Research paper

Swelling and erosion of pectin matrix tablets and their impact on drug release behavior

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Abstract

The aim of this study was to investigate swelling and erosion behaviors of hydrophilic matrix tablets using pectin and their impact on drug release. The matrix tablets were prepared by direct compression using different types of pectin. Swelling and erosion studies of pectin matrix tablets were carried out in various media. The pectin matrix tablets formed a continuous gel layer while in contact with the aqueous medium undergoing a combination of swelling and erosion. The swelling action of pectin matrices was controlled by the rate of its hydration in the medium. Release studies showed that the swelling and erosion of matrices influenced the drug release. The extent of matrix swelling, erosion and diffusion of drug determined the kinetics as well as mechanism of drug release from pectin-based matrix tablets. The release data showed a good fit into the power law or the Korsmeyer–Peppas equation indicating the combined effect of diffusion and erosion mechanisms of drug release.
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1. Introduction

Hydrophilic matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications because of their good compatibility [1]. They are usually easy and economical to formulate [2]. Drug release from hydrophilic matrix tablets is controlled by the formation of a hydrated viscous layer around the tablet which acts as a barrier to drug release by opposing penetration of water into the tablet and also movement of dissolved solutes out of the matrix tablet [3]. The hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release [4], any change in the properties of the hydrated surface layer caused by a change in pH is likely to influence the performance of hydrophilic polymer as a sustained release or controlled-release carrier.

Recently, many controlled-release formulations based on hydrophilic matrices have been developed. Pectin has been the successful choice for this purpose (e.g., [5,6]). The non-toxicity and the low production costs of pectin make them of great interest for the formulation of controlled-release dosage forms. Pectin, a structural component of plant cell walls, is an important water-soluble polysaccharide of plant origin and is of considerable interest for food industry as a gelling agent and a stabilizer in jams, fruit jellies, yogurt drinks and lactic acid beverages. The basic chemical structure of pectin is a linear polymer of D-galacturonic acid units and their methyl esters connected with α-(1,4)-glycosidic bonds. The linear structure of pectin is partly interrupted by (1,2)-linked side chains

consisting of L-rhamnose residues and some other neutral sugars [7]. The composition of pectin varies depending on plant origin. Citrus pectins appear to contain less neutral sugars and have smaller molecular size than apple pectins [8]. Functional properties of pectin are derived from their molecular weight distribution and from the degree of methoxylation of carboxyl groups [9]. Industrial pectins have the degree of methyl esterification (molar ratio of methanol to galacturonic acid or DE) of about 70% [8].

The ability of pectin to rapidly form viscous solutions and gels on contact with aqueous media has been exploited by the pharmaceutical industry, in its wide application as a carrier in hydrophilic matrix controlled-release oral dosage forms. Matrices incorporating pectin have been employed to successfully prolong release of many drugs (e.g., [10–14]). Some of these studies have demonstrated the influence of a wide range of pectin type, compression force, ratio of drug to pectin, the presence of calcium ions and the type of release medium on the drug release properties of pectin matrix tablets. However, there is no study investigating the influence of different types of pectin on the swelling and erosion behaviors and their impact on the drug release from matrix tablets. Such kind of approach can be very useful both for the interpretation of the behavior of the pectin hydrogel when used as a sustained/controlled-release matrix, and for the optimization of modified release dosage forms. Therefore, this study was aimed to investigate the effect of various types of pectin (with different DE) on swelling, erosion and drug release from pectin-based matrix tablets. The effect of types of release medium was also investigated.

2. Materials and methods

2.1. Materials

Different types of pectin (see Table 1) were donated by Herbstreith & Fox GmbH (Werder, Germany). Theophylline (P.C. Drug, Thailand) and all other materials were of pharmaceutical grade and used as supplied without further purification.

Table 1
Designation and properties of pectin used in the study

Product	Code	Degree of methyl esterification (%)	Degree of amidation (%)	Molecular weight (kDa)
Pectin type CU020	CU020	29	20	150
Pectin type CU201	CU201	70	0	200
Pectin type CU501	CU501	56	0	180
Pectin type CU701	CU701	38	0	80

Note: The specifications are reported by the manufacturer.

2.2. Preparation of pectin matrix tablets

Matrix tablets of pectin with or without drug were prepared by direct compression. For those without drug, i.e., pure pectin tablets, the tablets contained 100% of pectin (200 mg) and for those containing a model drug, 50 mg of theophylline was added into the formulations. All ingredients were passed through a 60-mesh sieve and thoroughly mixed in a blender for 15 min. The blend was compressed into tablet on a hydraulic press with 9.5-mm (3/8 in.) diameter flat-faced tooling. The tablets were compressed at compression forces of 20 kN and dwell time of 20 s.

