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International Journal of Pharmaceutics 287 (2004) 39–46
international journal of pharmaceutics
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Study on jelly fig extract as a potential hydrophilic matrix for controlled drug delivery

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Received 23 March 2004; received in revised form 16 August 2004; accepted 20 August 2004

Abstract

The principal component of aqueous extract of jelly fig (*Ficus awkeotsang* Makino) seeds is a pectin-type polysaccharide, gelling even at room temperature without adding any sugars, acids or ions. The objective of this study was to evaluate jelly fig extract (JF) as a matrix base for sustained release tablets. Drug release profile from JF tablet was examined using theophylline as a model drug, compared with those from USP graded pectin (USP-P). Release profile from JF tablet was a sustained release pattern and not affected by pH of medium. USP-P tablet showed a similar release profile of JF tablet, however, the release mechanisms differed. Matrix erosion studies revealed that the percentage of drug released from USP-P tablet was proportional to that of matrix eroded. On the other hand, JF tablet was eroded up to 50% of matrix for 4 h and showed a constant value thereafter. According to water uptake studies, JF tablet showed an initial burst swelling followed by slow water uptake, suggesting diffusion-controlled kinetics in later phase. Moreover, theophylline release rate from JF tablet was modified by drug content in the tablet, increasing with decrease in drug amount. These findings indicated JF was a potential hydrophilic matrix for controlled drug delivery.

Keywords: Jelly fig (*Ficus awkeotsang* Makino); Controlled drug delivery; Hydrophilic matrix; Sustained release; Theophylline; Pectin

1. Introduction

Ficus awkeotsang Makino, of the Noraceae family, is grown on the mountainsides of the central part of Taiwan. The seeds of its fruit, called jelly fig or "Ai-Yu-Tung," are used to make a dessert jelly cake in some oriental countries. The aqueous extract spontaneously forms a pudding-like gel even at room temperature without any additives. Since 1930, the unique gel-forming property of the jelly fig extract (JF) has been the subject of many chemical and physiochemical investigations. Early study (Oda and Tanaka,

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doi:10.1016/j.ijpharm.2004.08.023

1966) suggested that the gel-forming polysaccharide may be pectin, containing some neutral sugar components, i.e., arabinose, galactose and rhamnose. Afterward, the acidic polysaccharide in jelly fig seeds was an essentially linear polysaccharide containing α (1–4)-D-galacturonic acid residues and was devoid of L-rhamnose residues which were necessary for gel-formation of high methoxy pectin (Komae and Misaki, 1989). Studies on gel-forming mechanisms have suggested that the high methoxy polygalacturonide in JF would be converted into a methoxyl-free or low methoxylated polygalacturonide by action of endogenous pectinesterase, and calcium ions in JF were simultaneously placed between the polygalacturonide chains, leading to the formation of an ionic-bound type gel (Komae et al., 1989). Although a variety of studies have been conducted, there is no report on an application of JF to drug delivery systems. We considered that JF with unique mechanism of gel-formation was useful to develop a new device for drug delivery.

Recently, many controlled release formulations based on hydrophilic gel-forming matrix tablets have been developed. Numerous polymers, such as polysaccharides, have been used in the tablets (Melia, 1991). Among them, pectins have been successful choice for this purpose to some extent (Naggar et al., 1992; Sungthongjeen et al., 1999). Pectins are hydrophilic linear polysaccharides extracted from plant cell walls, chiefly consisting of partially methoxylated poly α (1–4)-D-galacturonic acids, like as main components of JF. They are generally regarded as nontoxic material, mainly used as gelling agents in many food industries. Therefore, first of all, we investigated JF in a form of hydrophilic matrix tablet in the course of studies on an application to controlled drug delivery.

In this study, hydrophilic matrix tablets were prepared from JF by direct compression. Drug release behavior of JF tablet was investigated compared with commercially available pectins, low methoxy pectin, high methoxy pectin and USP graded pectin, using theophylline as a model drug. In order to reveal the drug release mechanism of JF tablet, matrix erosion and water uptake studies were performed. In addition, the effects of pH in release medium and ratio of drug to JF on drug release from the tablets were examined.

