These systems can control the smart release of drugs once implemented in the human body. The implementation of polysaccharides such as Tragacanth gum is considered in this work as a possible vehicle for drug formulations. So, the understanding of the dynamics of these large macromolecules in the linear viscoelastic region and the situations upon which these structures are disrupted should be discussed.

Tragacanth gum grows mainly in central Asia and the Middle East countries such as Iran and Turkey. The best Tragacanth is driven from a plant that is grown in an altitude of 1300 m or higher. The color of gum depends upon the climate. The dry climate causes the color to turn yellowish. This gum consists of two macromolecules having a total molecular weight of 850,000 Dalton. The backbone is composed of Galactoronoic acid connected by 1,4 coordination substituted by Xylose and Oxy-Xylose. Collagen (natural gelatin) is usually formed from thousands of amine acids. The macromolecules are in the form of bundles, where each bundle is composed of a triple helix having a diameter of 14 A and a length of 3000° A.

In this work, the kinetics of swelling and release of drug imprinted inside the polymer will be evaluated using the UV-Vis measurements. Here, we prepared an imprinted drug delivery system using Tragacanth gum and Collagen. The stability of the gel will be assessed using viscoelastic measurements. The heat stability of the system as well as the dynamic stability and the relaxation spectra of various physical crosslinked systems will be characterized. The thermal stability of the imprinted system is determined by measuring heat stability of the hydrogel. Eventually the water uptake and pentoxifilline release will be compared for various formulations used.

Materials and Methods

The natural Tragacanth used in this work was the bright white in color obtained from the Impiran Co with the FTIR spectra shown in Figure 1. Figure 2 displays the FTIR spectra of the gelatin, acquired from Iran Gelatin Capsule Mfg. Co used in this work. We have also shown the FTIR spectra of a wet and dry mixture of these two natural polymers as depicted in Figure 3. The significance of this figure is to show whether new bonds form between Tragacanth gum and Collagen in the solution state. It seems that upon drying peaks in the range 1000–1700 cm^{-1} disappear as hydrogen boding may have occurred between Tragacanth and Collagen. Three samples of KG01, KGD01 and KGDCa01 made of Tragacant and Collagen in a ratio of 1:2 with and without pentoxifilline were prepared. KGDCa01 contains $CaCl_2$ as a curing agent. The crosslinking was also conducted implementing 1,8 octandiamine as the curing agent with and without Collagen in the presence of Calcium chloride. The samples prepared with this diamine curing agent include KDdiCa01 and KGDdiCa01. KddiCa01 contains no gelatin in contrast to KGDdiCa01 having 0.8 grams of gelatin.