2.3. Swelling or water uptake studies

The rate of test medium uptake by the pectin polymer was determined by equilibrium weight gain method similar to that reported by Efentakis and Vlachou [15]. The pure pectin matrix tablets were accurately weighed (W_0), placed in the closed plastic containers with the mesh underneath the tablets, rotating at 150 rpm using Environment Shaker–Incubator (model ES-20, Biosan, Latvia), with the dissolution medium of distilled water, normal saline solution (NSS), simulated gastric fluid USP without pepsin (SGF, pH 1.2), or simulated intestinal fluid (SIF, pH 6.8) at 37 ± 0.5 °C. After 2, 5, 10, 20, 60 and 120 min, each container was removed from the incubator, the tablet with the pre-weighed mesh was withdrawn from the medium and lightly blotted with tissue paper to remove excess test liquid and then reweighed (W_1) on an analytical balance (model AG204, Mettler-Toledo, Greifensee, Switzerland). The experiment was performed in triplicate for each time point and fresh samples were used for each individual time point. The percentage increase in weight due to absorbed liquid or water uptake was estimated at each time point from the following equation:

$$\% \text{ weight change} = \frac{W_1 - W_0}{W_0} \times 100 \qquad (1)$$

2.4. Matrix erosion studies

Matrix erosion studies were performed by a method similar to those of Roy and Rohera [16]. After the swelling studies, the wet samples were then dried in an oven at 80 °C for 24-h time period, allowed cooling in desiccator and finally weighed until constant weight was achieved (final dry weight, W_2). The experiment was performed in triplicate for each time point. The tablet erosion (ES) at different times was estimated from the following equation:

$$\text{ES} = \frac{W_0 - W_2}{W_0} \times 100 \qquad (2)$$

The percentage remaining of tablets after erosion was calculated from the following equation:

$$\% \text{ remaining} = 100 - ES \tag{3}$$

2.5. Gel structure analysis

Gel layer formation and its dynamics as a function of time were evaluated by texture profiling analysis (Texture Analyzer, TA-XTplus, Stable Micro Systems, UK). The procedure for texture profiling analysis of hydrated matrices of four different pectins in different media was modified from a previous report [17]. The matrix tablets were placed in the plastic containers with the mesh underneath the tablets and proceeded as mentioned in the swelling or water uptake studies (see Section 2.3). This allows medium ingression from all the directions and simulates the actual process of gel dynamics that occurs in the release studies. At predetermined time intervals, tablets ($n = 3$) were removed and subjected to texture analysis. A flat-tipped stainless steel probe, 2 mm in diameter, was connected to a force transducer that measured the force of resistance encountered by the probe during advancement into the sample. Test parameters fixed for all samples included, pre-test speed of 0.2 mm/s; test speed of 2 mm/s; post-test speed of 5 mm/s; maximum force of 50 N; and auto trigger force of 0.0098 N. Data acquisition and analysis was performed using a computer equipped with the Texture Expert® software. The data (load and deflection) were converted to stress–strain curves. The elastic or Young's modulus is defined as the ratio of stress to strain and it can be calculated from the slope of the initial linear portion (i.e., between 0.05% and 0.25%) of stress–strain curves [18].

2.6. Morphology of swollen tablets

Morphological examination of the swollen tablets was carried out using a digital camera (Model SD10, Sigma, Japan) equipped with lens 105E (Sigma, Japan). Photo imaging was performed on each tablet formulation after hydrating in different media (i.e., distilled water, NSS, SGF, or SIF) for 1 h. The tablets were taken out from the medium and were photographed by a digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate.

2.7. In vitro release studies

To examine the effects of pectin type and release medium on drug release, the release studies were carried out using USP dissolution apparatus II equipped with paddles which was operated at the speed of 50 rpm. Nine hundred millilitres of either SGF (pH 1.2) or SIF (pH 6.8), as the dissolution medium, was placed in the glass vessel, assembled the apparatus, and equilibrated the dissolution medium to 37 ± 0.5 °C. The amount of drug release was measured at the suitable time interval and was then determined spectro-

photometrically (model DU 605i, Beckman Instrument, Fullerton, USA) in a 1-cm cell at 271 nm. Each in vitro release study was performed in triplicate. Mean dissolution time (MDT) was calculated from dissolution data using Eq. (4), and has been used for comparison

$$MDT = \frac{n}{n+1} \cdot k^{-1/n} \tag{4}$$

where n is the release exponent and k is release rate constant [19] derived from exponential or Korsmeyer–Peppas equation (discussed later).