2. Materials and methods

2.1. Materials

Dried seeds of jelly fig were provided by Mansho Co. (Yokohama, Japan). Low methoxyl pectin (LM-P, GENU type LM-13CG) with a degree of esterification 38% and high methoxy pectin (HM-P, GENU type D slow set confectionery) with a degree of esterification 62–65% were generously supplied by CP Kelco Japan ApS (Tokyo, Japan). USP grade pectin (USP-P) with a degree of esterification 74% and theophylline anhydrous (TH) was purchased from Sigma Chemical Co. (St. Louis, MO). TH and three kinds of pectins were used after sieving through a 100-mesh sieve (less than 150 μm). All other chemicals were of reagent grade and used as received.

2.2. Extraction from jelly fig seeds

The jelly fig seeds (6 g) were soaked in distilled water (100 mL) and extracted for 15 min while stirring. The resulting extract was passed through nylon cloth, and the filtrate was immediately freeze-dried. The powdered extract was used after sieving through a 100-mesh sieve (less than 150 μm) for further examinations.

2.3. Preparation of hydrophilic matrix tablets

Flat-faced tablets (200 mg, 8 mm in diameter and about 3.2 mm in thickness) were prepared by compressing mixtures of TH and matrix base directly under 150 kgf/cm^2 for 30 s using a hydraulic press (Shimadzu Co. Ltd., Kyoto, Japan). TH and matrix base, such as JF, LM-P, HM-P or USP-P, were mixed by a mortar and pestle, at the ratio of 1:4 except especially mentioned.

2.4. Drug release study

Release experiments were conducted by a rotating basket method (100 rpm) at 37 ± 0.5 °C. The dissolution media used were 900 mL of JP XIV 1st fluid (pH 1.2, 0.07 M HCl and 0.0342 M NaCl), 2nd fluid (pH 6.8, 0.05 M H_2KPO_4 and 0.0236 M NaOH), and acetate buffer (pH 4.0, 0.04 M CH_3COONa and 0.168 M CH_3COOH). Five mL samples were withdrawn from the dissolution vessel at 0.25, 0.5, 1, 2, 4, 6, and 8 h and

filtered with a membrane filter (pore size 0.45 μm). The filtrate was analyzed spectrophotometrically for TH content at 274 nm. An equal volume of the same dissolution medium was added to maintain a constant volume. The data represents an average of three determinations.

2.5. Erosion study

Tablet erosion studies were performed by a method similar to the drug release study. Tablet placed in a basket was subjected to dissolution in 900 mL of JPXIV 2nd fluid at 37 °C at a rotation speed of 100 rpm. At appreciate time, the tablet remaining in the basket was removed and dried to a constant weight in a hot air oven at 60 °C. The amount of TH released at the same time was also determined spectrophotometrically at 274 nm in order to calculate the amount of drug remaining in the tablet. Three different tablets were measured for each time point, and fresh tablets were used for each individual time point. The percent eroded at each time point was calculated from

$$\text{erosion}\,(\%) = \left[\frac{M_\text{i} - (W_\text{d} - (X_\text{i} - X_t))}{M_\text{i}}\right] \times 100 \quad (1)$$

where M_i and X_i are the initial weights of matrix and drug loaded, respectively, W_d is the dried weight of the tablet and X_t is the amount of TH released at time, t. All experiments were carried out in triplicate.

2.6. Water uptake study

Water uptake studies were also performed by a method similar to the drug release study. A weighted tablet placed in a basket was subjected to dissolution in 900 mL of JPXIV 2nd fluid at 37 °C at a rotation speed of 100 rpm. At a selected time interval (1, 2, 4, 6, and 8 h), the tablet was withdrawn and excess water removed, then weighed. The amount of TH released at the same time was also determined spectrophotometrically at 274 nm in order to calculate the amount of drug remaining in the tablet. The water sorption characteristics of the tablets were expressed as percent water uptake according to the following equation:

$$\text{water uptake}\,(\%) = \left[\frac{W_t - (W_\text{i} - X_t)}{W_\text{i}}\right] \times 100 \quad (2)$$

where W_t and W_i are the wetted and initial weights of the same tablet, respectively, and X_t is the amount of TH released at time, t. All experiments were carried out in triplicate.