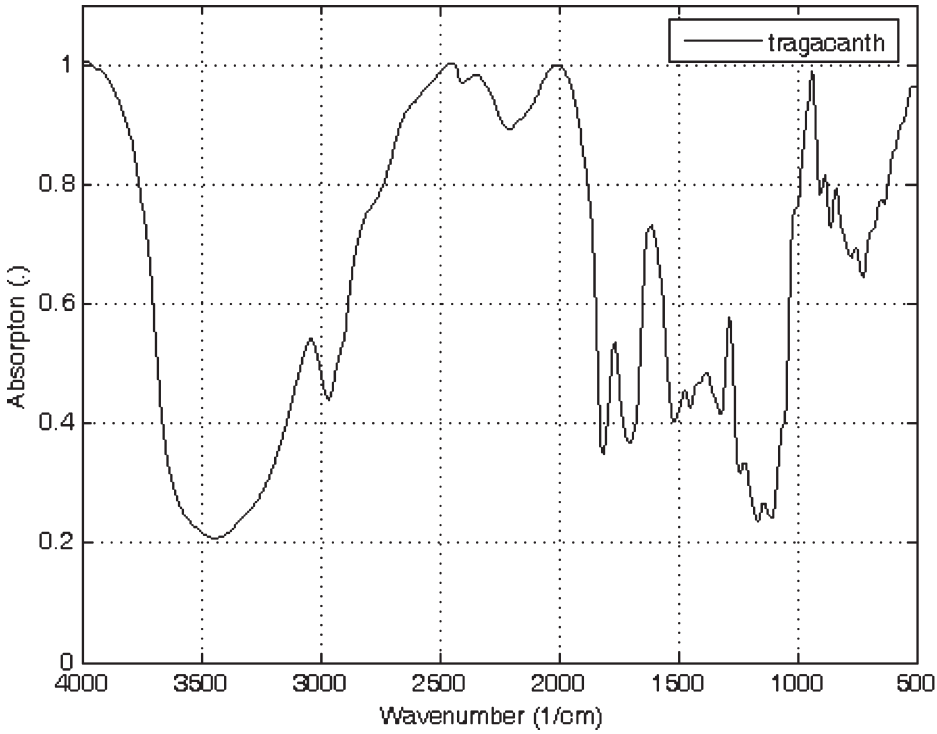


Figure 1.
FTIR spectra of the Tragacanth gum. The vertical axis shows the absorption and horizontal denotes the wave number (cm^{-1}).

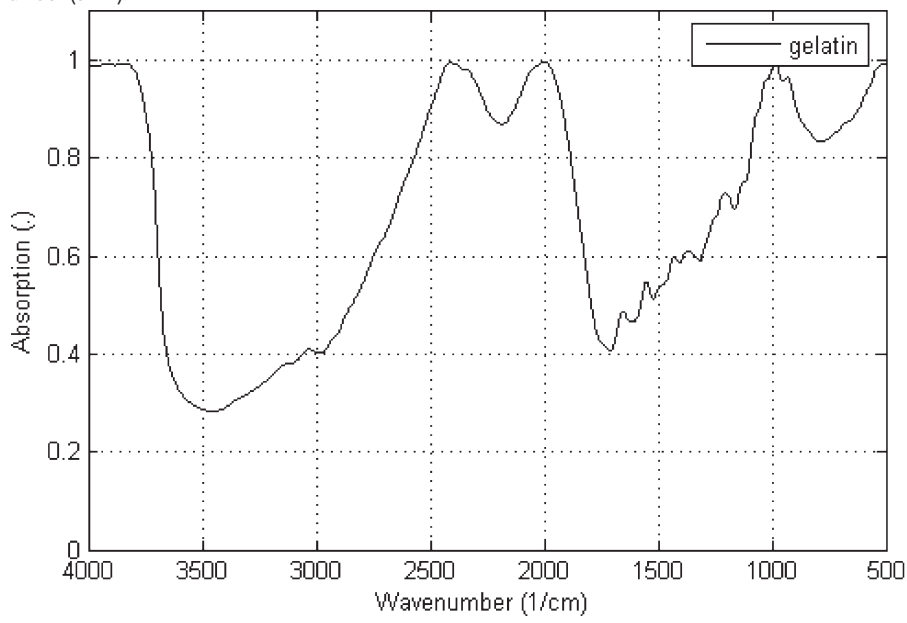


Figure 2.
FTIR spectra of the Collagen. The vertical axis shows the absorption peak fraction (.) and horizontal one shows the wave number (cm^{-1}).