2.8. Analysis of release data

To study the release kinetics from pectin-based matrix tablets, the release data in SGF or SIF were fitted to the well-known exponential equation (power law or Korsmeyer–Peppas equation), which is often used to describe the drug release behavior from polymeric systems when the mechanism is not well known or when more than one type of release phenomenon is involved [20]

$$\frac{M_t}{M_f} = k \cdot t^n \tag{5}$$

where M_t/M_f is the drug released fraction at time t, k is a constant incorporating the structural and geometric characteristics of the matrix tablets, n is the release exponent, indicative of the drug release mechanism. When determining the n exponent, only the portions of the release profile where $M_t/M_f \leqslant 0.6$ were employed. To clarify the release exponent for different batches of matrices, the log value of percentage drug released was plotted against log time for each batch according to the following equation:

$$\log \left[\frac{M_t}{M_f} \right] = \log k + n \log t \tag{6}$$

In case of Fickian release (diffusionaly controlled-release), the n has the limiting values of 0.45 for release from cylinders. Case II transport or relaxation controlled delivery, the exponent n is 0.89 for release from cylinders. The non-Fickian release or anomalous transport of drug occurred when the n values are between the limiting values of Fickian and Case II transport. The non-Fickian kinetics corresponds to coupled diffusion/polymer relaxation. Occasionally, values of $n > 0.89$ for release from cylinders have been observed, which has been regarded as Super Case II kinetics [20].

3. Results and discussion

3.1. Water uptake and erosion of pectin matrix tablets

The water uptake and erosion studies were carried out in all types of pectin. The results of these tests in various media are provided as the percentage weight change and percentage remaining of tablet mass (Fig. 1). The swelling behavior indicated the rate at which this formulation
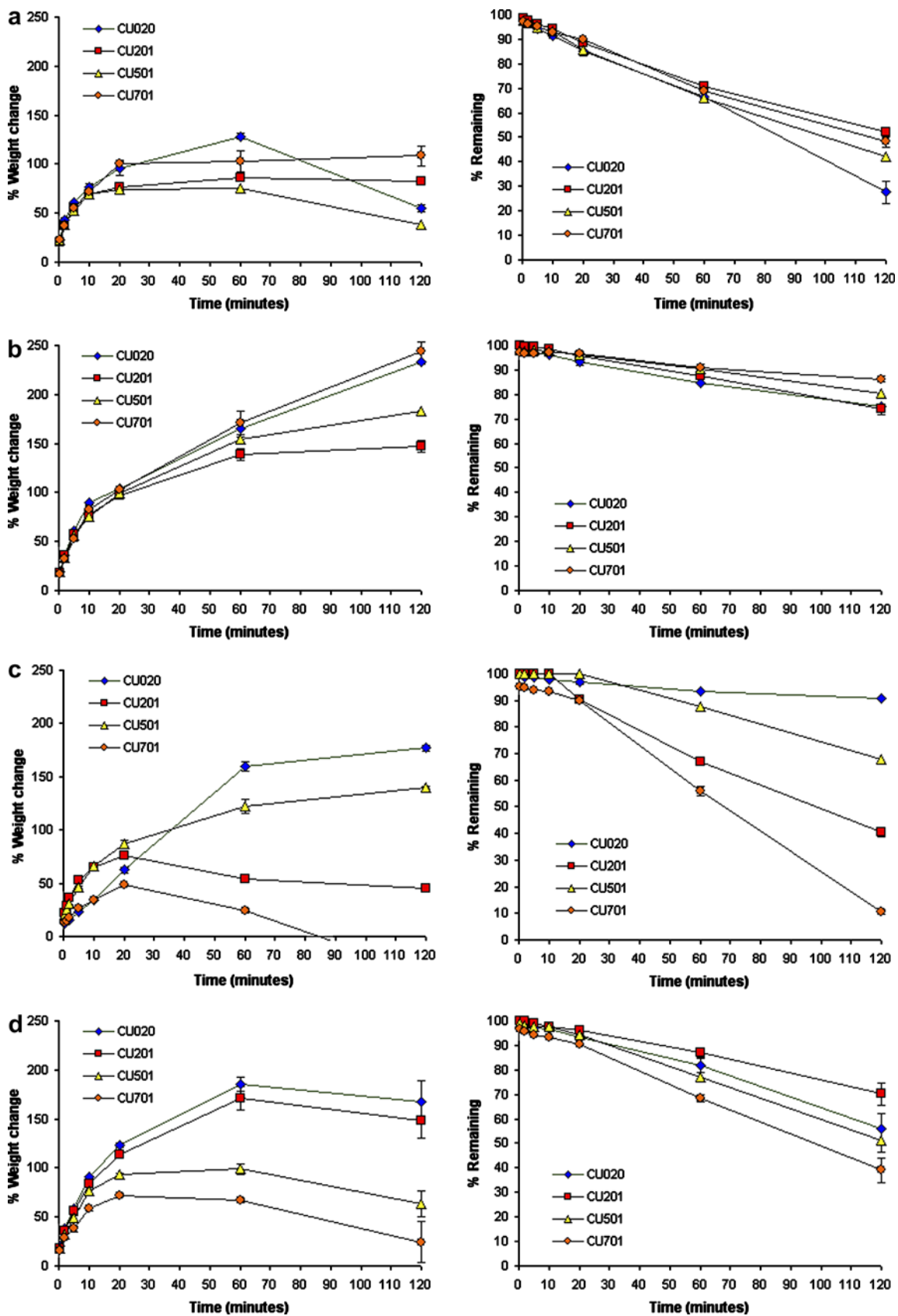
Fig. 1. Percentage weight change (left) and percentage remaining (right) of different formulations of pectin matrix tablets ($n = 3$) in (a) distilled water, (b) normal saline solution (NSS), (c) simulated gastric fluid (SGF) and (d) simulated intestinal fluid (SIF).

