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Research paper

# Swelling, erosion and release behavior of alginate-based matrix tablets

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**Abstract**

Hydrophilic matrix tablets based on the alginate system have been used in relation to their possible function in modified drug delivery formulations using metronidazole as a model drug. The matrix tablets were prepared by direct compression using different grades of alginate. The effect of some factors (i.e. particle size of drug, additive used, and pH of medium) on drug release from alginate-based matrix tablets was also investigated. Swelling, erosion, and *in vitro* release studies of the matrix tablets were carried out in 0.1 N HCl or phosphate buffer (pH 6.8). The alginate-based 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. The swelling action of alginate matrices is controlled by the rate of its hydration in the medium. Different grades of alginate insignificantly influenced the matrix swelling in acidic medium but significantly influenced in neutral medium. The presence of ammonium or calcium salts induced tablet disintegration in acidic medium. However, incorporation of calcium acetate and sodium bicarbonate can alter the tablet swelling in acidic medium. Release studies showed that all investigated factors influence the drug release. The extent of matrix swelling, erosion, and diffusion of drug determined the kinetics as well as mechanism of drug release from alginate-based matrix tablets. Most of the release data in acidic medium showed a good fit into Korsmeyer–Peppas equation but fitted well with zero-order release model, in neutral medium.


*Keywords:* Alginate; Swelling; Hydration; Erosion; Drug release; Matrix tablet

## 1. Introduction

Alginates, which are commonly available as sodium salt, are a natural polymer extracted from brown seaweed, having high biological safety. They are a family of linear unbranched polysaccharides, which contain varying amounts of (1–4)-linked β-D-mannuronic acid (M) and α-L-guluronic acid (G) residues. The residues may vary widely in composition and sequence and are arranged in a pattern of blocks along the chain. These homopolymeric regions of M and G blocks are interspersed with regions of alternating structure (MG blocks) [1,2]. The composition and extent of the sequences and the molecular weight determine the physical properties of the alginates. The molecular variability is dependent on the organism and tissue from which the alginates are isolated. Commercial alginates are derived from a variety of weed sources and differ in monomeric composition and block structure, a given alginate has its own characteristic calcium reactivity and gelation properties. Alginates are usually referred to as "high M" or "high G", depending on the proportions of M and G they contain. Most commercial products are of the high M type [3].

One of the most important and useful properties of alginates is the ability to form gels in the presence of metal ions such as calcium. In principle, the controlled addition of these ions leads to insoluble alginate gel formation. In general terms, high G alginates produce strong, brittle gels that are heat stable, while high M alginates provide weaker, more elastic gels that have less heat stability but more freeze/thaw stability. The calcium reactivity of alginate is

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the result of calcium-induced dimeric association of the G-block regions. Depending on the amount of calcium present in the system, these inter-chain associations can be either temporary or permanent. With low levels of calcium, temporary associations are obtained, giving rise to highly viscous, thixotropic solutions. At higher calcium levels, precipitation or gelation results from permanent associations of the chains [3].

Compressed hydrophilic matrices are commonly used as oral drug delivery systems and being increasingly investigated for controlled-release applications because of their good compatibility [4]. They are usually easy and economical to formulate [5]. 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 tablet and also movement of dissolved solutes out of the matrix tablet [6]. Water-soluble drugs are released primarily by diffusion of dissolved drug molecules across the gel layer, whereas poorly water-soluble drugs are released predominantly by erosion mechanisms. The contribution of each release mechanism, to the overall drug release process is influenced not only by drug solubility but also by the physical and mechanical properties of the gel barrier that forms around the tablet [7]. The hydration characteristics of the polymer and the subsequent physical properties of the hydrated gel layer may critically influence drug release [8], 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 carrier.

The ability of alginate, sodium salt, 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 alginate salts or a combination of alginate with other polymers have been employed to successfully prolong release of many drugs (e.g. [9–13]). Some of these studies have demonstrated the influence of a wide range of alginate grades on the drug release properties of alginate matrix tablets (e.g. [11,12]). However, there is no study investigating the effect of different grades of alginate on the swelling and erosion behaviors and the influence of these behaviors on the drug release from matrix tablets. Such kind of approach can be very useful both for the interpretation of the behavior of the alginate hydrogel when used as a sustained/controlled-release matrix, and for the optimization of modified release dosage forms. Hence, this paper was aimed to investigate the effect of various grades of alginate (with different chemical composition, size or viscosity), especially a combination of alginate salts, i.e., sodium/calcium alginate and ammonium/calcium alginate, which defines as self-gelling alginates, on swelling, erosion and drug release from alginate-based matrix tablets. The effects of particle size of model drug (metronidazole; MZ), additive used, and pH of medium were also investigated.

## 2. Materials and methods

### 2.1. Materials

Different grades of alginate (see Table 1) were obtained from International Specialty Products (Bangkok, Thailand). MZ (Batch 34211, P.C. Drug, Bangkok, Thailand), calcium acetate (Batch 0525/01/04, Polskie Odezynniki Chemiczne S.A., Poland), and all other materials were of pharmaceutical grade and used as supplied without further purification.

### 2.2. Preparation of alginate-based matrix tablets

Matrix tablets were prepared by direct compression. Each tablet contained 50% MZ (200 mg), 46–50% alginate, and other excipients as shown in Table 2. All ingredients were passed through a 60-mesh sieve and thoroughly mixed in a blender for 15 min without lubricant and for a further 5 min after addition of magnesium stearate (0.5%). The blend was compressed into tablet on a hydraulic press (Model 15011, Specac, USA) with 9.5-mm diameter

Table 1
Typical properties of alginate used[a]

| Product | Code | Alginate type | Particle size (μm) | Form | Viscosity[b] | M/G ratio[c] | Bulk density[d] (g/mL) |
|---|---|---|---|---|---|---|---|
| Manugel® DMB (Batch No. 991131) | MG | Sodium alginate (high G) | 106 | Granular | 300 | 0.59 | 0.781 |
| Manucol® DMF (Batch No. 951111) | MC | Sodium alginate (high M) | 106 | Granular | 300 | 1.56 | 0.845 |
| Keltone® LVCR (Batch No. 015821 A) | KLV | Sodium alginate (high M) | 106 | Fibrous | 35 | 1.50 | 0.606 |
| Keltone® HVCR (Batch No. 2D0164 A) | KHV | Sodium alginate (high M) | 180 | Fibrous | 400 | 1.50 | 0.706 |
| Kelset® (Batch No. 1F8181A) | KS | Sodium/calcium alginate | 180 | Fibrous | Gel (at 2%) | 1.50 | 0.753 |
| Keltose® (Batch No. 1B7152A) | KT | Ammonium/calcium alginate | 180 | Granular | Semigel | 1.50 | 0.688 |

[a] Size, form, viscosity, M/G ratio are specified and reported by the manufacturer.
[b] One percent as is viscosity, except where noted. Viscosity is generally measured using a Brookfield LV viscometer at 60 rpm with a No. 2 spindle.
[c] Mannuronic acid to guluronic acid ratio.
[d] Average from three repeated tests of tapping method.

Table 2
Unit formula of the prepared tablets[a,b]

| | MZ (<150 μm) | MZ (150–210 μm) | Alginate | Calcium acetate | Sodium bicarbonate |
|---|---|---|---|---|---|
| S-MG | 200 | – | 200 | – | – |
| S-MC | 200 | – | 200 | – | – |
| S-KLV | 200 | – | 200 | – | – |
| S-KHV | 200 | – | 200 | – | – |
| S-KS | 200 | – | 200 | – | – |
| S-KT | 200 | – | 200 | – | – |
| L-MG | – | 200 | 200 | – | – |
| L-MC | – | 200 | 200 | – | – |
| L-KLV | – | 200 | 200 | – | – |
| L-KHV | – | 200 | 200 | – | – |
| L-KS | – | 200 | 200 | – | – |
| L-KT | – | 200 | 200 | – | – |
| S-MG/BC2 | 200 | – | 192 | – | 8 |
| S-MG/Ca0.5 | 200 | – | 198 | 2 | – |
| S-MG/Ca0.5/BC2 | 200 | – | 190 | 2 | 8 |
| S-MG/Ca2/BC2 | 200 | – | 184 | 8 | 8 |
| S-MC/BC2 | 200 | – | 192 | – | 8 |
| S-MC/Ca0.5 | 200 | – | 198 | 2 | – |
| S-MC/Ca0.5/BC2 | 200 | – | 190 | 2 | 8 |
| S-MC/Ca2/BC2 | 200 | – | 184 | 8 | 8 |

*Abbreviations*: MZ, metronidazole; MG, Manugel; MC, Manucol; KLV, Keltone LVCR; KHV, Keltone HVCR; KS, Kelset; KT, Keltose.
[a] Amount of ingredients was given as milligrams.
[b] The powder blends were further added with magnesium stearate (0.5%).

flat-faced tooling. The tablets were compressed at compression forces of 20 kN for 20 s.