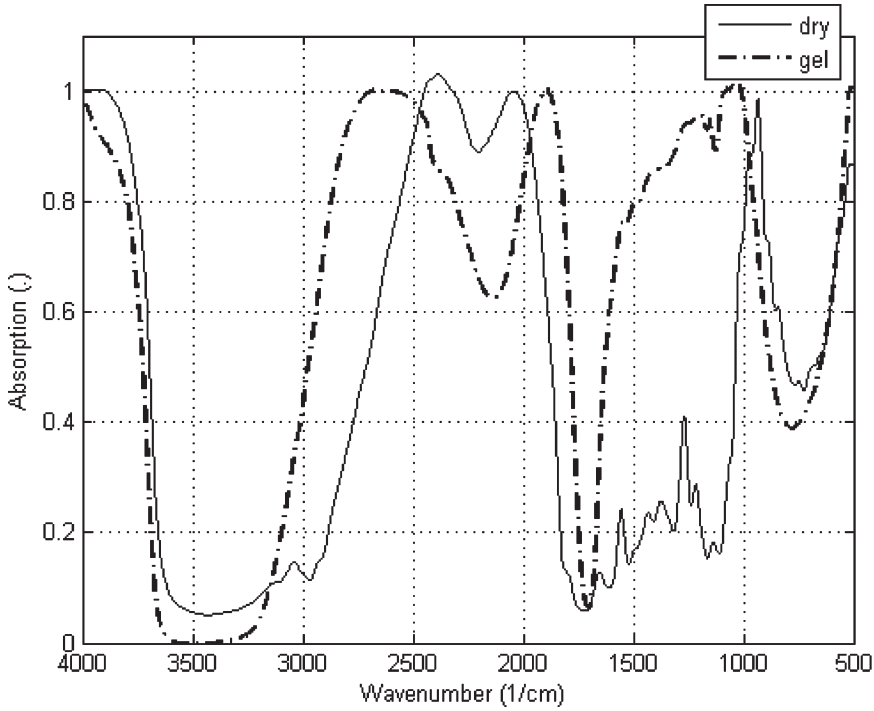


Figure 3.
The wet and dry mixture of Tragacanth/Collagen composite.

The complete composition of ingredients are listed in Tables 1 and 2.

Samples for swelling measurements were prepared such that a dried tablet weighing 0.28 g was placed in a beaker containing 500cc water. In Figure 8 total water uptake is drawn against time for the sample KG01. The weight of the swollen gel reaches 4.5 grams after 1500 min. The series of steps preparing the gel is shown in Scheme 1. In pictures (a), (b) and (c) these steps are schematically illustrated.

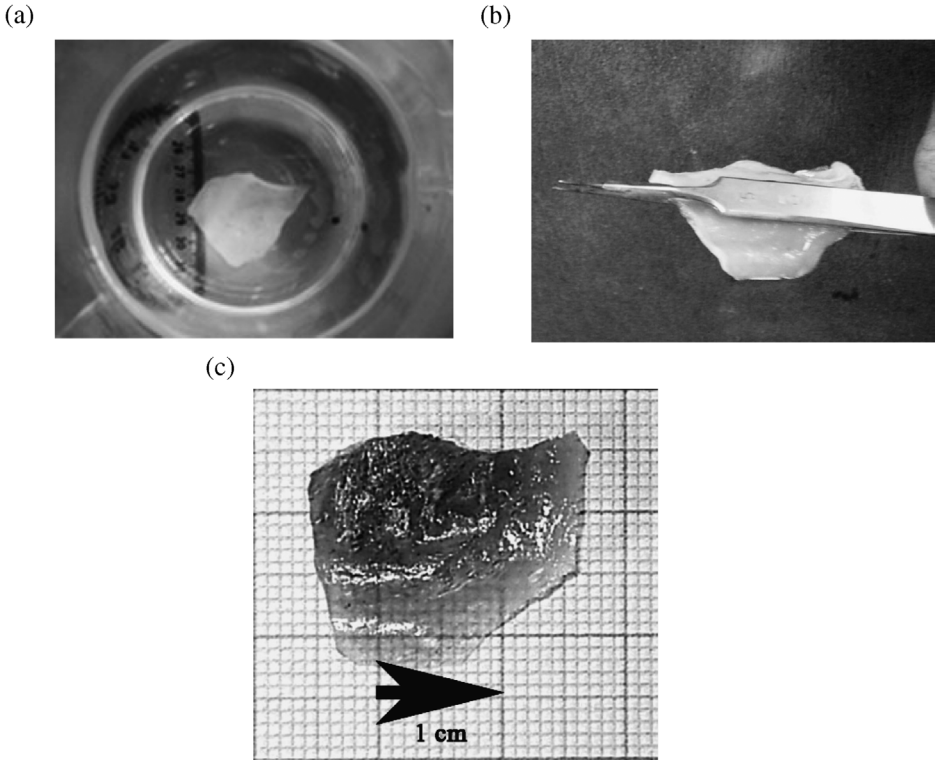
The rheological and viscoelastic measurements were carried out to see how the dynamics of polymers translate into the drug delivery properties. Pentoxifilline was used as a drug to characterize the drug delivery of the polymer formulation and its molecular structure is depicted in Scheme 2. Pentoxifilline structure is shown to explain