absorbed water from dissolution media and swelled. The changes in weight, characteristic of water uptake and swelling, started from the beginning and continued until 120 min of experiment. The percentage remaining of the matrices reflects the amount of polymer dissolved and the erosion of matrix in different media during the dissolution process. Weight loss from the tablets increased progressively with the swelling time. The extent of erosion in water and SIF increased progressively, as the percentage remaining of tablet mass decreased, with the increased swelling time (Figs. 1a and d). On the other hand, the presence of sodium chloride (i.e., NSS) enhanced the water uptake and reduced the erosion of pectin matrix tablets, which never exceeded 30% of the tablet mass (Fig. 1b). The increased ionic strength due to the presence of sodium chloride would influence the swelling and water uptake of pectin matrix tablets. The pectin matrix tablets exhibited low water uptake in acidic medium owing to the high tablet erosion, especially CU201 and CU701 at 120 min (Figs. 1c and 2). The pKa of pectin ranges between 3 and 4, depending on the type and source of pectin. Therefore, changes in pH from 6.8 to 1.2 influence matrices' hydration, due to the ready interconversion of carboxylate anions (pectin salt) to free carboxyl groups (pectinic acid), as the concentration of hydrogen ions increases [21]. Different types of pectin exhibited diverse swelling and erosion behaviors in different media. The matrix tablets of low DE pectin (CU701) showed a higher ability to swell in neutral medium (e.g., water, NSS and SIF) than in acidic medium (SGF), except for the CU020 tablets where the water uptake in SGF was higher than in water and SIF.

Visual observation indicated that the matrices appeared to swell almost from the beginning, a viscous gel mass was created when they came into contact with the medium (Fig. 2). In the case of hydration of pectin matrix tablets in acidic medium (pH 1.2), the outer hydrated surface layer formed around the tablets could be seen visually to possess a very different consistency from that of the tablets hydrated in neutral medium. The hydrated layer (in acidic medium) was not viscous and adhesive in nature but represented a tough and rubbery texture (Fig. 2). This is probably due to the fact that pectin is rapidly converted to pectinic acid, at pH 1–2, which has the ability to swell on hydration being virtually insoluble. Varying patterns of deformation (e.g., the presence of some cracks, grooves and lamination) were also observed in the tablets immersed in acidic medium (Fig. 2), as also noted in sodium alginate matrix tablets by other reports [22]. It is likely that, in acidic medium, the pressure built-up within the matrix could not be released by the matrix swelling and then the ruptured surface was generated. Amidated pectin (CU020) demonstrated a more deformation and expansion (e.g., in a form of cracked and laminated tablet shape) than other pectins (see Fig. 2). The substitution of carboxyl group by amide groups may hinder the ion-exchange phenomena during the immersion of CU020 tablets in acidic medium.
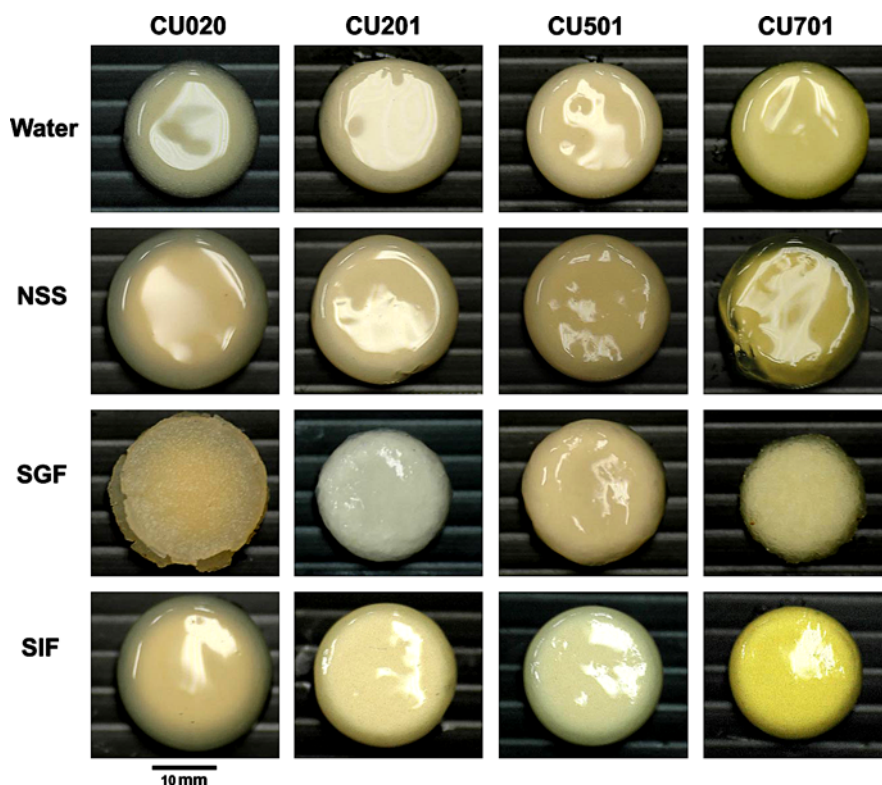

