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Research Article

Inter-Grade and Inter-Batch Variability of Sodium Alginate Used in Alginate-Based Matrix Tablets

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Abstract. The purpose of this study is to characterize the inter-grade and inter-batch variability of sodium alginate used in the formulation of matrix tablets. Four different grades and three batches of one grade of sodium alginate were used to prepare matrix tablets. Swelling, erosion, and drug release tests of sodium alginate matrix tablets were conducted in a USP dissolution apparatus. Substantial differences in swelling and erosion behavior of sodium alginate matrix tablets were evident among different viscosity grades. Even different batches of the same grade exhibit substantial differences in the swelling and erosion behavior of their matrix tablets. The erosion behavior of sodium alginate matrix tablets can be partly explained by their rheological properties (both apparent viscosity and viscoelasticity) in solution. Sodium alginate with higher apparent viscosity and viscoelasticity in solution show slower erosion rate and higher swelling rate. Compacts prepared from grades or batches with higher viscosity and higher viscoelasticity show slower drug release. For grades or batches with similar apparent viscosities, apparent viscosities of sodium alginate solution at low concentration alone are not sufficient to predict the functionality of sodium alginate in matrix tablets. Viscoelastic properties of sodium alginate solutions at one high concentration corresponding to the polymer gel state, may be suitable indicia of the extended release behavior of sodium alginate matrix tablets.

KEY WORDS: drug release; erosion; matrix tablets; rheology; sodium alginate; swelling.

INTRODUCTION

Hydrophilic polymer matrices have been widely employed in peroral controlled drug release systems. Polymer matrix tablets are relatively easy and economical to formulate and manufacture (1). Drug release from hydrophilic polymer matrices is controlled by the hydration characteristics (swelling and/or erosion) of the polymer and the physical properties of the resultant polymer gel layer formed around the matrices (2–5). Water-soluble drugs are primarily released by diffusion of dissolved drug molecules through the polymer gel layer, while poorly water-soluble drugs are mainly released by erosion of the polymer layer at the interface between the polymer gel and the bulk solution (6).

Sodium alginate, which is able to form viscous solutions when in contact with water, has been employed to produce matrices such as beads, microspheres, and tablets for extended drug release (4,7–9). Sodium alginate matrix tablets can be manufactured by direct compression, which is preferred industrially due to the low cost of manufacturing (1,10).

A useful approach to understand sodium alginate's functionality in extended release matrix tablets is to study the swelling and erosion behavior of sodium alginate matrix tablets. The differences between swelling and erosion behaviors of tablets prepared from multiple grades of sodium alginate, varying in both molecular weight and chemical composition have been investigated by several groups. Efentakis and Buckton's study on sodium alginate matrix tablets prepared from two grades of sodium alginate concluded that the high viscosity grade of sodium alginate formed a more substantial gel layer and eroded at a much lower rate in water than the low viscosity grade (4). The two grades of sodium alginate were specified as 14 and 0.2 Pa s (determined on 2% solution at 25°C). However, viscosity measurement method was not specified. Sriamornsak *et al.*, investigated the swelling and erosion behavior of sodium alginate matrix tablets prepared from three grades of sodium alginate (Viscosity grade: 0.3 Pa s (high %guluronic acid), 0.3 Pa s (low %guluronic acid), and 0.035 Pa s, respectively). Viscosity was determined on 1% solution using Brookfield LV viscometer at 60 rpm with No. 2 spindle; temperature was not specified in both 0.1 M HCl solution and phosphate buffer (pH 6.8) (11). Their results demonstrated that the swelling and erosion behavior of these three grades of sodium alginate were not significantly different in an acidic medium, but were significantly different in phosphate buffer. Higher viscosity grades swelled to a higher degree and eroded to a lower extent than the low viscosity grade in phosphate buffer (11). The two grades with same viscosity but different %G did not show any significantly differences in their swelling and erosion behavior (11). Chan *et al.* (12) also compared the swelling and erosion behavior of two grades of sodium alginate (kinematic viscosity 3 and 108 mm^2/s, respectively). Kinematic viscosity was determined

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on 1% solution using suspended-level viscometer at 37°C) in both acidic and neutral media and reached the same conclusion as Sriamornsak *et al.* (11).