3. Results

3.1. Release profiles from tablets

Fig. 1 shows TH release profiles from various tablets obtained by a rotating basket method at a rotation speed of 100 rpm. LM-P and HM-P tablets showed initially rapid release profiles up to 80% released and then slow release patterns thereafter. Sungthongjeen et al. (1999) observed similar findings using high methoxy pectin (GENU pectin type B). LM-P and HM-P contain some solid sucrose in order to modulate gelling ability. The rapid release of TH may be owing to dissolution of sucrose molecules, leading to rapid swelling and erosion of the tablets. Drug release rates of LM-P and HM-P tablets were similar to each other, although the solubility of pectin decreased as the degree of esterification increased. It was probably due to the rapid dissolution of sugar, covering up the influence of solubility of pectins. On the other hand, USP-P and JF tablets showed sustained release profiles over 8 h. Although the release rates of JF and USP-P tablet were similar, the release mechanisms seemed to differ. It was because at the end of release test USP-P tablets were completely dissolved, however JF tablets maintained rigid gel matrices. Therefore, we performed further studies for characterizing JF tablet compared with USP-P tablet.

3.2. Kinetics of drug release

In order to understand the mode of drug release from JF and USP-P tablets, the release data (≤70%) were fitted to the following power law equation (Ritger and Peppas, 1987).

$$\frac{M_t}{M_\infty} = kt^n \quad (3)$$

where M_t/M_∞ is the fraction of drug released at time, t, k is the proportionality constant which accounts for the structural and geometrical properties of the matrix, and n is the diffusional exponent indicative of the mechanism of drug release. According to Ritger

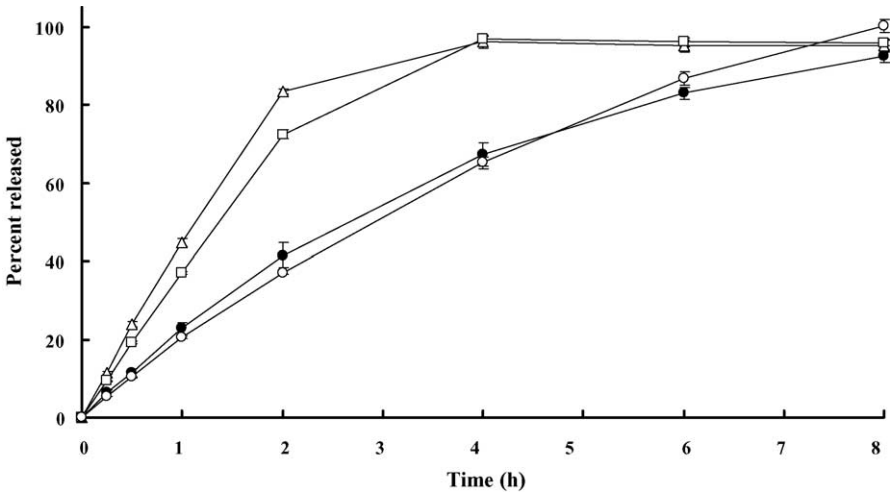

Fig. 1. Drug release profiles from tablets prepared from JF (●), USP-P (◯), LM-P (△), HM-P (□). The experiments were performed using the JP XIV 2nd fluid at 37 °C. Each point represents the mean ± S.D. ($n = 3$).

and Peppas (1987), a value of the exponent, $n = 0.45$, $0.45 < n < 0.89$, $0.89 < n < 1.0$ indicates Fickian diffusion, non-Fickian (anomalous) diffusion and zero-order transport, respectively. The results are summarized in Table 1. The release data for JF and USP-P tablets give a good fit in Eq. (3). As seen in Table 1, the values of diffusional exponent, n, for JF and USP-P tablet were 0.87 and 0.90, respectively, indicating non-Fickian kinetics and zero-order transport, respectively.

3.3. Matrix erosion

In hydrophilic matrix tablets, hydration of polymer results in the formation of a gel layer, followed by matrix bulk hydration, swelling and erosion (Bamba et al., 1979). Therefore, we examined the tablet erosion by a similar method of drug release study. Fig. 2 shows TH release from matrix as measured spectrophotometrically and according to tablet erosion studies. In Fig. 2a, TH release from USP-P tablet was identical to the rate of the matrix dissolution. This suggests that there is a constant amount of drug present in the eroding polymer during specified time intervals. These results also indicate that drug release may be described as a process that is controlled solely by erosion of the tablet. On the other hand, erosion of JF matrix was ended within 4 h at 50% eroded as shown in Fig. 2b. Initial weight loss of the matrix may be caused by dissolution of small molecular components of JF, because aqueous extract from jelly fig seeds contains about 7% of inorganic ions (Suzuno et al., 1997) and low molecular weight polysaccharide to some extent, and so on. Then gelation appeared to be occurred, being not viscous but tough and porous, also less susceptible to erosion. It was also evident, from Fig. 2b, that the amount of drug released from JF tablet was difference in the magnitude of that of matrix eroded. Therefore, in later phase, drug release from JF tablet may be more likely to be by diffusion of drug than by erosion of matrix.