Fig. 2. Photographs of different pectin tablets hydrated in distilled water, normal saline solution (NSS), simulated gastric fluid (SGF) and simulated intestinal fluid (SIF) for 1 h.

3.2. Gel structure analysis

Varma et al. [17] and Zuleger et al. [23] demonstrated the potential and application of a texture analysis in characterization of the swelling behavior of hydrophilic matrices. The advantage of this technique over other techniques (e.g., image analysis) is its simultaneous interpretation of the gel layer growth and the mechanical consistency of the gel layer formed. With the texture analyzer, the force necessary for penetration of a cylindrical probe into a swollen tablet is precisely measured. The movement of the probe is microprocessor controlled. A contact of the probe with the surface of the swollen tablet (erosion front), a data acquisition is initiated when reaching a threshold load necessary for penetration into the gel layer. At the beginning of the tests only low forces are necessary to penetrate the probe through the swollen gel layer. A sharp increase in the load required for further penetration indicates the position of the boundary between the gel layer and the dry core (swelling front) of the tablet. Once the maximum force is reached, reverse movement starts withdrawing the probe from the swollen tablet. Fig. 3 shows the typical plot of stress–strain data for pectin matrix tablets from the penetration test.

The slope of the stress–strain curves can give an indication of the resistance of a material to deformation, i.e., the stiffness or rigidity. The greater the slope of the curve, the higher the elastic modulus and the greater the stiffness of the gel layer. The elastic modulus–time profiles for gel layer of matrix tablets in various media are shown in Fig. 4. It is obvious that the pectin matrices have different degree of hydration/swelling at different time points. The gel layer of swollen tablets is softer (i.e., the elastic moduli decreased) when the swelling time increased. In this context, a high elastic modulus at the beginning of the tests is likely to provide erosion resistance to the hydrated layer whereas a highly swollen layer with a low elastic modulus is likely to be washed away more quickly by the dissolution

Fig. 3. A typical plot of stress–strain data for pectin matrix tablets (CU020, in simulated intestinal fluid) from the mechanical tests.

medium. In distilled water, the swollen matrix tablets showed the slow decrease in elastic moduli, suggesting that the gel layer formed slowly after the ingress of liquid medium. In NSS, the tablets swelled quicker than in water and achieved the plateau by 15–30 min. The pectin matrix tablets those swelled in SGF during the first 60 min were considered to be stronger or tougher, particularly the tablets made of pectin with low DE (i.e., CU701). The high elastic modulus of the CU701 tablets is probably associated with the gel structure/morphology (see Fig. 2). The insoluble surface layer is likely to inhibit the gel formation at the surface and may induce the erosion of the pectin particles. The matrix tablets made of high DE pectin (i.e., CU201 and CU501) gave a higher elastic modulus in water and NSS but demonstrated a lower elastic modulus in acidic medium, comparing to those of low DE pectin (CU701 and CU020). This associated with the swelling results, that is, the matrix tablets of high DE pectin showed a lower ability to swell in neutral medium (e.g., water, NSS and SIF) but exhibited a higher swelling ability in acidic medium.

3.3. Release behavior of pectin matrix tablets and their release kinetics

Fig. 5 shows the in vitro drug release profiles of pectin matrix tablets in SGF and SIF. The drug release was apparently influenced by the pH of release media, i.e., drug release in SGF was faster than that in SIF. In SGF, the drug release was fairly rapid with essentially complete release within 120 min. It is perhaps reasonable to expect faster release in acidic medium than in neutral medium as the pectin tablets showed a lower ability to swell in acidic medium. Different pectin matrix tablets showed comparable drug release except for CU201 tablets which showed a faster drug release and lower MDT (Fig. 5 and Table 2), which is resulted from a high erosion rate. The low tablet hardness and high friability (data not shown) may also have an effect on a faster drug release of CU201 tablets.