### 2.3. Matrix tablet evaluations

#### 2.3.1. Tablet weight variation testing

Twenty matrix tablets were randomly selected and accurately weighed using a Mettler analytical balance (model AG204, Mettler–Toledo, Greifensee, Switzerland). The results were expressed as mean values of 20 determinations.

#### 2.3.2. Tablet thickness testing

The thickness of the matrix tablets was determined using a caliper (Mitutoyo Dial Thickness Gauge, Mitutoyo, Japan) and the results were expressed as mean values of 10 determinations.

#### 2.3.3. Hardness determination

Ten matrix tablets were sampled and individually subjected to test for hardness using Texture Analyzer (TA.XT plus, Stable Micro Systems, UK). The tablet hardness was expressed in kilogram (kg) unit. The mean and standard deviation of the tablet hardness were calculated.

#### 2.3.4. Disintegration test

The standard USP test (USP27) with discs was employed to assess the disintegration times, using an Erweka Disintegration tester (model ZT31, Germany). Tests were carried out in 800 mL of distilled water at $37 \pm 0.5$ °C. All tests were run in triplicate. The disintegration time was defined as the time necessary for complete disintegration of the matrix tablets.

### 2.4. Swelling and erosion studies

Measurement of swelling and erosion rates of alginate-based matrix tablets was carried out, after immersion of tablets in the test medium, to relate the observed phenomena of drug release with the rate of polymer hydration. Weighed tablets ($W_0$) were 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 0.1 N HCl (HCl, pH 1.2) or phosphate buffer (pH 6.8) at $37 \pm 0.5$ °C. After 2, 5, 10, 20, 60, and 120 min, each container was removed from the incubator, the tablet with the mesh was withdrawn from the medium and blotted to remove excess water and then weighed ($W_1$) on an analytical balance (model AG204, Mettler–Toledo, Greifensee, Switzerland). The wet samples were then dried in an oven at 80 °C for 24-h time period, allowed cooling in a desiccator and finally weighed until constant weight was achieved (final dry weight, $W_2$). 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 following equation:

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

The percentage remaining of tablets after erosion (ES) was calculated from following equation:

$$\% \text{ Remaining} = 100 - \text{ES} \quad (2)$$

where ES was estimated from the following equation:

$$\text{ES} = \frac{W_0 - W_2}{W_0} \times 100 \quad (3)$$

### 2.5. Morphological examination of swollen tablets

Morphological examination of the swollen tablets was carried out using a digital camera (Model EOS350D, Canon, Japan) equipped with zoom lens EF-S 18–55 mm (Canon Inc., Taiwan). Photo imaging was performed on each tablet formulation after hydrating in 0.1 N HCl or pH 6.8 phosphate buffer for 30 min. The tablets were taken out from the medium and were imaged by a digital camera. Under the same optical conditions, an image of a linear scale was used to calibrate.

### 2.6. In vitro release studies

To examine the effects of alginate grades, additives, and particle sizes of active drug on drug release, the dissolution 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 0.1 N HCl (pH 1.2) or phosphate buffer (pH 6.8), as the dissolution medium, was placed in the glass vessel, the apparatus assembled, and the dissolution medium equilibrated to 37 °C. The amount of drug released was measured at the suitable time interval and was then determined spectrophotometrically (model DU 605i, Beckman Instrument, Fullerton, USA) in a 1-cm cell at 277 nm. Each *in vitro* release study was performed in triplicate.

Analysis of variance (ANOVA) and Levene's test for homogeneity of variance were performed using SPSS version 10.0 for Windows (SPSS Inc., USA). *Post hoc* testing ($p < 0.05$) of the multiple comparisons was performed by either the Scheffé or Games–Howell test depending on whether Levene's test was insignificant or significant, respectively.

### 2.7. Analysis of release data

The mechanism of drug release from alginate-based matrix tablets during dissolution tests in 0.1 N HCl and phosphate buffer pH 6.8 was determined using zero-order, first-order, and Higuchi equation. These models fail to explain drug release mechanism due to swelling (upon hydration) along with gradual erosion of the matrix [14]. Therefore, the dissolution data were also fitted to the well-known exponential equation (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 phenomena is involved [14]:

$$\frac{M_t}{M_f} = k \cdot t^n \quad (4)$$

where $k$ is a constant incorporating the structural and geometric characteristics of the matrix tablets, $n$ is the release exponent, indicative of the drug release mechanism and $M_t/M_f$ represents the drug dissolved fraction at time $t$. 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 the percentage drug released was plotted against log time for each batch according to Eq. (5).

$$\log\left[\frac{M_t}{M_f}\right] = \log k + n \log t \quad (5)$$

In case of Fickian release (diffusionally controlled release), the $n$ have the limiting values of 0.45 for release from cylinders. Case II transport or relaxation controlled delivery, the exponent $n$ is 0.89 for the release from cylinders. The non-Fickian release or anomalous transport of drug occurred when the $n$ values fall between the limiting values of Fickian and Case II transport. The non-Fickian kinetics correspond 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 [14]. This mechanism could result from an increased plasticization at the relaxing boundary (gel layer).

## 3. Results and discussion

### 3.1. Physical properties of alginate-based matrix tablets

The comparison of physical properties of the matrix tablets containing alginate alone or in combination with other additives (i.e. calcium acetate and/or sodium bicarbonate) is shown in Table 3. The weight and thickness of the formulations ranged from 396.17 to 404.22 mg and from 3.97 to 4.26 mm, respectively. All tablets prepared in this study meet the USP 27 requirements for weight variation tolerance; coefficient of variation of all formulations was less than 1%. The hardness of different tablet formulations ranged from 1.41 to 11.60 kg. It is probably due to difference in the compactibility of alginate used in the formulations. The fibrous form of alginate samples (i.e. KLV, KHV, and KS) provided a higher hardness of the tablets. The mechanical interlocking could not be excluded as a contributing factor to tablet hardness or strength, especially in the case of fibrous and irregularly shaped particles [15]. The matrix tablets containing ammonium/calcium alginate (i.e. KT) disintegrated rapidly within 30 min in distilled water. The increased tablet hardness of KT tablets containing different sizes of a model drug delayed the disintegration time. The disintegration times of other formulations (e.g. formulations containing sodium alginate, sodium/calcium alginate, or sodium alginate plus

Table 3
Physical properties of alginate-based matrix tablets[a]

| | Weight (mg), $n = 20$ | Thickness (mm), $n = 10$ | Hardness (kg), $n = 10$ | Disintegration time (min), $n = 3$ |
|---|---|---|---|---|
| S-MG | 401.25 (0.49) | 4.06 (0.20) | 3.65 (0.51) | 94.3 (4.1) |
| S-MC | 400.11 (0.59) | 4.09 (0.02) | 2.92 (0.64) | 90.7 (2.1) |
| S-KLV | 402.06 (0.23) | 4.08 (0.03) | 6.52 (0.60) | 70.7 (10.1) |
| S-KHV | 396.17 (0.44) | 3.97 (0.01) | 9.67 (0.55) | 96.3 (2.9) |
| S-KS | 403.97 (1.05) | 4.08 (0.02) | 4.37 (0.61) | 61.6 (4.7) |
| S-KT | 404.03 (0.65) | 4.26 (0.03) | 2.95 (0.28) | 16.7 (1.2) |
| L-MG | 399.31 (0.44) | 3.99 (0.01) | 6.75 (1.16) | 100.0 (3.6) |
| L-MC | 400.70 (1.19) | 4.04 (0.02) | 4.37 (0.88) | 84.0 (13.9) |
| L-KLV | 404.08 (0.69) | 4.06 (0.01) | 9.50 (0.44) | 65.3 (3.8) |
| L-KHV | 402.68 (0.64) | 3.98 (0.02) | 11.60 (1.04) | >120 |
| L-KS | 404.06 (0.89) | 4.01 (0.02) | 7.88 (1.40) | >120 |
| L-KT | 403.01 (0.78) | 4.23 (0.03) | 3.83 (0.41) | 26.3 (1.2) |
| S-MG/BC2 | 400.21 (0.62) | 4.16 (0.03) | 3.27 (0.27) | >120 |
| S-MG/Ca0.5 | 401.53 (0.25) | 4.09 (0.02) | 4.17 (0.07) | >120 |
| S-MG/Ca0.5/BC2 | 400.34 (0.33) | 4.02 (0.02) | 3.61 (0.16) | >120 |
| S-MG/Ca2/BC2 | 403.28 (0.15) | 4.06 (0.01) | 2.60 (0.27) | >120 |
| S-MC/BC2 | 402.61 (0.39) | 3.99 (0.03) | 1.98 (0.05) | 95.2 (10.2) |
| S-MC/Ca0.5 | 404.22 (0.68) | 4.06 (0.02) | 1.49 (0.07) | >120 |
| S-MC/Ca0.5/BC2 | 401.91 (0.71) | 4.13 (0.01) | 1.80 (0.25) | 83.4 (6.3) |
| S-MC/Ca2/BC2 | 402.33 (1.05) | 4.03 (0.03) | 1.41 (0.12) | 87.3 (3.1) |

[a] Values in parentheses represent SD.

additives) were more than 60 min or not disintegrated even after 120 min, which is a matrix behavior. This suggested that most of sodium alginates can be used as a material for compressed non-disintegrating porous, swellable matrices for sustained/controlled release tablets. However, the disintegration time of some formulations, e.g. tablets containing ammonium/calcium alginate and sodium/calcium alginate, in acidic medium was very short (data not shown). The presence of high amount of ammonium or calcium salts may induce the tablet disintegration in acidic medium. This will be discussed more in the later section.