Table 1
Coefficients and exponents of drug release functions based on Eq. (3) for JF and USP-P tablets

Matrix tablet	Coefficient parameter (k)	Diffusional exponent (n)	Correlation coefficient (r^2)
JF tablet	21.5	0.87	0.997
USP-P tablet	19.5	0.90	0.999

3.4. Water uptake by tablet

The results of water uptake studies are presented in Fig. 3. The water uptake by JF tablet shows a constant rate up to 8 h, as shown in Fig. 3a. On the other hand, the water uptake by USP-P tablet could not be determined because rapid erosion of the matrix was occurred. In general, swelling kinetic of matrix, which

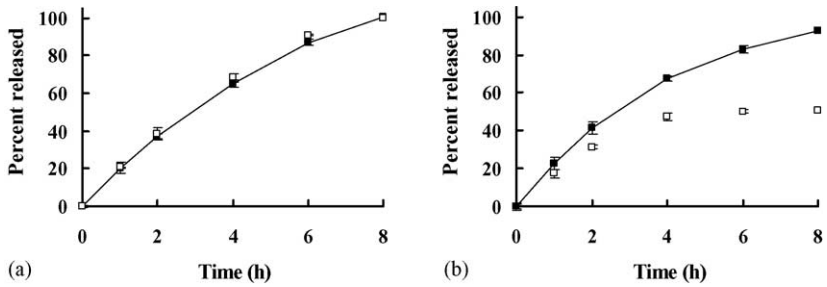

Fig. 2. Dissolution of USP-P (a) and JF (b) matrix tablets. Each point represents the mean ± S.D. ($n = 3$). Key: (■) drug release, (□) tablet erosion.

control the matrix dissolution, was an important determinant of drug release. The water uptake data obtained for JF tablet were subjected to the Vergnaud model (Vergnaud, 1993) to determine the rate of water uptake. The generalized form of the Vergnaud model is showed as follows:

$$M_t = kt^n \quad (4)$$

where M_t represents the amount of liquid transferred at time, t, and k is a constant which depends on the amount of liquid transferred after infinite time, the porosity of matrix, and diffusivity. The exponent, n, indicates the mechanism of water uptake. According to Ebube et al. (1997) and Roy and Rohera (2002), a value of the exponent, $n \leq 0.5$, $0.5 < n < 1.0$, $n = 1.0$ indicates diffusion-controlled, anomalous diffusion and stress relaxation-controlled mechanisms, respectively. The data plotted according to the Vergnaud model shown in Fig. 3b indicated that rapid hydration of the matrix was occurred by contact with the release medium, and slow water uptake continued to 8 h after. The kinetic of water uptake by the tablets was determined by fitting the water uptake data to Eq. (4). The data showed a good fit in the model which the value of exponent, n, being 0.20 ($r^2 = 0.982$), suggesting the rate of diffusion of the liquid is much less as compared with the rate of relaxation of the polymer segment. The result in this study, being extremely small value, indicated that the kinetic of water uptake was very complex, owing to an initial burst swelling of the tablets. The initial swelling may be caused by dissolution of low molecular weight compounds in JF, and then followed by gelation of JF, making a rigid gel layer.

3.5. Effect of pH on drug release

The effect of pH in the medium on TH release from USP-P and JF tablets is shown in Fig. 4. In both systems, the drug release in 1st fluid, pH 1.2, was slightly slower than those in acetate buffer, pH 4.0, and JP XIV 2nd, pH 6.8. These may be due to deionization of carboxyl residue of polymer chain, resulting in decreased expansion of polymer. So, the matrices were more rigid to retard drug release. It was not crucial factor affect-

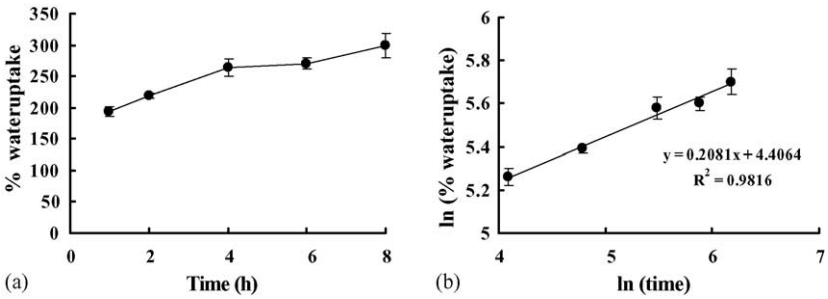

Fig. 3. Water uptake profile by JF tablet. Each point represents the mean ± S.D. ($n = 3$). Key: (a) plot of percent water uptake as a function of time, (b) plot of log percent water uptake as a function of log time.