According to the hydration of pectin particles in neutral medium resulted in extensive swelling, as also shown by the low elastic modulus (see Fig. 4). This caused initially well-separated particles to come into contact and then the swollen particles coalesced. This resulted in a continuous viscoelastic matrix which fills the interstices, maintaining the integrity of the tablet and retarding further liquid penetration. As a result of a high swelling, pectin matrix tablets can sustain drug release in SIF for at least 6–8 h. Release from matrix tablets is essentially constant until about 80–90% of the payload has been released. The matrix tablets containing low DE pectin (CU701) were expected to release the drug faster than those containing pectins with higher DE (e.g., CU501 and CU201), according to its higher hydrophilicity and solubility resulted from the larger number of ionized carboxyl groups, which was in a good agreement with a previous report [13]. Another reason that could explain the faster drug release of matrix tablets with CU701 is a higher elastic modulus (Fig. 4d) caused by the
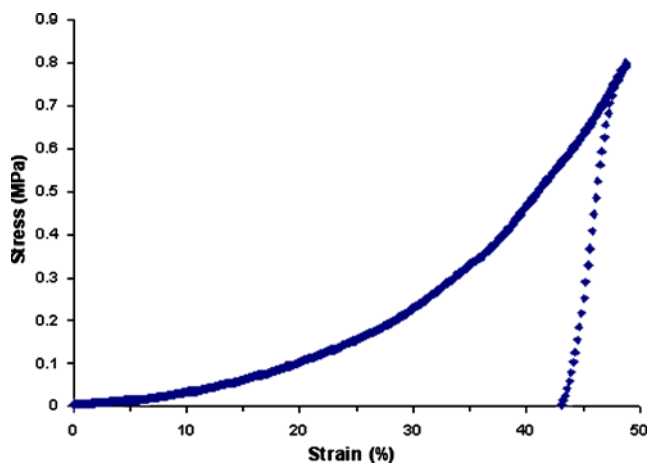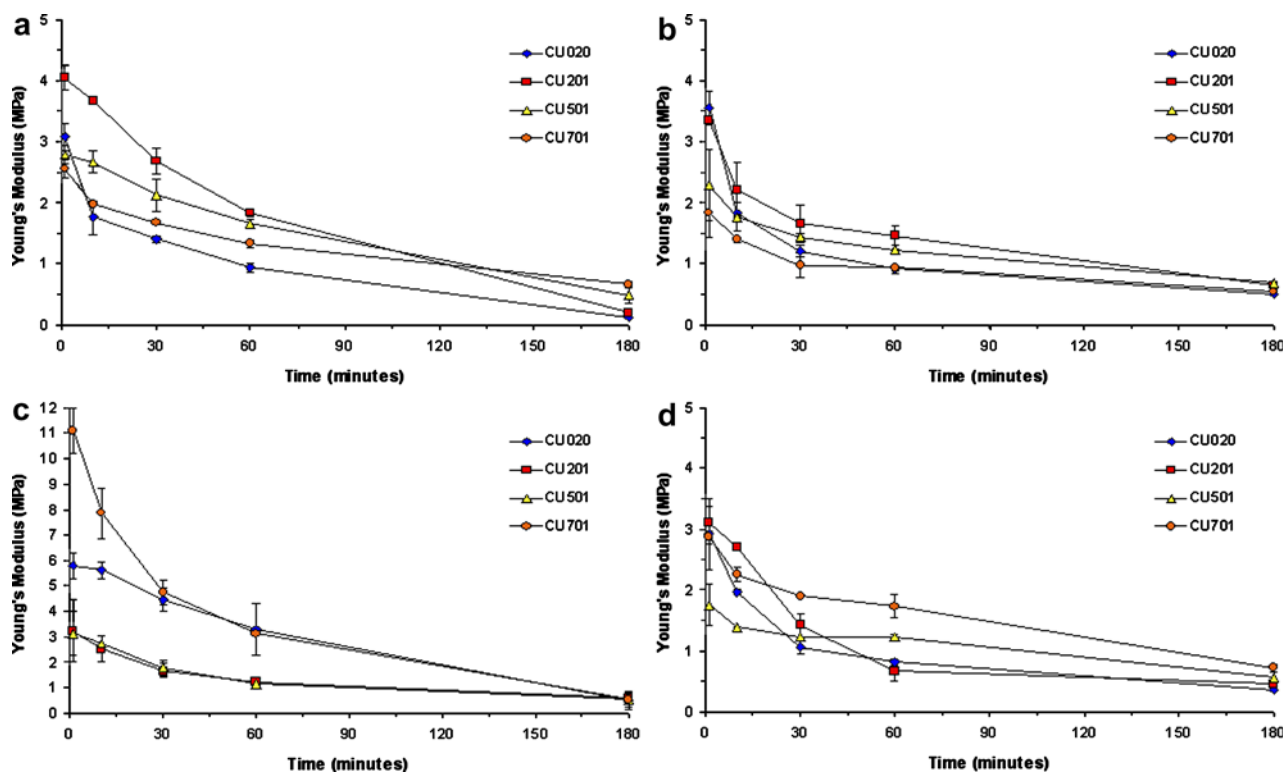
Fig. 4. Effect of the pectin type on the modulus of elasticity (Young's modulus) of gel formed around the swollen tablets at various time points, when tested in (a) distilled water, (b) normal saline solution (NSS), (c) simulated gastric fluid (SGF) and (d) simulated intestinal fluid (SIF).
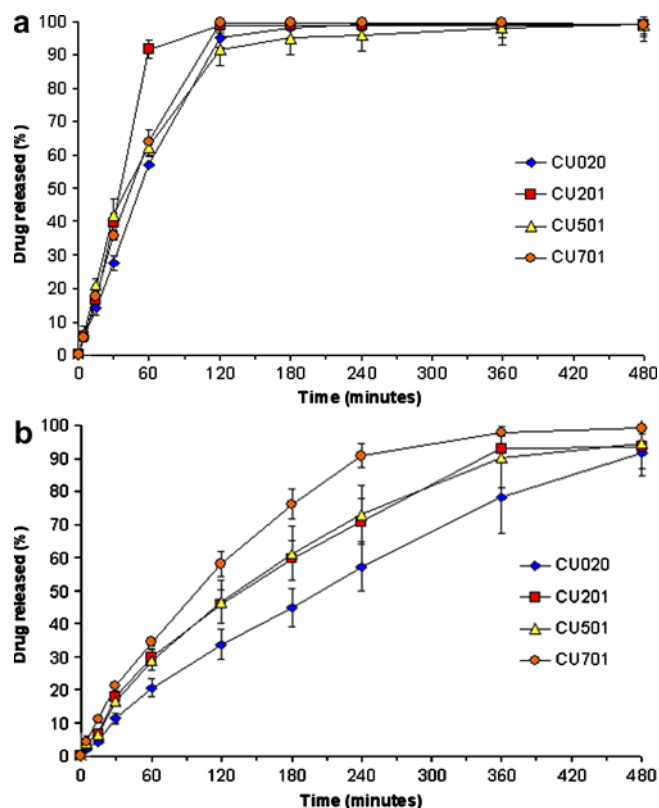