### 3.2. Swelling and erosion behavior of alginate-based matrix tablets

#### 3.2.1. Influence of pH of the medium

The swelling and erosion studies were carried out in all grades of alginate and also the combination of alginate and additives. The results of these tests in 0.1 N HCl and phosphate buffer (pH 6.8) are provided as the percentage weight change and percentage remaining of tablet mass, as shown in Figs. 1 and 2. The swelling behavior indicated a rate at which this formulation 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. These matrices generally showed a higher ability to swell in neutral medium (phosphate buffer, pH 6.8) than in acidic medium. The $pK_a$ of alginic acid (by virtue of the carboxyl groups on the components of uronic acid residues) ranges between 3.4 and 4.4, depending on the type of alginate and the salts present in the mixture [3]. Therefore, changes in pH from 6.8 to 1.2 influence polymer hydration and alginate gel rheology, due to the ready interconversion of carboxylate anions (sodium alginate) to free carboxyl groups (alginic acid), as the concentration of hydrogen ions increases [16].

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 neutral medium (Fig. 3), as observed previously in the other report [7]. In the case of hydration of sodium alginate matrix tablets in acidic medium (below pH 3), the outer hydrated surface layer formed around the tablets could be seen visually to possess a very different consistency to that formed around sodium alginate tablets which were 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. 3). This is probably due to sodium alginate rapidly converted to alginic acid, at pH 1–2, which has the ability to swell on hydration but which is virtually insoluble. The matrix erosion measured the weight loss from matrix tablets immersed in dissolution media as a function of time. The percentage remaining of the matrices is also shown in Figs. 1 and 2, and reflects the amount of polymer dissolved and the erosion of matrix during the dissolution process. Weight loss from the tablets increased progressively with the erosion time. The extent of erosion in acidic conditions never exceeded 30% of the alginate mass (Fig. 1a) except for the combination of alginate salts. These observations are in keeping with the gel being more "tough and rubbery" than what was produced in neutral medium.

#### 3.2.2. Influence of alginate grade

The different grades of alginate did not significantly influence the swelling of the matrix tablets in acidic medium (Fig. 1a) but significantly affected the swelling in neutral medium (Fig. 1b). The matrix tablets using sodium

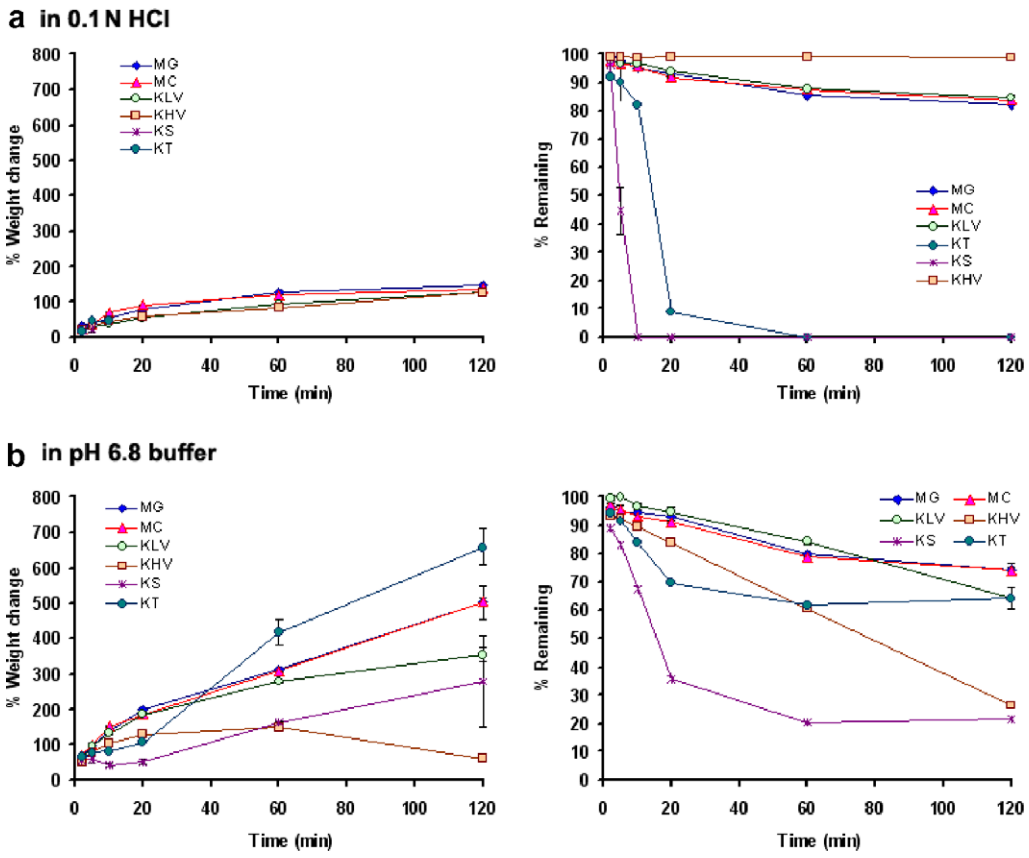


Fig. 1. The percentage weight change (left) and percentage remaining (right) of different formulations of alginate-based matrix tablets, in (a) 0.1 N HCl and (b) pH 6.8 phosphate buffer ($n = 3$).

alginate with the same particle size (106 μm) and viscosity (300 cps at 1%) (i.e. MG and MC) showed the same swelling and erosion properties, regardless of the different M/G ratios. Using alginate with lower viscosity (KLV) provided slightly less in % weight increase at 120 min, which is probably due to the higher erosion rate (in pH 6.8 buffer) of low viscosity alginate (Fig. 1b). This is somewhat different from the previous study by Efentakis and Buckton [11] in which the rapid and complete erosion of the matrices made of alginate (low viscosity grade, 250 cps at 2%) was observed. High viscosity alginate (KHV) showed a lower swelling and greater erosion rate in neutral medium. It is possible that the KHV, which has the larger particle size, hydrated slower, leading to the slower gel barrier formation and hence the faster erosion or dissolution of alginate particle. The use of smaller alginate particles would favor interparticulate contact, contributing to better polymer particle coalescence and create a less permeable gel barrier for more effective sustained action of drug release [12]. The integrity of the matrices of sodium alginate (i.e. MC, MG, KLV and KHV) was unfavorably affected during the test in acidic medium. Varying patterns of deformation (e.g. the presence of some cracks, grooves, and lamination) were observed (Fig. 3), as also noted by other reports [11,12]. The high G alginate deformed and expanded into a form of cracked and laminated tablet shape (see Fig. 3a). 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.

A low swelling and high erosion rate for the matrix tablets of a combination of alginate salts (i.e. sodium/calcium alginate (KS) and ammonium/calcium alginate (KT)) was observed on 0.1 N HCl (Fig. 1a). The tablets were completely disintegrated in acidic medium within 10–20 min (Figs. 3e and f). This is probably due to the presence of high amount of ammonium and/or calcium salts inducing tablet disintegration. The insoluble calcium alginate may promote the disintegration by capillary action while the dissolution of ammonium salts may create pores in the tablet to facilitate a slow erosion/disintegration. In pH 6.8 buffer, KS tablets showed a lower swelling and a higher rate of erosion than that of KT tablets. This indicates that the sodium/calcium alginate would partially form gel when in contact with aqueous medium at the neutral pH. Formation of calcium alginate gel reduced the solubility of alginate, as calcium formed cross-links between two alginate molecules in a section of the G units [16].

### 3.2.3. *Influence of additive incorporated*

The incorporation of sodium bicarbonate, as a pH modifier, is a strategy to alter the microenvironmental pH within, and in the close vicinity of the matrix tablets.