Table 1.
The drug formulation for two different samples

Drug formulation	KddiCa01	KGDdiCa01
Persian Tragacanth (g)	0.8	0.4
1,8 octandiamine (g)	0.1	0.05
Calcium chloride (g)	2.0	1.0
Gelatin (g)	–	0.8
Pentoxifilline (g)	0.04	0.02
total dried weight (g)	2.94	2.27
Tablet weight (g)	0.4	0.62
drug portion in tablet (mg)	5.44	5.46
drying temperature (°C)	65	65
drying time (hr)	72	72

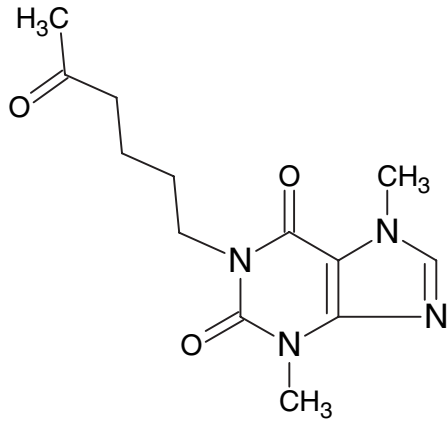
Table 2.
The drug formulation for three different samples

Drug formulation	KG01	KGD01	KGDCa01
Persian Tragacanth (g)	0.5	0.5	0.5
Calcium chloride (g)	–	–	0.5
Gelatin (g)	1	1	1 g
Pentoxifilline (g)	0.04	0.02	0.02
tablet weight (g)	0.21	0.24	0.24
film thickness (mm)	1.0	1.5	1.7
drying temperature (°C)	50	50	50
drying time (hr)	72	72	72



Scheme 1.
Three different patterns KG01. (a) While being swollen; (b) as being squeezed; (c) the drying film (note the porous surface in the scale shown).

the significance of UV-Visible measurements on characterizing its release from the composite. The drug delivery measurements were performed using UV-Vis spectroscopy carried out on drug formulations dissolved in water. Calibration of the instrument in two wavlengths of 208 and 274 nm was achieved to measure the amount of drug released from the tablet.



Scheme 2.
Pentoxifilline used as model drug in this study has two absorption peaks once dissolved in water; 208 nm and 274 nm.

The frequency sweep measurements were conducted on a 1wt. % solution of KG01, KDG01, and KDGCa01 at a temperature of $37 \pm 0.1\,^{\circ}C$. Rheological measurements of this hydrogel mixture were carried out using a MCR300 stress rheometer (Anton-Paar Physica). A 25 mm cone and plate geometry with a cone angle of 2° was implemented in this study. To minimize the evaporation of water in the sample, paraffin oil was placed around the edge of the sample such that the entire edge was covered. The effect of slip was determined to be negligible. A strain of 0.5% secured the linear viscoelastic behavior of the systems measured in this study.

The drug delivery of the system was characterized using a LKB International UV-Vis instruments having capability to measure UV and visible absorption within the ranges required for this study.