Fig. 5. Release profiles of theophylline from pectin matrix tablets in (a) simulated gastric fluid (SGF) and (b) simulated intestinal fluid (SIF), plotted as a function of time ($n = 3$).

less water uptake and higher erosion (Fig. 1). This resulted in a shorter pathlength for drug diffusion into release medium. Moreover, the difference in molecular weight of pectin may also influence the drug release from matrix tablets. As expected for any polymer, the lower the molecular weight, the weaker the gel [7]. Therefore, the swelling capacity of the matrix was low and provided a faster drug release. Matrix tablets made of amidated pectin (CU020) showed a slower drug release and a higher MDT. This is probably due to the highest swelling (i.e., water uptake) and a low erosion of tablets of CU020 in SIF (Fig. 1). The presence of amide groups along the chain of pectin CU020 promotes association of the pectin chains through hydrogen bonding [24].

The drug release data were fitted to the power law or the Korsmeyer–Peppas equation as shown in Table 2. The mechanism of drug release from matrices containing swellable polymers is complex and not completely understood. Some systems may be classified as either purely diffusion or erosion controlled, while most systems exhibit a combination of these mechanisms [25]. Previous report showed that the release of metronidazole (in acidic medium) from alginate-based matrix tablets fitted well with the Korsmeyer–Peppas equation [26]. In this study, the theophylline release, in acidic medium, from matrix tablets containing different types of pectin showed a good fit into the Korsmeyer–Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release [20]. As illustrated in Table 2, release data fit well with this model

Table 2
Korsmeyer–Peppas model fitting of release data and mean dissolution time (MDT) of pectin matrix tablets ($n = 3$)

Type of pectin	Korsmeyer–Peppas model				Mean dissolution time min (SD)
	Correlation coefficient, r^2	Kinetic constant, k	Diffusional exponent, n	Order of release	
In simulated gastric fluid (SGF) pH 1.2					
CU020	0.9970	0.012	0.92	Super case II	54.01 (5.57)
CU201	0.9954	0.009	1.09	Super case II	35.90 (7.53)
CU501	0.9898	0.015	0.94	Super case II	49.53 (3.07)
CU701	0.9966	0.011	1.01	Super case II	49.96 (2.01)
In simulated intestinal fluid (SIF) pH 6.8					
CU020	0.9889	0.005	0.88	Non-Fickian	218.72 (29.64)
CU201	0.9670	0.009	0.86	Non-Fickian	161.29 (13.79)
CU501	0.9805	0.010	0.85	Non-Fickian	171.86 (32.05)
CU701	0.9832	0.013	0.81	Non-Fickian	130.63 (4.70)