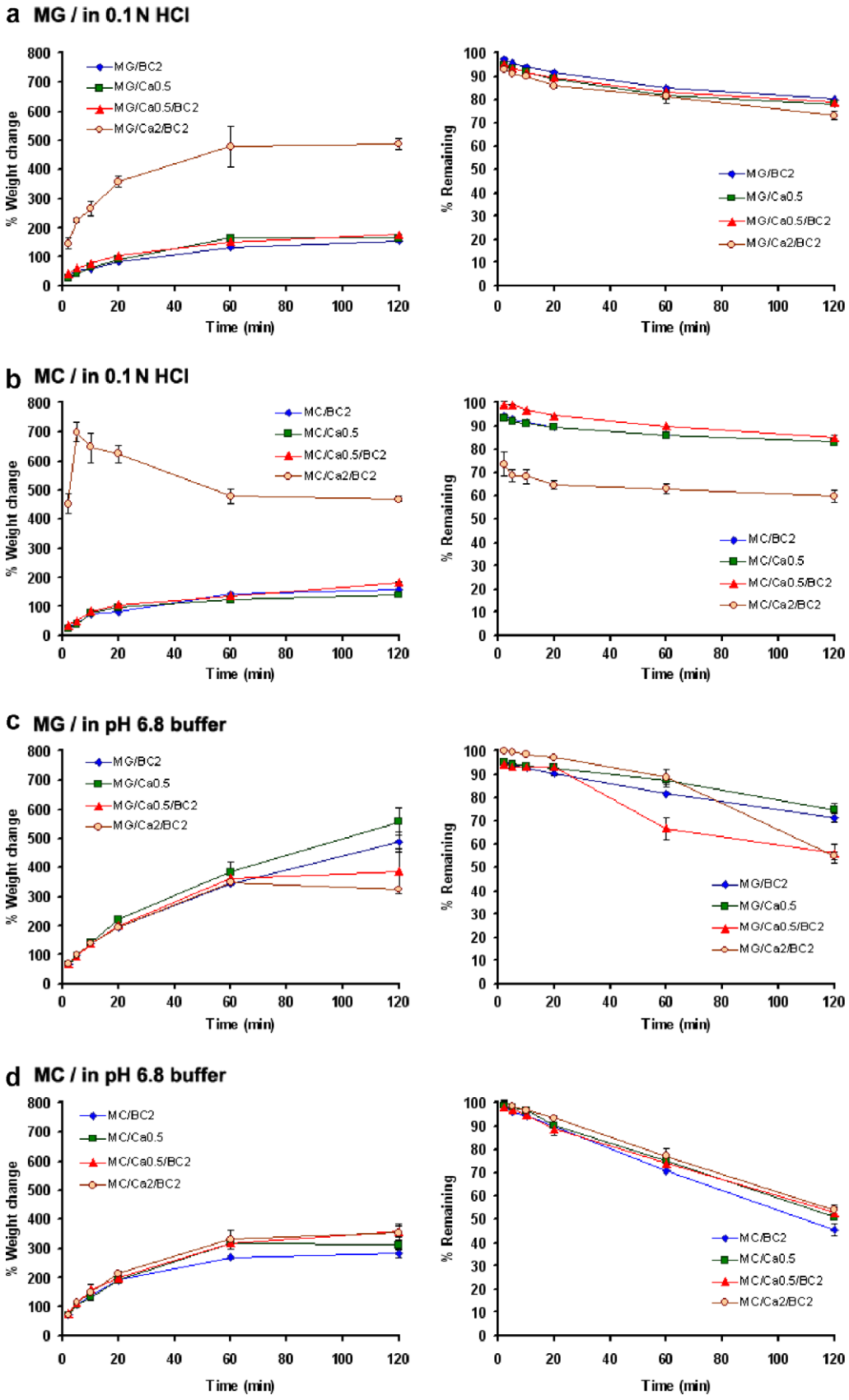


Fig. 2. Effect of additive on the percentage weight change (left) and percentage remaining (right) of different formulations of alginate-based matrix tablets; (a) MG and (b) MC in 0.1 N HCl, and (c) MG and (d) MC in pH 6.8 phosphate buffer ($n = 3$).

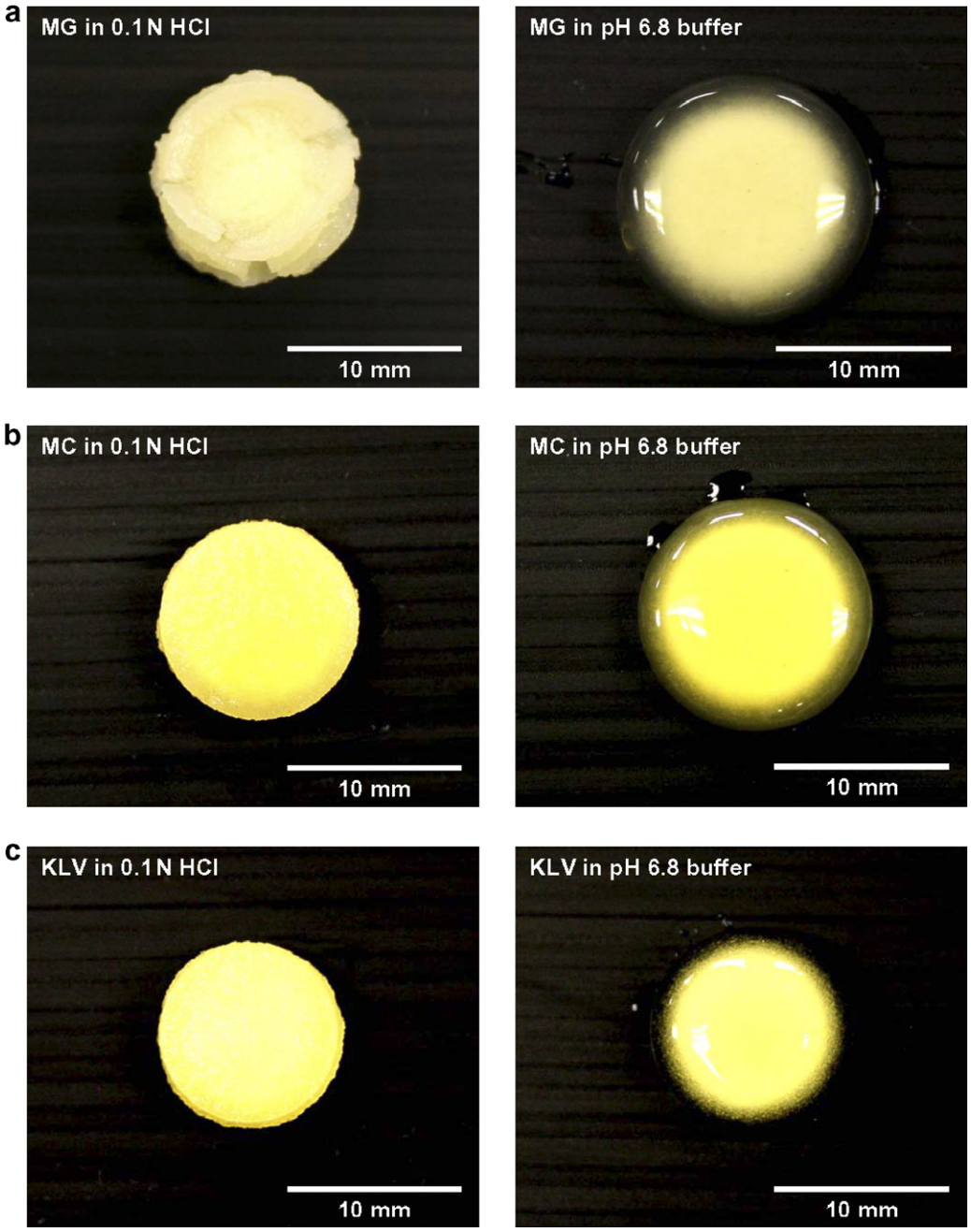


Fig. 3. Photo images of the alginate-based matrix tablets hydrated for 30 min in 0.1 N HCl (left column) and pH 6.8 phosphate buffer (right column).

Incorporation of sodium bicarbonate showed a similar effect on swelling and erosion in both media (Fig. 2). However, in acidic medium, the morphology of alginate matrix tablets containing sodium bicarbonate is noticeably different from the tablets without sodium bicarbonate; less lamination and cracks were found (Fig. 4b). It is possible that addition of sodium bicarbonate resulted in a constant basic environment within the investigated period and allowed the alginate to swell in acidic medium to some extent.

The presence of calcium acetate was in relation to the importance of calcium ions to the alginate gelling mechanism. In fact the ionic interactions between G blocks of alginate and calcium ions determine the formation of a cross-linked gel. Adding a lower amount of calcium acetate (i.e. 0.5%) in the formulation seemed not to influence the swelling and erosion of matrix tablets in both media (Fig. 2). It is most likely that calcium ions in the cross-linked calcium alginate could be replaced by the protons in the acidic medium and converted to insoluble alginic acid [16]. Therefore, the morphology of the calcium-added tablets in 0.1 N HCl is almost the same as the tablets without calcium acetate (Fig. 4c).