Results and discussion

Figure 4 shows the elastic modulus against angular frequency at a strain of 0.5% at a temperature of $37 \pm 0.1\,^{\circ}C$ to ensure linear viscoelatic framework. The slope of G′ with frequency for the three composite systems stays the same indicating the same structures for all three systems. This is the schematic representation of a composite system where no interpenetration (IPN) forms. Fig. 5 schematically represents G′ and G″ versus angular frequency for two samples of pure Tragacanth and Tragacanth/Collagen. G′ tops G″ for whole the frequency range applied showing a gel-like behavior. Here, when there is a mixture of 1:1 Tragacanth/Collagen, the slope of storage modulus against frequency is similar to that of the pure Tragacanth. Once the amount of gelatin becomes twice as much as Tragacanth a phase inversion occurs and the Slope of G′ becomes smaller compared with the case of 1:1. We can conclude that gelatin acts as the continuous phase and Tragacanth as the disperse phase (porous route). Due to the low mobility of gelatin molecules no interpenetration network would form as appears from the porous surface structure depicted in Scheme 1-(c).

Fig. 7 exhibits thermal stability of the structures formed using a curing system of 1, 8 Octandiamine and KG01 (1:2 Tragacanth/gelatin). As one can see, heat distorts the structure as temperature rises for KG01 indicating the weak interface structure between the phases and proving the idea of porous composite structure of these two natural polymers. In the case of curing with diamines as shown in Table 2, a strong crosslinked system yield with no defects as one can infer from Fig. 6.

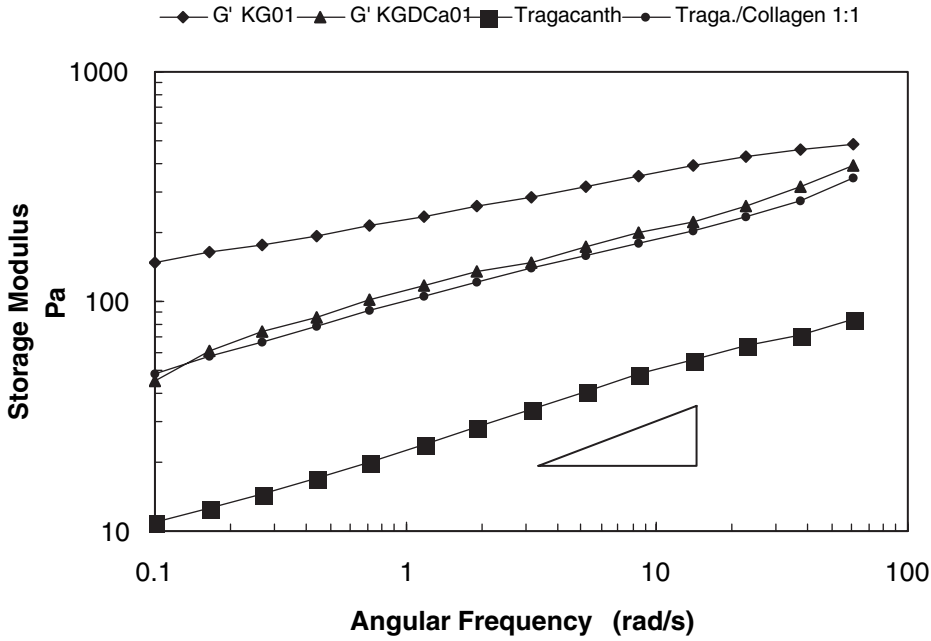


Figure 4.
Storage modulus (G′ and G″) against angular frequency for 1 wt.% aqueous solutions of Tragacanth, Tragacanth/Collagen, KG01 and KGDCa01.