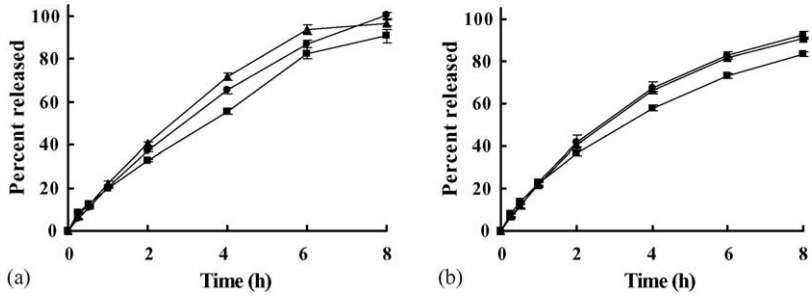

Fig. 4. Drug release profiles from USP-P (a) and JF (b) tablets in various media. The experiments were performed using acetate buffer, pH 4.0, (▲), JP XIV 1st (■) and 2nd fluid (●) at 37 °C. Each point represents the mean ± S.D. ($n = 3$).

ing drug release rate, however, because differences in percent released at 8 h were within 10% in both system.

3.6. Effect of drug/polymer ratio on drug release

Finally, we investigated the effect of drug/polymer ratio on drug release from the viewpoint of regulation of drug release rate. The effect of TH/JF ratio on drug release is shown in Fig. 5. Decreasing JF concentration in the tablet reduced TH release rate, as shown in Fig. 5a. As described above, the drug release after 2 h was more likely to be by diffusion than by erosion. Therefore, the release data after 2 h were characterized by fitting to the Higuchi's model (Higuchi, 1961) which is given as follows:

$$Q(t) = k\sqrt{t} \qquad (A \gg C_s) \tag{5}$$

$$k = (2A\,D\,C_s)^{1/2} \tag{6}$$

where $Q(t)$ is the amount of drug released per unit area of matrix at time, t, A is the total amount of the drug in unit volume of matrix, D is a diffusion coefficient of the drug in the matrix, k is a kinetic constant and C_s is the drug solubility. In this case, the fraction of drug released at time, t, was expressed by following equation.

$$\frac{M_t}{M_\infty} = \frac{Q(t)S}{AV} \tag{7}$$

where M_t/M_∞ is the fraction of drug released at time, t, S is the surface area of the matrix and V is the volume of the matrix. Then, Eqs. (5) and (6) are substituted to Eq. (7).

$$\frac{M_t}{M_\infty} = \frac{S}{V}\left(\frac{2DC_s}{A}\right)^{1/2} \times \sqrt{t} \tag{8}$$

Eq. (8) indicates that the percentage of drug released is proportional to the square roots of time. The plots for the release data of 2–8 h according to Higuchi's model are shown in Fig. 5b. The percentage of drug released as a function of square root of time is lin-

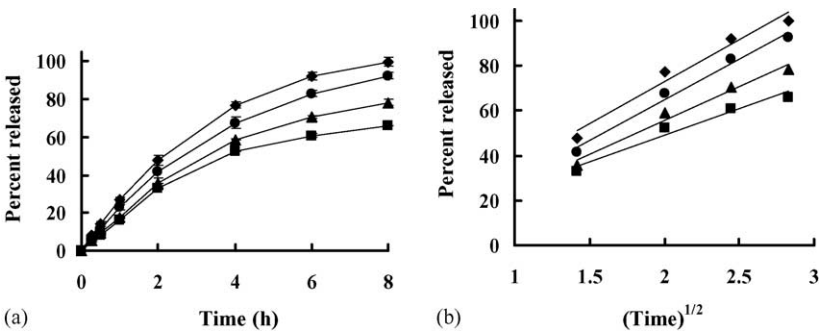

Fig. 5. Plot of percent released from JF tablets containing 10% (♦), 20% (●), 30% (▲), and 40% (■) of theophylline as a function of time (a) and square root of time (b). The experiments were performed using the JP XIV 2nd fluid at 37 °C. Each point represents the mean ± S.D. ($n = 3$).