The grades of sodium alginate used in these three studies are substantially different in their apparent viscosities. Thus, it would not be surprising to detect substantial differences in the swelling and erosion behavior of alginate-based matrix tablets. Grades with similar viscosity specifications, whether produced by the same manufacturer or by different manufacturers, are likely to be considered to be interchangeable. Hence, it is necessary to investigate the swelling and erosion behavior of sodium alginate grades with similar viscosities to determine the potential variability that may be observed once a product's formulation has been defined. Second, the apparent viscosity data for the various grades of sodium alginate used in the previous studies are "one-point" viscosity data obtained at one concentration, one shear condition, and one temperature. A study of the rheological properties of sodium alginate solutions has shown that "one-point" viscosity data obtained by simple viscometry do not adequately reflect the rheological behavior of sodium alginate solutions at higher concentrations (13). Inter-grade and inter-batch variability of sodium alginate is insufficiently characterized by their "one-point" apparent viscosities. Third, the aforementioned swelling and erosion studies were conducted by exposing the whole tablet to the dissolution medium. Consequently, the changing surface area and volume of the swelling tablets during the experiment can be expected to markedly affect the apparent erosion and swelling behavior of the whole tablets. Finally, no studies were performed to investigate the effect of batch variability on sodium alginate matrix tablets functionality. Sodium alginate is extracted from seaweeds. Batch-to-batch variability could be derived from differences in seaweeds harvested throughout the year.

To address these issues, four grades of sodium alginate, and three batches of one grade were selected to study the swelling and erosion behavior of sodium alginate matrix tablets. Among the four grades, two are in the same viscosity range as specified by the manufacturer. The other two grades are in relatively higher viscosity range (<500% difference in viscosity among these four different grades). For swelling and erosion experiments, a specially designed cylindrical tablet holder was employed to expose only the upper flat surface of the tablets to the dissolution medium. Weight changes due to water uptake and polymer dissolution were determined at various time points. Furthermore, the continuous changes of the hydrated polymer layer thickness of sodium alginate matrix tablets were determined by the texture analysis method proposed by Yang *et al.* (14). The release profile of a model drug, acetaminophen, from sodium alginate matrix tablets was also studied. Finally, the relationship between the rheological properties of sodium alginate solutions and the functionality of the sodium alginate matrix tablets was investigated.

MATERIALS AND METHODS

Materials

Four grades (one batch each) and three batches of one grade of sodium alginate (LF120M, grade B) were provided by FMC Biopolymer (Drammen, Norway). Rheological properties, previously determined for these grades and batches are listed in Table I. Apparent viscosity of alginate solutions increases from grade A to grade D. Batches I to III were named based on their manufacturing date with batch I as the earliest batch. Deionized water was obtained from a *Milli-Q* ultrapure water system (Millipore Corp., Billerica, MA, USA). Acetaminophen (USP grade) was purchased from Spectrum Chemicals (Gardena, CA, USA) and the particles <53 μm (passing through a 270 mesh sieve) were used in drug release studies from sodium alginate matrix tablets.

Methods

Rheological Measurements of Sodium Alginate Solutions

The procedures employed in generating the steady shear and small amplitude oscillatory data for the sodium alginate solutions were described in Fu *et al.* (13).

Preparation of Sodium Alginate Matrix Tablets

Sodium alginate matrix tablets were prepared by direct compression using an Instron Universal Testing Machine (model 5869) equipped with a 50 kN load cell (Instron, Norwood, MA, USA). Sodium alginate powder (400±1 mg) were filled into a 12-mm cylindrical die (Carver, Inc., Wabash, IN, USA) and were compressed using flat-faced punches (Carver, Inc., Wabash, IN, USA) at 10 mm/min to 30 kN (*i.e.*, 265 MPa). The load was held for 10 s, before decompression occurred at 10 mm/min. All powders and compacts were stored at room temperature (typically 20–22°C) and controlled humidity (31–33% relative humidity) which was achieved by saturated $MgCl_2$ solution (15).