The mixture of 0.5% calcium acetate and 2% sodium bicarbonate also did not influence the swelling and erosion

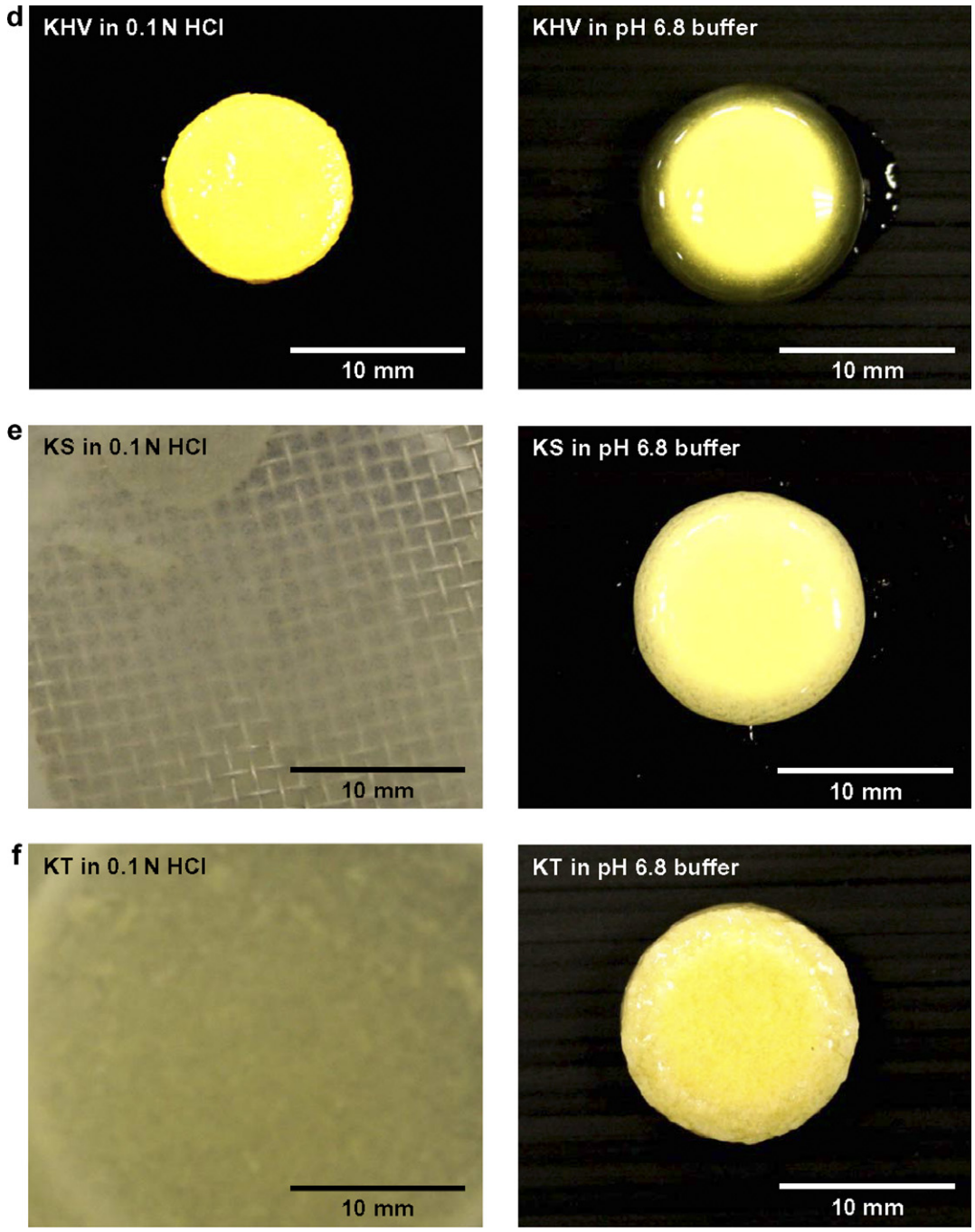


Fig. 3 (*continued*)

of the matrix tablets made of MC or MG in both tested media (Fig. 2). However, the appearance of swollen tablets containing both calcium acetate and sodium bicarbonate in acidic medium was clearly changed (Fig. 4d), compared to MC or MG tablets without additives. No surface crack or lamination was found but the tablets seemed to swell into irregular shape. The increased calcium amount to 2% in the formulations (plus 2% of sodium bicarbonate) did not affect the swelling in neutral medium but acidic medium (Fig. 4e). The alteration of microenvironmental pH within the matrix tablets by sodium bicarbonate prohibited the conversion of carboxylate anions (sodium alginate) to free carboxyl groups (alginic acid) and also allowed the calcium ions to partially form gel with soluble sodium alginate. As a result, the highest swelling (i.e. percentage weight change) of the alginate-based matrix tablets containing 2% calcium acetate and 2% sodium bicarbonate was observed in acidic medium (Fig. 2). The percentage weight increase of MC tablets containing 2% calcium acetate and 2% sodium bicarbonate declined after 5 min of the test in acidic medium, resulting from the erosion of the matrices. In neutral medium, pore-formation derived from dissolving additives

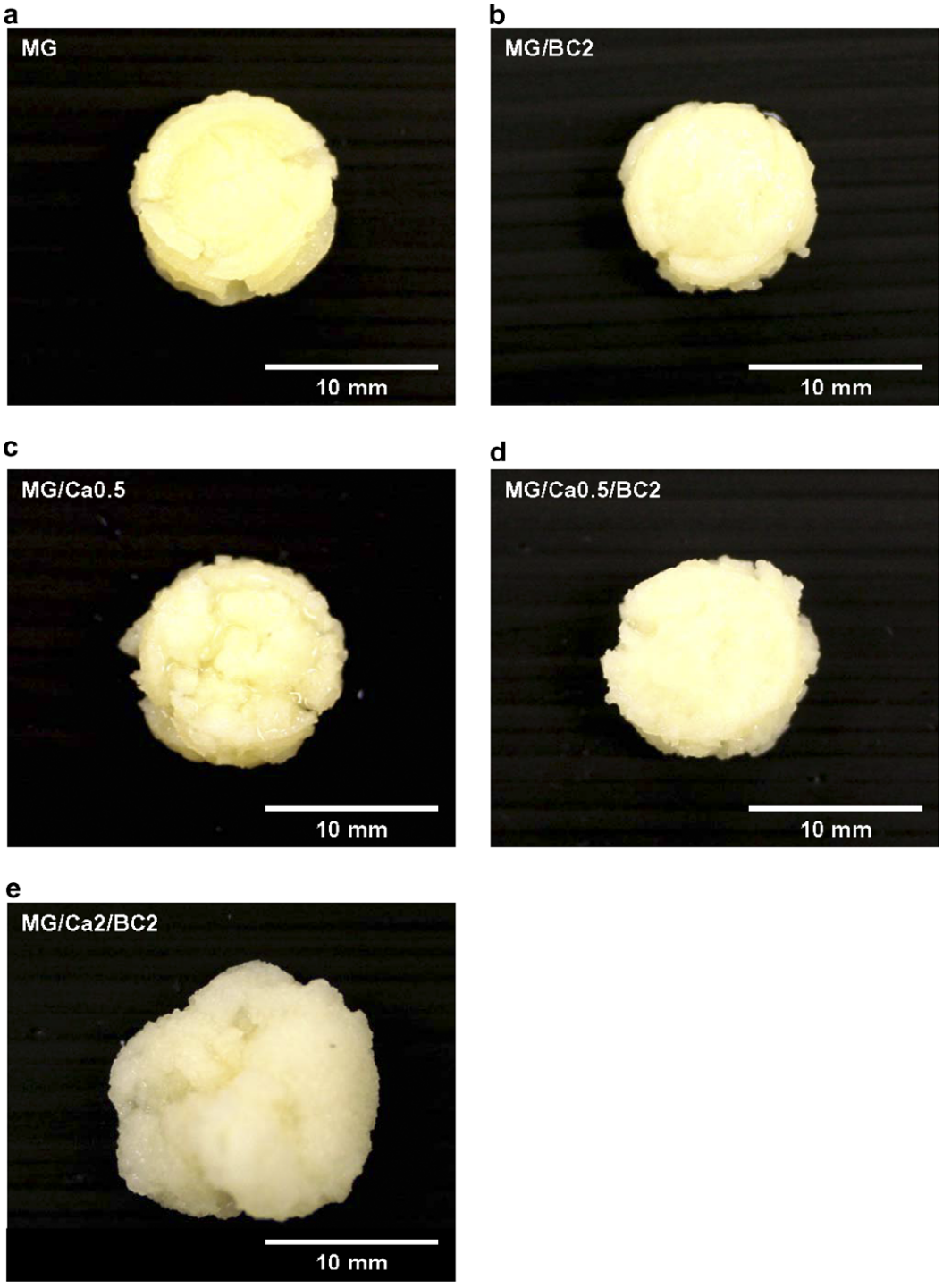


Fig. 4. Effect of additives (i.e. calcium acetate and/or sodium bicarbonate) on the morphology of alginate-based matrix tablets hydrated in 0.1 N HCl for 30 min.

may additionally influence erosion by altering the gel layer properties. This could be a possible explanation for the relatively high erosion in presence of additives.