ear, indicating that drug release is diffusion-controlled manner. The slope of each curve in Fig. 5b decreased as the loading dose, A, increased (slope = $108.3 \times (1/\text{drug content})^{1/2} + 14.9$, $r^2 = 0.707$), as expected from Eq. (8). This result is in accordance with the result of curdlan matrix tablet using TH as a model drug, reported by Kanke et al. (1992). The JF matrix was not eroded at 24 h after immersion into water (data not shown), similar to curdlan matrix tablet. The results indicated that release rate was modulated by changing the drug amount in the tablets.

4. Discussion

In this study, hydrophilic matrix tablets were prepared from mixtures of TH and JF by direct compression. The tablets showed pH-independent sustained release behaviors which were regulated by drug amount in the tablets. The matrix tablet was characterized by a rapid swelling in initial phase and a tightly gel-forming in later phase. This is the first ever application of JF to controlled drug release.

Pectins, most derived from citrus peel or apple pomace, have been studied for sustained release preparations. The major problem encountered with pectins, in the field of hydrophilic matrix tablets, is their solubility and swelling properties in aqueous media. As a consequence, the matrix tablet consisting of this polymer alone will be unable to prevent the release of drugs for sufficient time (Rubinstein and Radai, 1995). Therefore, calcium pectinate has been studied for more water resistant derivatives. According to Liu et al. (2003), the cross-linking of pectin with calcium ions inhibits the release of incorporated drug from the pectin tablets by suppressing the dissolution and swelling of pectin macromolecules. Nevertheless, it does not inhibit the diffusion of incorporated water soluble drugs from the surfaces of the compressed tablets to the surrounding medium upon the drug's hydration. Moreover, the drug release will be strongly reflected by mechanical stress in the gastrointestinal tract because of susceptibility of matrix to erosion.

On the other hand, JF tablets were not disintegrated (Fig. 2b) but rapidly swelled to large extent (Fig. 3a), and their drug release rate was also suppressed (Fig. 1). This was probably due to unique gel-forming property of JF as mentioned above. It is important that JF contains pectinesterase and calcium ions, because the binding of calcium ions to low methoxylated polygalacturonide originated from high methoxy polygalacturonide in JF by action of endogenous pectinesterase lead to the formation of a rigid gel layer. The high amount of calcium ions in an aqueous extract of the seeds contributes to the formation of an ionic-bound, so-called "egg-box" (Komae et al., 1989). Although initial burst matrix erosion was caused by dissolution of low molecular weight compounds in JF, the polymeric matrix maintained durable gel, lead to diffusion-controlled release mechanism in the later phase.

From the results in this study, JF had an advantage over traditional vehicles, such as carboxymethylcellulose, alginate, pectin, for a controlled release tablet, since the matrix, which was formed on the drug release process, was tight enough to maintain after 8 h and porous sufficient to complete drug release. This might be related to oral controlled absorption system, OCAS (Sako et al., 1996), which has a fast and fully swelling ability for complete drug release and form a durable matrix to resistant for mechanical destructive force in the gastrointestine.

Besides, pectins are microbially degradable polysaccharides. Therefore, they have been studied for colonic drug delivery (Sinha and Kumria, 2001). From this view point, JF is probably degraded by bacterial inhabitants of human colon and drug release behavior from JF tablet will be affected by the degradation of polysaccharides in JF. So, it may be an attractive idea that JF apply to colonic drug delivery by mean of enzymatic degradation.

Further studies are needed to describe any other possibilities, however, these findings prompt us to application of JF for other drug delivery systems, e.g., hydrogels, microspheres, and so on.

5. Conclusion

We studied on JF having a unique gel-formation mechanism for controlled drug delivery as a form of hydrophilic matrix tablet. TH release behavior from JF tablet was sustained and not affected by pH of media. The drug release rate was modulated by drug amount in the tablet. According to erosion and water uptake study, the matrix was characterized by initial rapid swelling and erosion, and forming tight gel in later phase lead to

refrain from additional erosion. Thus, the drug release mechanism in later phase was found to be diffusion-controlled kinetics. These results demonstrated that JF was a useful material for a sustained release tablet.

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