Porosity of Matrix Tablets and Tensile Strength

Matrix tablet dimensions (diameter and thickness) were determined after compression and relaxation at room temperature (typically 20–22°C) and controlled humidity (31–33% relative humidity) by using an electronic digital caliper (Marathon Ltd., Richmond Hill, Ontario, Canada). Tablet porosity (ε) was calculated according to Eq. 1:

$$\varepsilon = 1 - \left(\frac{m}{0.25\pi t \rho D^2} \right), \tag{1}$$

where m is the tablet weight, D is the tablet diameter, t is the tablet thickness, and ρ is the true density of the sodium alginate powder stored at room temperature (typically 20–22°C) and controlled humidity (31–33% relative humidity).

Water Uptake

A specially designed tablet holder, *i.e.*, a cylindrical polyacetal block (diameter, ~15 mm; height, ~15 mm) with a cavity in the middle (diameter, ~12 mm; depth, ~12 mm), was used in the swelling and erosion studies (Fig. 1).

Vacuum grease (Dow Corning Corporation, Midland, MI, USA) was carefully applied to the bottom flat surface and the side of the cylindrical alginate compacts before

Table I. Viscosity Specification by Manufacturer, Guluronic Acid Percentage (%G), and Intrinsic Viscosity of the Four Grades and Three Batches of Sodium Alginate Used in the Compression Studies

Sodium alginate	FMC product name	Apparent viscosity[a], Pa s	tan δ[b]
A	Protanal LF240D	0.49	1.012
B	Protanal LF120M	0.69	1.109
C	Protanal LF200M	1.90	1.066
D	Protanal LF200DL	2.52	1.522
Batch I	LF120M 19338	1.29	0.710
Batch II	LF120M 19961	0.92	0.811
Batch III	LF120M 20228	0.81	1.277

[a] Viscosity of 2% *w*/*w* sodium alginate solutions at 25°C determined by a rotational rheometer at 1 Pa shear stress (13)
[b] tan δ of 8% *w*/*w* sodium alginate solutions at 37°C determined at angular frequency of 1 rad/s (13). Lower tan δ indicates higher elasticity

placing the compacts into the tablet holder. Only the upper flat surfaces of the sodium alginate tablets were exposed to the dissolution medium, *i.e.*, deionized water. Swelling and erosion studies were performed in a type II USP dissolution apparatus (Vanderkamp®600, Vankel, Palo Alto, CA, USA) with paddles stirring at 50 rpm. Accurately weighed tablets (W_0) were placed in the tablet holder (weight, W_h) and immersed into 900 mL deionized water at 37±0.5°C. The tablet holder was placed in the center of the vessel bottom. At predetermined time points, 0.5, 1, 2, 3, 4, 5, 6, 7, 10, and 15 h, each tablet holder was withdrawn from the medium and blotted to remove excess water and weighed (W_t) on an analytical balance (Mettler Toledo, Columbus, OH, USA). The increase in total weight due to water penetration into the matrix tablets and polymer dissolution was determined for each time point according to the following equation:

$$\%\text{Increase-in-Total-Weight} = \frac{W_t - W_0 - W_h}{W_0} \times 100\%, \quad (2)$$

Erosion

The swollen matrix tablets collected at each time point were then dried in a vacuum oven (Isotemp® Model 280A, Fisher Scientific, Pittsburgh, PA, USA) at 85°C for at least 24 h, cooled in a desiccator until constant weights ($W_{t,\,dry}$) was achieved. Three matrix tablets were used for each time point. Three of the original tablets were dried, cooled, and weighed to determine the average dried weight ($W_{0,\,dry}$) of the initial matrix tablets. The remaining weight percentage of tablets throughout polymer dissolution was estimated for each time point according to the following equation:

$$\%\text{Polymer Remaining} = \frac{W_{t,dry}}{W_{0,dry}} \times 100\%, \quad (3)$$