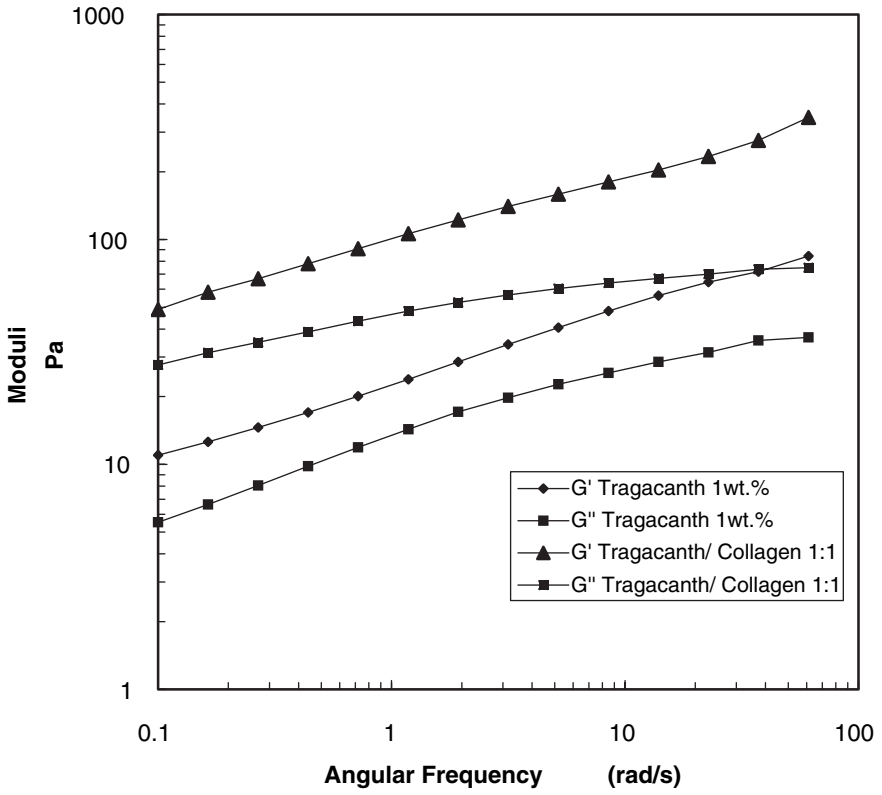


Figure 5.
Elastic and loss moduli (Pa) versus angular frequency for two samples of pure Tragacanth and Tragacanth/ Collagen 1:1 (37 °C).

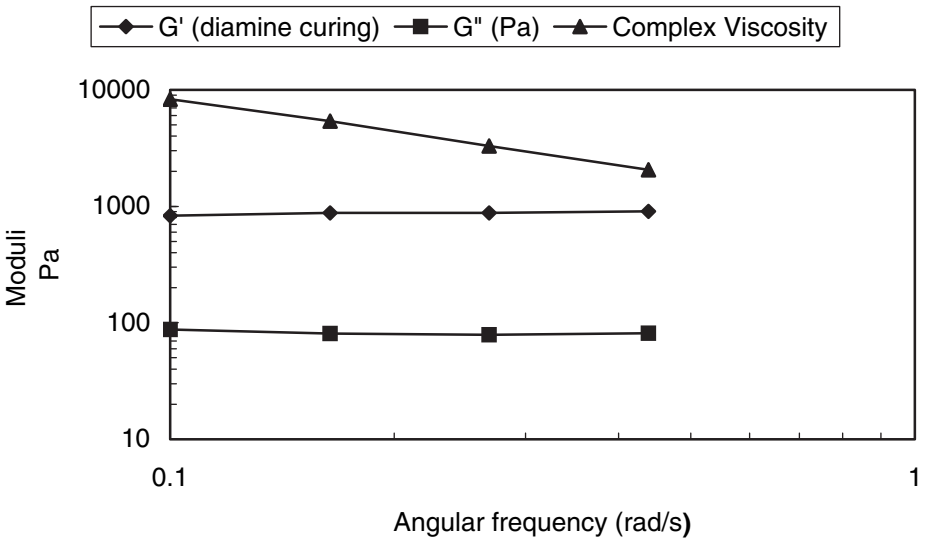


Figure 6.
A gel-like behavior observed from a swollen crosslinked film of KGDdiCa01 at 20 °C (Table 1).