### 3.3. Release behavior of alginate-based matrix tablets

The release profiles of MZ from some alginate-based matrix tablets in 0.1 N HCl (pH 1.2) and pH 6.8 phosphate buffer are shown in Fig. 5. The drug release from matrix tablets was influenced by pH of release media. Drug release from some formulations was fairly rapid with essentially complete release within 60–90 min. Some alginate-based matrix tablets can sustain drug release for at least 8–10 h. Release from matrix tablets is essentially constant until about 80–90% of the payload has been released. In order to see the influence of pH of the medium, grade of alginate, particle size of MZ and additive used on drug release from alginate-based matrix tablets, the time (in min) to achieve

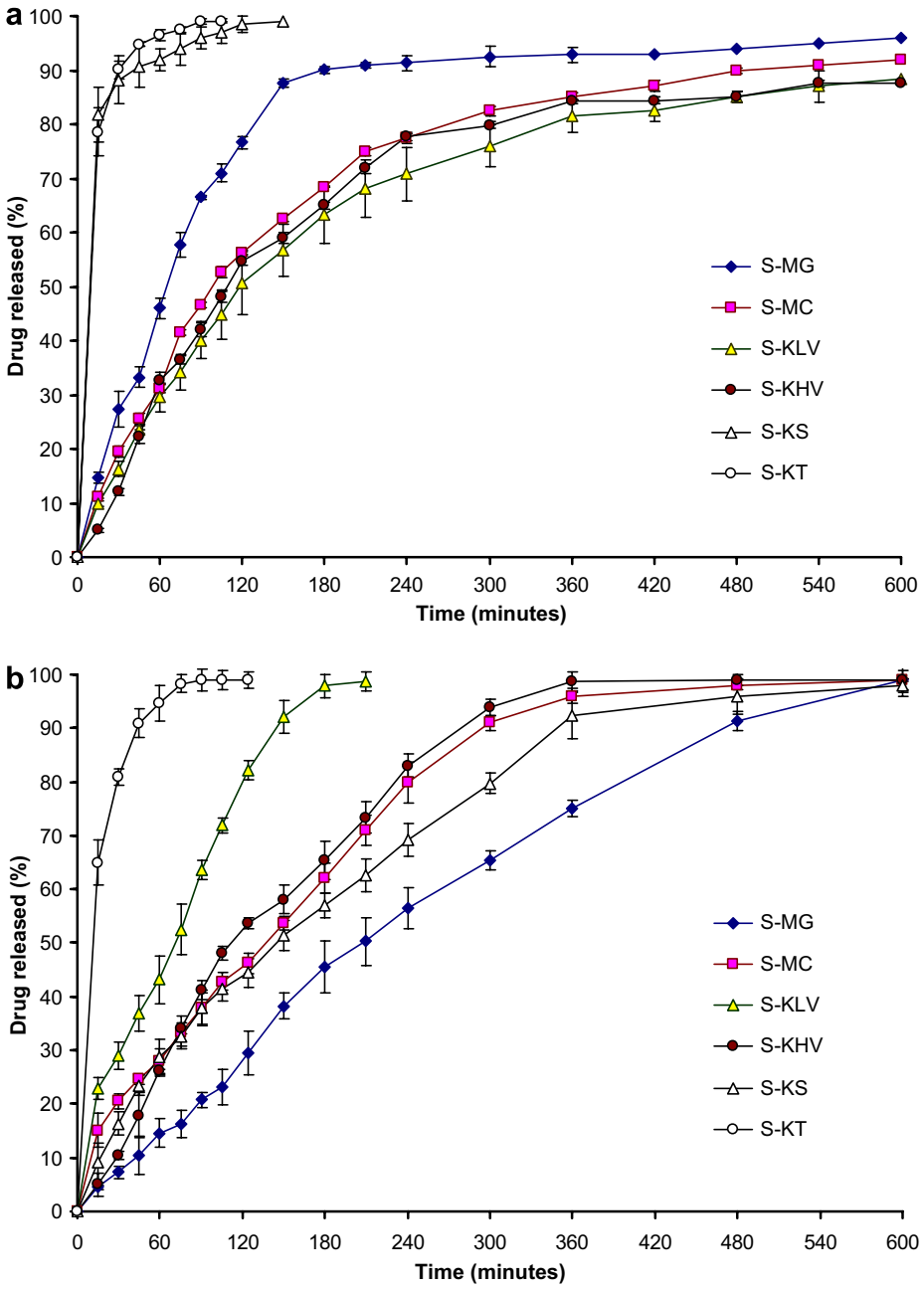


Fig. 5. Release profiles of metronidazole from some formulations of matrix tablets in (a) 0.1 N HCl and (b) pH 6.8 phosphate buffer, plotted as a function of time ($n = 3$).

release of 80% of the payload was measured and designated as $T_{80}$. The comparison of the $T_{80}$ (in 0.1 N HCl and pH 6.8 phosphate buffer) from matrix tablets is shown in Figs. 6 and 7.

### 3.3.1. Influence of pH of the medium and alginate grade

It can be seen from the $T_{80}$ in Figs. 6 and 7 that the drug release in 0.1 N HCl is apparently different from that in pH 6.8 phosphate buffer. Although the matrices generally showed a higher ability to swell in neutral medium than in acidic medium, the drug release in neutral medium, from high M alginate tablets, was faster than in acidic medium. It is perhaps reasonable to expect faster release in neutral medium than acidic medium as the alginate will be more soluble at higher pH [11]. This is the case for the high M alginates, namely MC, KLV and KHV. However, for high G alginate (MG), the $T_{80}$ is much faster in 0.1 N HCl than in pH 6.8 buffer. It is likely that the high G alginate formed more rigid gels upon hydration in neutral medium than high M alginate. The unusual behavior observed between the high M and high G alginates has been reported in the literature [11,12], specifically, the faster release from tablets of high M alginate in neutral medium in contrast to the faster release from tablets of high G alginate in acidic medium. The higher erosion, in neutral medium, of tablets composed of high M alginates may contribute to the faster drug

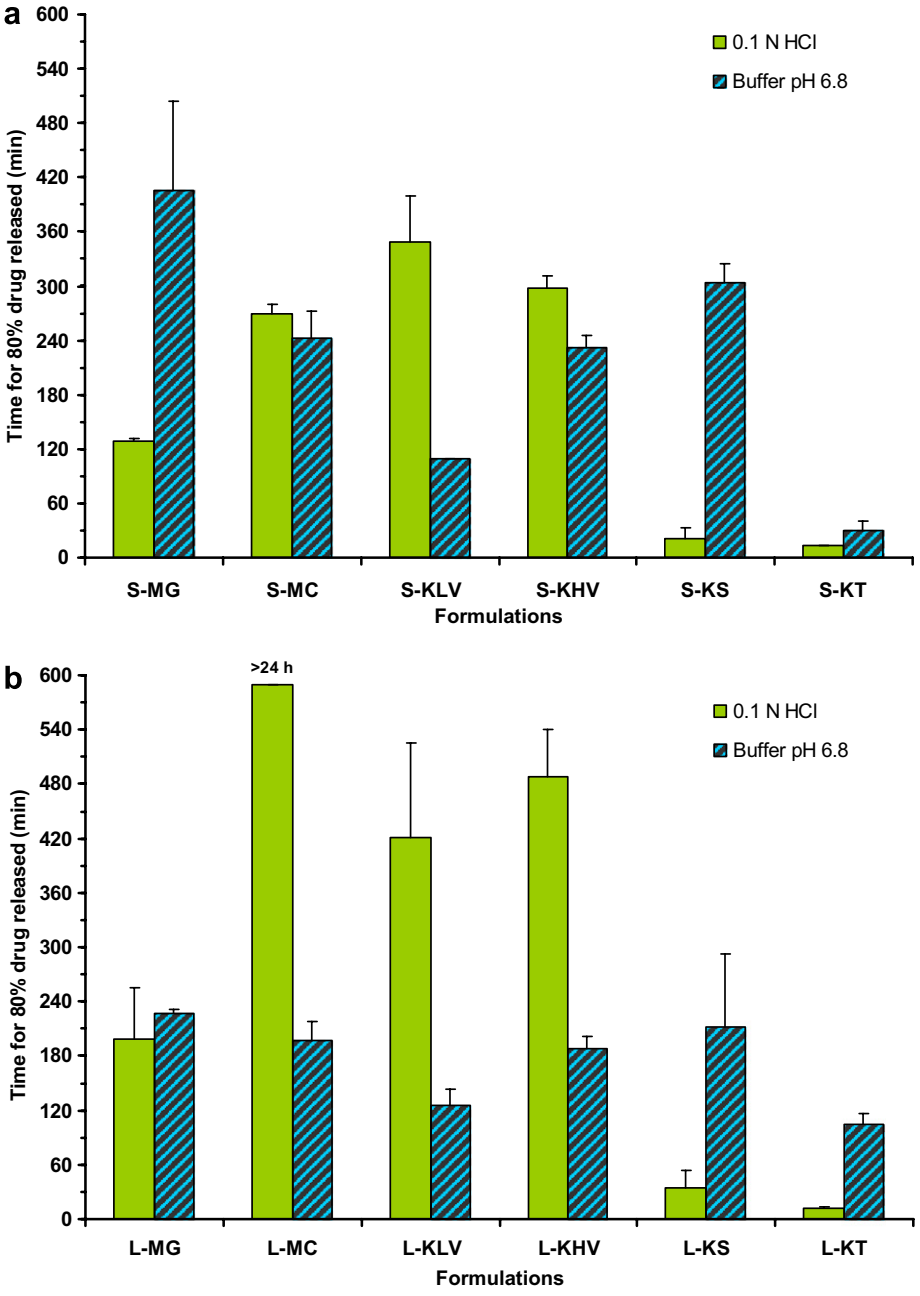


Fig. 6. Time for 80% of drug release ($T_{80}$) from alginate-based matrix tablets in 0.1 N HCl and pH 6.8 phosphate buffer using (a) small and (b) large particle size of metronidazole, $n = 3$.

release. The $T_{80}$ values of the matrix tablets show a slight but not significant difference between the different viscosity grades (KLV and KHV) in acidic medium. However, the $T_{80}$ values in pH 6.8 buffer show that higher viscosity alginate tablets provided the slower drug release, compared to lower viscosity alginate tablets. This is in agreement with other research findings [12], where lower-viscosity alginate matrices showed faster drug release compared to higher-viscosity alginate matrices.