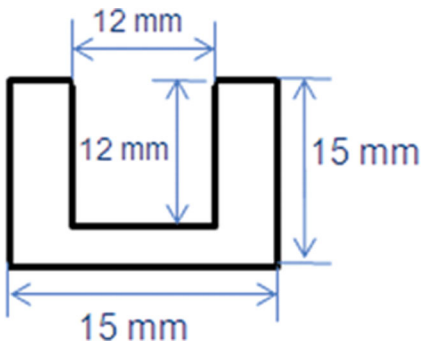

Fig. 1. Schematic illustration of the tablet holder

Hydrated Polymer Layer Thickness

The movement of the water penetration front and the dynamics of the hydrated polymer layer formation as a function of time were evaluated by texture profiling analysis method modified from a previous report (14). The test was performed with an Instron Universal Testing Machine (model 5869) equipped with a 50 N load cell (Instron, Norwood, MA, USA). A right-cylindrical probe (2 mm in diameter) attached to the load cell was driven at constant speed (10 mm/min) into the swollen tablets inside the tablet holder while the force of resistance encountered by the probe and the distance traveled by the probe during the test were measured. Measurements started at a trigger force of 0.01 N indicative of the swollen gel surface (the solution-gel interface or the erosion front) and stopped at a predetermined stop force chosen to distinguish between the hydrated polymer layer and the remaining solid core of the tablet (the swelling front). The stop force was based on measurements on dry tablets, for which the recorded force-displacement curve was very steep: the gradient of the curve was larger than 150 N/mm. The force-displacement curves for the dry tablets and the partially swollen tablets were comparable for forces above 15 N. Thus, the stop force was set to be 15 N. An initial indentation of 100 μm on dry tablets was recorded under 15 N load. Thus, 100 μm was deducted from the displacement between trigger force and stop force for the calculation of the thickness of the hydrated polymer layer.

Drug Release

Acetaminophen and sodium alginate (1:9 *w*/*w*) powder (4 g in total) was mixed using a Thinky Mixer (Model ARM 310, Thinky USA, Laguna Hills, CA, USA) at 2,000 rpm for 1 min. The blending endpoint was determined when the relative standard deviation (%RSD) of the acetaminophen content in samples taken from three different locations in the mixing container was <5%. Acetaminophen (40 mg)-sodium

alginate (360 mg) matrix tablets were prepared using Instron Universal Testing Machine (model 5869, Instron, Norwood, MA, USA) with circular flat-faced punches (12 mm in diameter, Carver, Inc., Wabash, IN, USA) at a speed of 10 mm/min, a maximum load of 30 kN (*i.e.*, 265 MPa), and a dwell time of 10 s. Tablets were placed inside the same tablet holders as described in the *Water uptake* section.

Drug release test were performed on a VanKel® Dissolution Apparatus (Palo Alto, CA, USA) using USP Apparatus II with paddle rotation speed at 50 rpm. The dissolution medium was 900 mL of deionized water with temperature maintained at 37±0.5°C. At predetermined time points, 5 mL samples were collected from the dissolution medium followed by addition of an equal volume of preheated deionized water. The acetaminophen concentrations of the samples were determined by UV absorption at 244 nm on a Cary 3 UV/Vis Spectrometer (Varian/Agilent technologies, Santa Clara, CA, USA) according to a standard curve generated from 0.1 to 50 μg/mL (R^2=0.9999). Three samples were tested for each time point.

Data Analysis

The obtained data for the different grades and batches were analyzed *via* analysis of variance (ANOVA) and Levene's test for homogeneity of variance using PASW Statistics 18 for Windows (SPSS Inc., Chicago, USA). *Post hoc* testing (P<0.05) of the multiple comparisons was performed by either the Tukey HSD (Honestly Significant Difference) test or Games–Howell test depending on whether Levene's test was insignificant or significant, respectively. GraphPad Prism (version 5, GraphPad Software, Inc., La Jolla, CA, USA) was used for the linear and nonlinear regression analysis of the data where appropriate.

RESULTS AND DISCUSSION

Inter-Grade Variability

Porosity of the sodium alginate matrix tablets prepared from four different grades varied from 0.17 to 0.19 as shown in Table II. The tensile strength of sodium alginate tablets, ranging from 5.13 to 5.85 MPa, did not differ significantly among the four grades.