as a correlation coefficient (r^2) greater than 0.989 was obtained in all cases in acidic medium. The value of 'n' and 'k' was found to vary slightly with the type of pectin. Similar n values of larger than 0.89 have been reported by other authors [14,26]. In this report, the values of $n > 0.89$ of the drug release in SGF, from pectin matrix tablets, were ascribed to a 'Super case II' transport, in which the drug release seemed to be controlled by polymer relaxation. However, in this study, the situation is somewhat different. It cannot be simply explained by polymer relaxation because pure pectin matrices did not show signs of Super case II transport. Other mechanisms would be involved in the drug release in acidic medium. The transformation of pectin to pectinic acid would exert the significant effect on pectin matrices.

Drug release in SIF also fitted with the Korsmeyer–Peppas equation as a correlation coefficient (r^2) greater than 0.98 was obtained in most cases except for CU201 tablets in which the r^2 was 0.967. The release exponent ranged from 0.81 to 0.88 in SIF for all pectin matrices, exhibiting an anomalous or non-Fickian transport. This suggested that more than one mechanism may be involved, i.e., combination of matrix erosion and diffusion of the drug in the hydrated pectin matrices, but approached Case II transport. Fig. 6 shows a good relationship between matrix erosion and drug release from pectin matrix tablets in SGF and SIF. These results are in agreement with the one published by Sujja-areevath et al. [27] that established a correlation among the swelling, erosion and drug release in matrices elaborated from xanthan, karaya and locust bean gum.

4. Conclusion

Pectin-based matrix tablets were easily prepared by blending drug and pectin, and then tableting. The matrix tablets swelled or eroded while in contact with the aqueous medium and formed a continuous gel layer or underwent combination of swelling and erosion. Drug release from matrix tablets was apparently influenced by pH of release medium. The extent of matrix swelling, erosion, and release of drug determined the kinetics as well as mechanism of
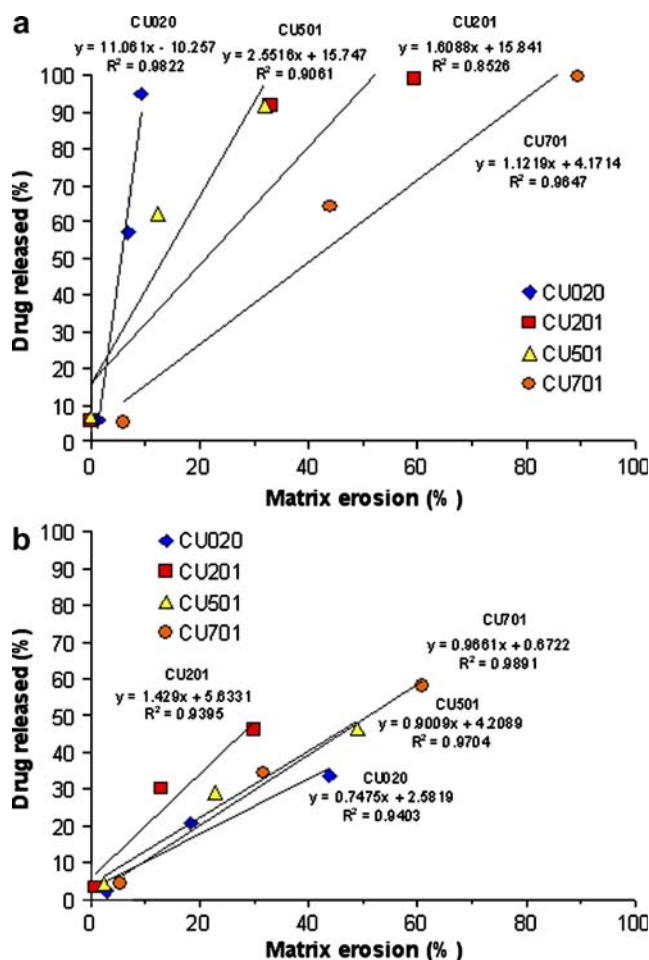

Fig. 6. Relationship between the matrix erosion and the drug release from pectin matrix tablets in (a) simulated gastric fluid (SGF) and (b) simulated intestinal fluid (SIF). The correlation coefficient of each formulation is shown.

drug release from pectin matrix tablets. The release data showed a good fit into the Korsmeyer–Peppas equation, indicating combined effect of diffusion and erosion mechanisms for drug release.

These findings were attributed to the effect of swelling and erosion on the drug release from hydrophilic matrix tablets, which is an interesting way of formulating oral

sustained/controlled-release matrix tablets using a process that is easy and inexpensive and does not require special production equipment.

Acknowledgements

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