The rapid drug release of matrix tablets containing sodium/calcium alginate (KS) and ammonium/calcium alginate (KT), in acidic medium, resulted from the disintegration of the matrix tablets. The ammonium and/or calcium salts of alginate could be replaced by protons in acidic medium to form alginic acid which stimulated the tablet disintegration. Alginic acid, a water insoluble, could swell when in water and has been used traditionally as a tablet disintegrant in compressed tablets designed for immediate drug release. In pH 6.8 buffer, ammonium salts may create pores in the tablet to facilitate a slow disintegration, resulting in the fast release of MZ or low $T_{80}$ values.

### 3.3.2. *Influence of particle size of metronidazole*

The influence of drug particle size depends on its aqueous solubility, being especially important with moderately soluble drugs [17]. In this study, MZ, which is slightly

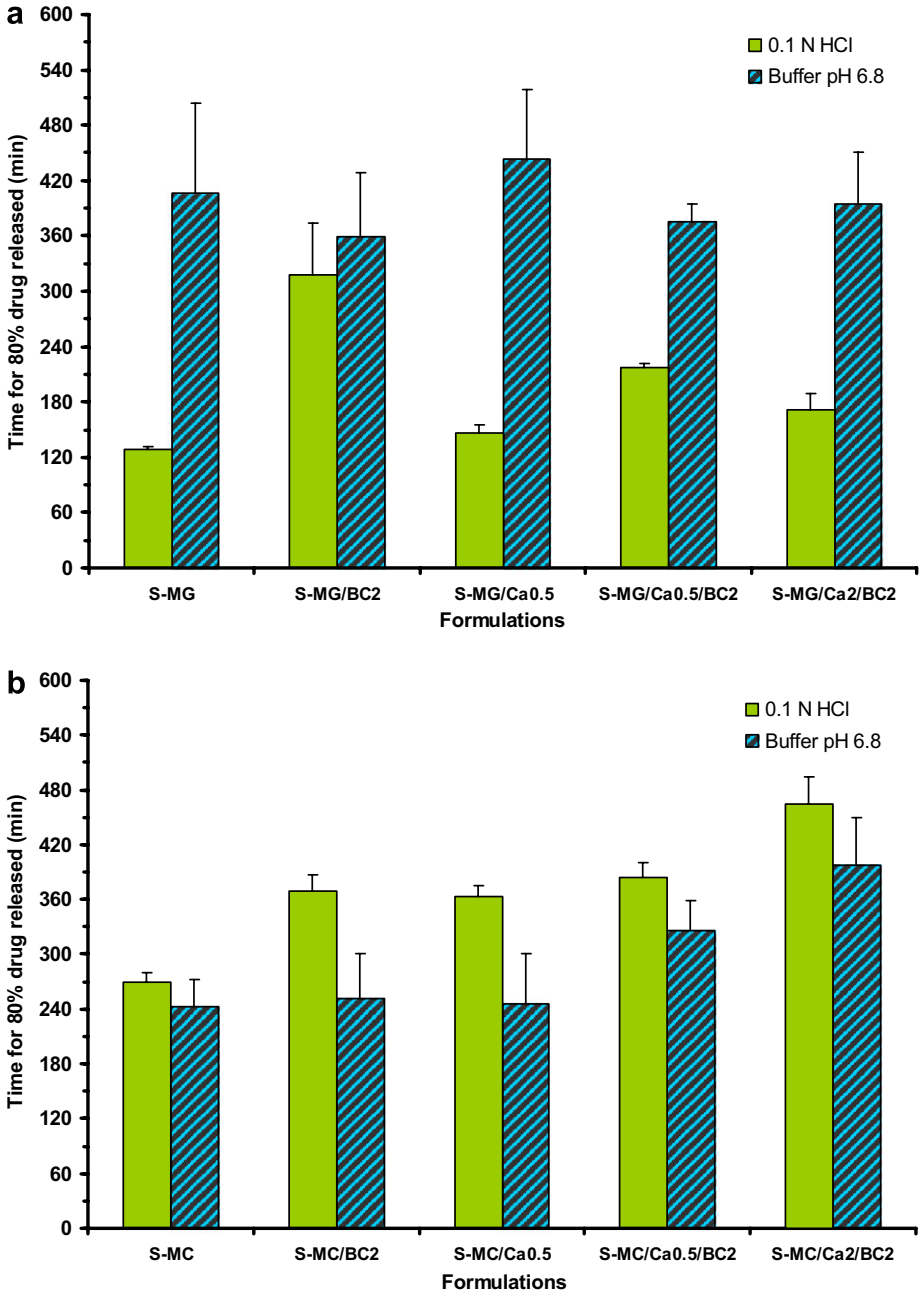


Fig. 7. Effect of additives (i.e. calcium acetate and/or sodium bicarbonate) on the time for 80% of drug release ($T_{80}$) from alginate-based matrix tablets prepared with (a) MG and (b) MC, in 0.1 N HCl and pH 6.8 phosphate buffer, $n = 3$.

soluble in aqueous solution (about 100 mg/mL in water), was used. The drug release from matrix tablets composed of different sizes of MZ particles was statistically significantly different. The $T_{80}$ values of the formulations containing smaller drug particle size were lower, showing the faster drug release, in acidic medium. Such results may be explained by the effective surface area of the drug particles. The smaller particle size of drug will dissolve more easily when dissolution media penetrate through the matrices resulting in a greater role for diffusion. The larger particle sizes would dissolve less readily and therefore be more prone to erosion at the matrix surface. A similar dependence has been shown for the less soluble drug, diclofenac sodium [18]. Moreover, a faster drug release also may be due to a less tablet hardness of the tablets containing smaller particle size of drug. On the other hand, the $T_{80}$ values in neutral medium of the formulations containing smaller drug particle size were slightly greater (i.e. slower drug release) than those containing larger size, probably because the dissolution of the drug in the neutral medium is faster when the drug particle size is smaller, then, the drug molecules had to diffuse through the gel matrices and some of

them might be entrapped in the matrices. It is perhaps reasonable to explain the faster drug release from the tablets using large particle size of drug by erosion of the matrix. This release behavior may also provide a possible mechanism for dose dumping from matrix tablets of this type.

*3.3.3. Influence of additive incorporated (sodium bicarbonate and/or calcium acetate)*

The incorporation of a pH modifier, sodium bicarbonate, in the matrix tablet formulations (both MG and MC tablets) significantly retarded the drug release in acidic medium by creating a more basic microenvironment, thereby resulting in enhanced swelling and, consequently, decreased dissolution rates. In neutral medium, the addition of sodium bicarbonate did not influence the modification of drug release, no significant difference in $T_{80}$ values (Fig. 7).

Calcium ions can react with sodium alginate, as previously discussed, to cross-link the polymer through the carboxylate and modify rheological properties and gel layer integrity. As a result, there may be an impact on release properties. Thus, the formulations studied here have been tested in the presence of calcium ions to ascertain how its presence affects drug release profiles. Addition of calcium acetate in the formulations slightly delayed the drug release from MG tablets in acidic medium. The MC tablets exhibited the more pronounced effect on prolonged drug release.

The maintenance of a constant and basic microenvironment by sodium bicarbonate created the most favorable conditions for calcium alginate gel formation. Therefore, the drug release in acidic condition was more extended in the formulations containing both calcium acetate and sodium bicarbonate, compared to those containing calcium acetate alone or those without additive. In neutral condition, the drug release from MG tablets was not significantly changed when the additives were added (Fig. 7a). However, for the MC tablets, the drug release was delayed (higher $T_{80}$ values) with the addition of calcium acetate and sodium bicarbonate. Increasing the amount of calcium salts slightly increased the $T_{80}$ values (Fig. 7b). Similar results have previously been reported [19]. Increasing amount of calcium leads to a greater degree of cross-linking and aggregation of the initial dimers giving higher gel strength and results in the slower drug release pattern [19], as also discussed previously in Section 3.2.3.