Water Uptake and Erosion

Sodium alginate tablets exposed to water undergo swelling with the formation of a gel layer. The water uptake and erosion behavior of matrix tablets prepared from four grades of sodium alginate are depicted, as a function of time, in Fig. 2.

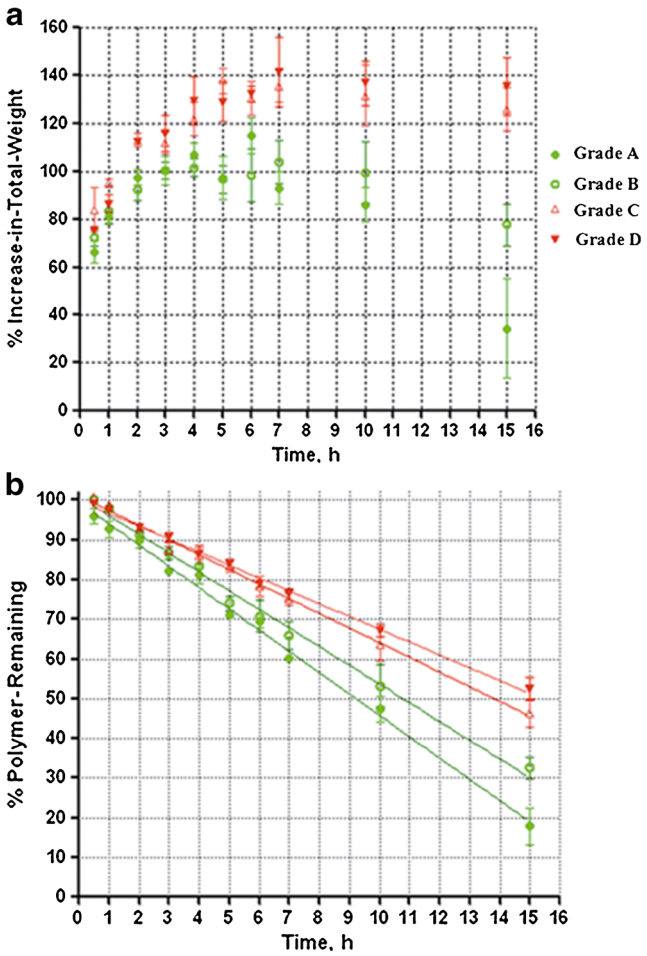

Fig. 2. Swelling and erosion behavior of sodium alginate matrix tablets: **a** the percentage of increase-in-total-weight; **b** percentage of polymer remaining. Data are shown as the mean and standard deviation of three replicates

For all four grades, the tablet weight continues to increase during the first 4 h as water penetrates into the matrix. Grades A and B show a drop in the % increase-in-total-weight from 7 to 15 h while the swollen tablet weight for grades C and D remains relatively constant over the duration of the experiment. Previous studies of the swelling behavior of sodium alginate matrix tablets showed similar water uptake profiles: water uptake increased at the beginning and remained approximately constant for high viscosity grades of sodium alginate but decreased for low viscosity grades at longer times (4,11).

The four grades of sodium alginate are comparable in their % increase-in-total-weight values in the first 4 h. Grades C and D have a similar % increase-in-total-weight profile over

Table II. Matrix Tablet Porosity and Tensile Strength for the Four Grades of Sodium Alginate

Sodium alginate	Matrix porosity[a]	Matrix tensile strength σ_T[a] (MPa)
Grade A	0.18±0.008	5.63±0.24
Grade B	0.19±0.007	5.26±0.36
Grade C	0.17±0.006	5.85±0.63
Grade D	0.17±0.003	5.13±0.25

[a] n=3

Table III. Slope and R^2 Values of the Linear Regression Fit for the Erosion Profile of the Four Grades of Sodium Alginate

Sodium alginate	Slope ± s.e.[a]	R^2
Grade A	−5.37±0.12	0.9873
Grade B	−4.71±−0.13	0.9805
Grade C	−3.70±0.09	0.9823
Grade D	−3.24±0.07	0.9881

[a] $n=3$

the whole time range investigated. Grades A and B demonstrate a significantly ($P<0.05$) smaller % increase-in-total-weight than grades C and D after 5 h. The % increase-in-total-weight of grade B is not significantly different from that of grade A during the first 10 h but becomes significantly higher than grade A by 15 h.