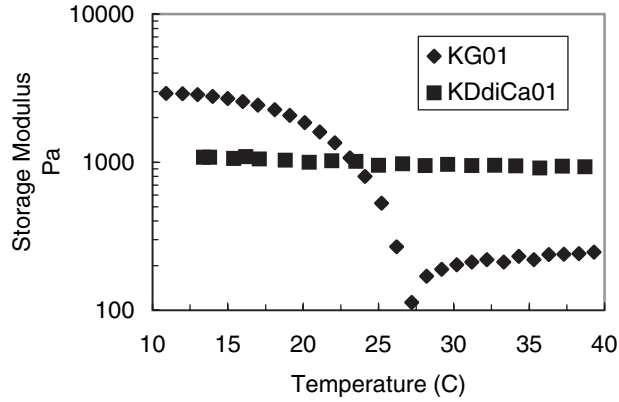


Figure 7.
Temperature frequency measurements on KG01 and KGDdiCa01 (Table 1) at a frequency of 1Hz and strain of 0.5%.

It is reported that the preparation procedure has an influence on the gel properties. This gel was prepared by imprinting the drug molecules in the blend of Tragacanth gum/Colagen; however crosslinking seems to facilitate the process of drug release by changing the microstructure into a dense network which diffusion of water into it and release of drug do not obey a same mechanism; in which case pentoxifilline tends to diffuse out of the network due to a lack of porosity corresponding to the low entropy of the system. Whereas in the case of Collagen and Tragacanth without crosslinking, the porous composite can imbibe enough water and do not allow any release of pentoxifilline. Fig. 10 shows how the addition of crosslinking $CaCl_2$ distorts the porous structure of the hydrogel and let the drug to diffuse out easily compared to absence of $CaCl_2$ in the system.

In Fig. 7 Storage modulus has been plotted against temperature for a mixture of Collagen and Tragacanth with a weight ratio of 1:1 and concentration of 1 wt.%.

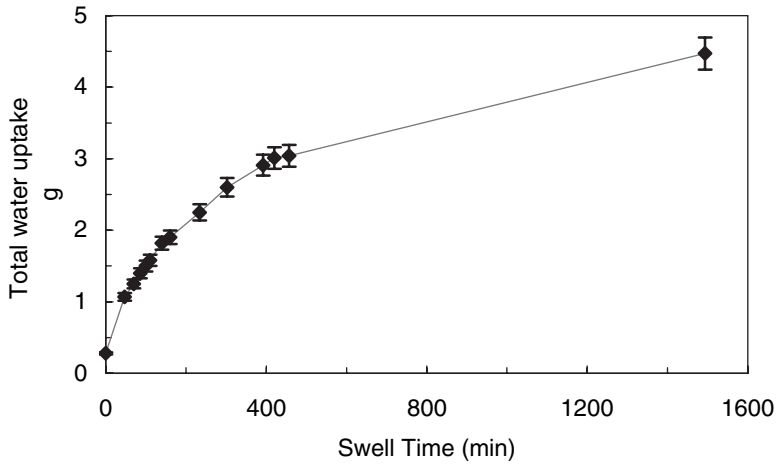


Figure 8.
Total water uptake for KG01 (Table 2). The primary weight of the sample was 0.26 g in 500 cc deionised water at 22 °C.

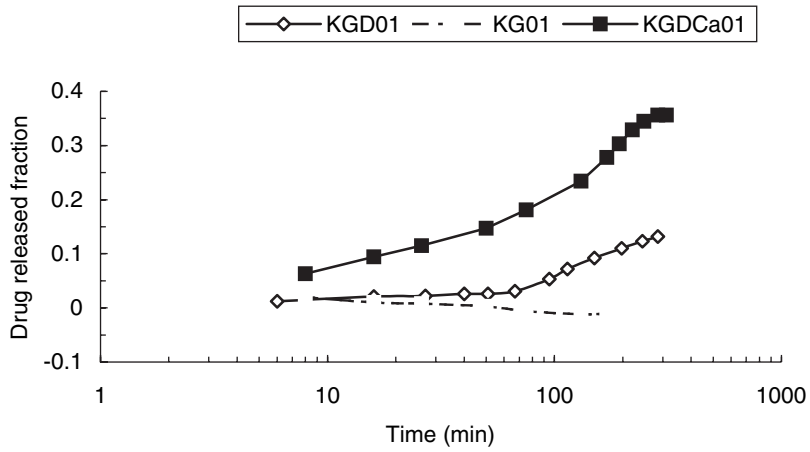


Figure 9.
The pentoxifilline release kinetics characterized using UV-Vis instrument.