*3.4. Analysis of release data*

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 [20]. The release kinetics for all the models is shown in Table 4. Previous report [13] showed that the release of theophylline (in both acidic and neutral media) from hard capsules containing different grades of alginate fitted well with both Higuchi equation and Korsmeyer–Peppas equation. Higuchi model is applicable if the release of drug is largely governed by diffusion through water-filled pores in the matrix. A good fit to Korsmeyer–Peppas equation indicated combined effect of diffusion and erosion mechanisms for drug release [14].

In this study, the MZ release (in acidic medium) from matrix tablets containing different grades of sodium alginate and those with additives showed a good fit into Korsmeyer–Peppas equation. As illustrated in Table 4, release data fit the Korsmeyer–Peppas model as well as a correlation coefficient ($r^2$) greater than 0.986 was obtained in all cases in acidic medium. The exception is for the tablets containing combination of alginate salts (KS and KT) which disintegrated rapidly (within 30 min) in the acidic medium. Then, the release exponents for these formulations could not be calculated because there were insufficient data points on the release profiles between 10% and 60% release to provide accurate values. The matrix tablets containing sodium alginate with or without additives exhibited an anomalous (non-Fickian) diffusion controlled release in acidic medium. The value of '$n$' and '$k$' was found to vary with the grade of alginate and additives used.

In neutral medium, on the other hand, drug release data of matrix tablets did not show a good fit into Korsmeyer–Peppas equation. Interestingly, most of the release data of matrix tablet formulations fitted well with zero-order release model with a correlation coefficient ($r^2$) greater than 0.980 (Table 4). This is probably due to the extensive swelling of tablets containing sodium alginate in neutral medium (as shown in Fig. 2). The release fitted with the Higuchi model equation of diffusion from the matrix tablets containing high viscosity alginate (KHV) or a combination of alginate salts (KS and KT). Similar result was observed by Khairuzzaman et al. [21] in tablets with methylcellulose glutarate. These authors studied the drug release from methylcellulose glutarate, a more hydrophilic salt form of methylcellulose, matrices comparing to methylcellulose matrices. The matrix tablets with methylcellulose (i.e. less hydrophilic polymer) provided the first-order release profile while those with methylcellulose glutarate showed the zero-order release profiles of all the drugs tested in water.

## 4. Conclusion

Alginate-based matrix tablets were easily prepared by blending drug and alginate with or without calcium acetate and/or sodium bicarbonate, 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. Different grades of alginate did not significantly influence the swelling of matrix tablets in acidic medium but significantly influenced in neutral medium. The presence of ammonium or calcium salts induced tablet disintegration in acidic medium. However, incorporation of calcium acetate and sodium

Table 4
Mathematic modeling and drug release kinetics of metronidazole from alginate-based matrix tablets[a]

| Formulation | Correlation coefficient, $r^2$ | | | | Kinetic constant, $k$ (Korsmeyer–Peppas model) | Diffusional exponent, $n$ (Korsmeyer–Peppas model) | Order of release (Korsmeyer–Peppas model) |
|---|---|---|---|---|---|---|---|
| | Zero-order | First-order | Higuchi model | Korsmeyer–Peppas model | | | |
| In 0.1 N HCl | | | | | | | |
| S-MG | 0.9818 | 0.8062 | 0.9874 | 0.9891 | 0.016 | 0.83 | Non-Fickian |
| S-MC | 0.8770 | 0.9629 | 0.9676 | 0.9959 | 0.013 | 0.79 | Non-Fickian |
| S-KLV | 0.8808 | 0.9646 | 0.9713 | 0.9984 | 0.012 | 0.78 | Non-Fickian |
| S-KHV | 0.8392 | 0.9159 | 0.9499 | 0.9740 | 0.003 | 1.10 | Super case II |
| S-KS | 0.8933 | 0.9683 | 0.9463 | n/a[b] | n/a | n/a | n/a |
| S-KT | 0.7460 | 0.9744 | 0.8477 | n/a | n/a | n/a | n/a |
| L-MG | 0.9401 | 0.9691 | 0.9864 | 0.9906 | 0.023 | 0.70 | Non-Fickian |
| L-MC | 0.9310 | 0.9787 | 0.9783 | 0.9866 | 0.029 | 0.57 | Non-Fickian |
| L-KLV | 0.8841 | 0.9144 | 0.9719 | 0.9928 | 0.019 | 0.68 | Non-Fickian |
| L-KHV | 0.9200 | 0.9786 | 0.9749 | 0.9866 | 0.031 | 0.57 | Non-Fickian |
| L-KS | 0.9879 | 0.9593 | 0.9988 | n/a | n/a | n/a | n/a |
| L-KT | 0.8328 | 0.5797 | 0.8854 | n/a | n/a | n/a | n/a |
| S-MG/BC2 | 0.9292 | 0.9526 | 0.9865 | 0.9893 | 0.015 | 0.73 | Non-Fickian |
| S-MG/Ca0.5 | 0.9684 | 0.8838 | 0.9948 | 0.9979 | 0.016 | 0.81 | Non-Fickian |
| S-MG/Ca0.5/BC2 | 0.9882 | 0.9863 | 0.9735 | 0.9908 | 0.037 | 0.56 | Non-Fickian |
| S-MG/Ca2/BC2 | 0.9824 | 0.9417 | 0.9824 | 0.9933 | 0.077 | 0.46 | Non-Fickian |
| S-MC/BC2 | 0.9431 | 0.9806 | 0.9951 | 0.9962 | 0.025 | 0.61 | Non-Fickian |
| S-MC/Ca0.5 | 0.9220 | 0.9746 | 0.9880 | 0.9938 | 0.031 | 0.57 | Non-Fickian |
| S-MC/Ca0.5/BC2 | 0.9717 | 0.9841 | 0.9893 | 0.9953 | 0.029 | 0.56 | Non-Fickian |
| S-MC/Ca2/BC2 | 0.9394 | 0.9853 | 0.9838 | 0.9939 | 0.122 | 0.49 | Non-Fickian |
| In phosphate buffer pH 6.8 | | | | | | | |
| S-MG | 0.9971 | 0.8928 | 0.9758 | 0.9812 | n/a | n/a | n/a |
| S-MC | 0.9989 | 0.9640 | 0.9726 | 0.9837 | n/a | n/a | n/a |
| S-KLV | 0.9943 | 0.9344 | 0.9579 | 0.9598 | n/a | n/a | n/a |
| S-KHV | 0.9682 | 0.9072 | 0.9924 | 0.9806 | n/a | n/a | n/a |
| S-KS | 0.9746 | 0.9759 | 0.9984 | 0.9821 | n/a | n/a | n/a |
| S-KT | 0.9279 | 0.9779 | 0.9898 | n/a | n/a | n/a | n/a |
| L-MG | 0.9893 | 0.9500 | 0.9544 | 0.9577 | n/a | n/a | n/a |
| L-MC | 0.9823 | 0.9813 | 0.9424 | 0.9113 | n/a | n/a | n/a |
| L-KLV | 0.9969 | 0.9806 | 0.9839 | 0.9913 | n/a | n/a | n/a |
| L-KHV | 0.9783 | 0.9849 | 0.9912 | 0.9716 | n/a | n/a | n/a |
| L-KS | 0.8735 | 0.9604 | 0.9898 | 0.9755 | n/a | n/a | n/a |
| L-KT | 0.8665 | 0.9520 | 0.9871 | 0.8979 | n/a | n/a | n/a |
| S-MG/BC2 | 0.9971 | 0.9209 | 0.9723 | 0.9790 | n/a | n/a | n/a |
| S-MG/Ca0.5 | 0.9979 | 0.9528 | 0.9761 | 0.9842 | n/a | n/a | n/a |
| S-MG/Ca0.5/BC2 | 0.9807 | 0.8733 | 0.9280 | 0.9624 | n/a | n/a | n/a |
| S-MG/Ca2/BC2 | 0.9824 | 0.8372 | 0.9724 | 0.9665 | n/a | n/a | n/a |
| S-MC/BC2 | 0.9953 | 0.8721 | 0.9684 | 0.9865 | n/a | n/a | n/a |
| S-MC/Ca0.5 | 0.9944 | 0.9320 | 0.9486 | 0.9773 | n/a | n/a | n/a |
| S-MC/Ca0.5/BC2 | 0.9878 | 0.8926 | 0.9761 | 0.9792 | n/a | n/a | n/a |
| S-MC/Ca2/BC2 | 0.9890 | 0.9494 | 0.9809 | 0.9715 | n/a | n/a | n/a |

[a] Analyzed by the regression coefficient method.
[b] n/a, not applicable.

bicarbonate can alter the tablet swelling in acidic medium. The drug release from matrix tablets was influenced by pH of release medium, grade of alginate, particle size of drug and additive used. The extent of matrix swelling, erosion, and release of drug determined the kinetics as well as mechanism of drug release from alginate-based matrix tablets. Most of the release data in acidic medium showed a good fit into Korsmeyer–Peppas equation but fitted well with zero-order release model, in neutral medium.

The results of this study enable us to state that the hydrophilic matrix tablets are 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. It is, therefore, possible to achieve a firmer basis of their use.

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