The temperature range applied on the sample was from 10 to 100 °C. Two different regions were observed for an imprinted hydrogel containing 1 wt. % Tragacanth and Collagen along with Pentoxyfilline. The imprinted drug containing vehicle was stored in deionised water for 48 hours and absorbed a large amount of water. It exhibits a gel-like behavior where $G' > G''$, manifesting a gel. The change of slope with frequency implies that there are some dangling chains emanating from the hydrogel though do not stand the expression for a perfect gel. This could be due to

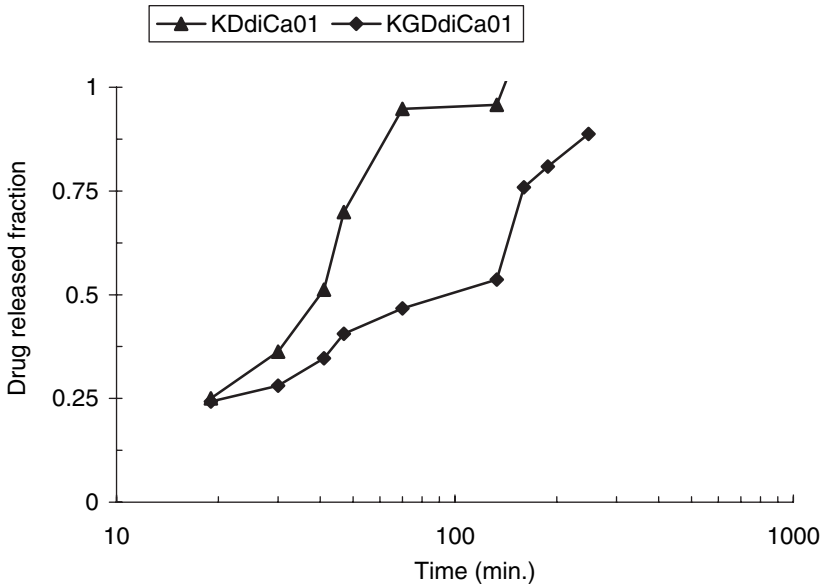


Figure 10.
UV-Vis measurements on our drug release from (Table 1 and 2). The weights and thicknesses of samples KG01, KGD01, and KGDCa01 are as listed in Table 2. The dotted line approximately set a reference as for the zero drug delivery.

the composite nature of the system where the interfaces of two polymers do not interpenetrate. The Tragacanth/Collagen has larger surface area of relaxation spectrum resulting in a higher elasticity and more relaxation modes.

Figures 8, 9 and 10 explain the water swelling and release of pentoxifilline from the formulations used in this study. The comparison of Figures 8 and 10 implies that, for instance, after absorption of water to an amount of seven times higher than the weight of the initial film, only about 10% of Pentoxifilline has been released, as understood from the UV spectroscopy measurements. The amount of release values at 40% for KGDCa01 (with $CaCl_2$), 80% for KGDdiCa01 (gelatin and $CaCl_2$) and 100% release for KDdiCa01 (no gelatin) (Fig. 9). This whole indicates that gelatin presence in Tragacanth as matrix will help forming a porous structure for better retaining and releasing mechanism.

Conclusions

We reached to this conclusion that cross-linking to an optimum point do not help the controlled drug release mechanism. To prepare an appropriate formulation for drug release the composite structure (not IPN) should form with a porous meso-structure. Here, the presence of a supporting more elastic component in the composite (Collagen) is influential in achieving the structure needed for appropriate drug delivery. Application of curing agents for enhancing the structure, although prepares a fine three dimensional hydrogel, but confines the path in which the drug can diffuse resulting in an early drug release.

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