Grades C and D are not significantly different in their % polymer remaining in the time range investigated, while grades A and B show significantly faster erosion rate than grades C and D as reflected in their smaller values of % polymer remaining after 5 h. The % polymer remaining in grades A and B is very similar through 10 h, but the amount of grade A remaining becomes significantly lower than B in the 15 h samples. The significant differences observed among grades for water uptake behavior after 5 h could be related to the significant differences in erosion behavior.

The process of erosion or polymer dissolution under defined fluid dynamics conditions from a swollen polymer gel layer has been envisioned as polymer disentanglement from the polymer gel followed by polymer diffusion through the diffusion layer to the bulk solution (16,17). The polymer dissolution process can be described by the following equation (16,17):

$$m_p = m_0 - (k \cdot A \cdot C_d \cdot t), \tag{4}$$

where m_p is the remaining polymer weight at time t, m_0 is the dry tablet weight at $t=0$, k is a constant dependent on the average diffusion coefficient (D_{ave}) of the polymer in the diffusion layer, A is the surface area of the swelling tablet exposed to the dissolution medium, and C_d is the disentanglement or critical concentration at which polymer chains start to disentangle from the polymer gel under the influence of external shear. The C_d values correspond to polymer solutions with a certain threshold viscosity/viscoelasticity high enough to resist the external shear (17–19). Under the same shear conditions, the C_d values of the matrix tablets prepared from the various grades of sodium alginate are a function, in part, of the rheological properties of the polymer solutions and would be constant during the polymer erosion process (17). The erosion data of the four grades of sodium alginate as shown in Fig. 2 were fitted to Eq. 4 by linear regression; the slopes and R^2 values are listed in Table III. All four grades show good fit with $R^2>0.98$. Slopes, representing the polymer dissolution rate, differ among the four grades with the following rank order: grade A>grade B>grade C>grade D.

The differences in erosion behavior of the four grades of sodium alginate matrix tablets could be partly explained by their rheological behavior in solution. The erosion rate of sodium alginate matrix tablets is determined by the average diffusion coefficient (D_{ave}) and critical concentration (C_d). According to the Stokes-Einstein equation:

$$D = \frac{kT}{6\pi\eta r}, \tag{5}$$

where D is diffusion coefficient, k is Boltzmann's constant, T is absolute temperature, η is apparent viscosity, and r is radius of particle, the polymer diffusion coefficient is inversely

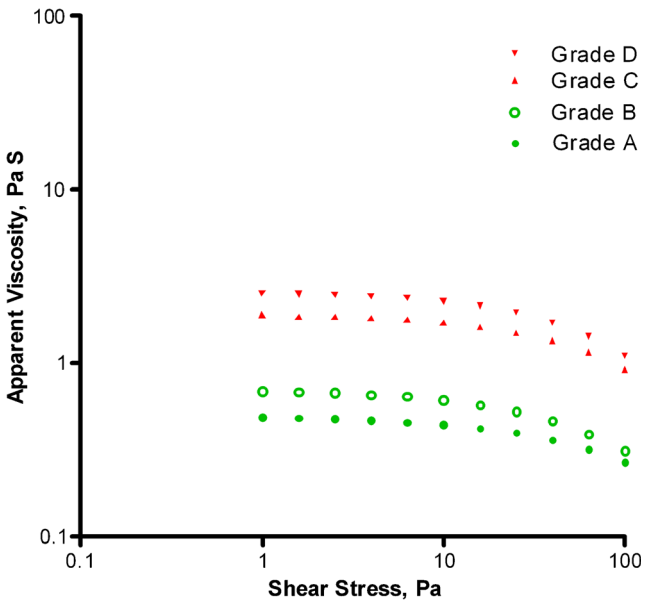

Fig. 3. Apparent viscosity of sodium alginate solutions (2% *w/w*) at 25°C

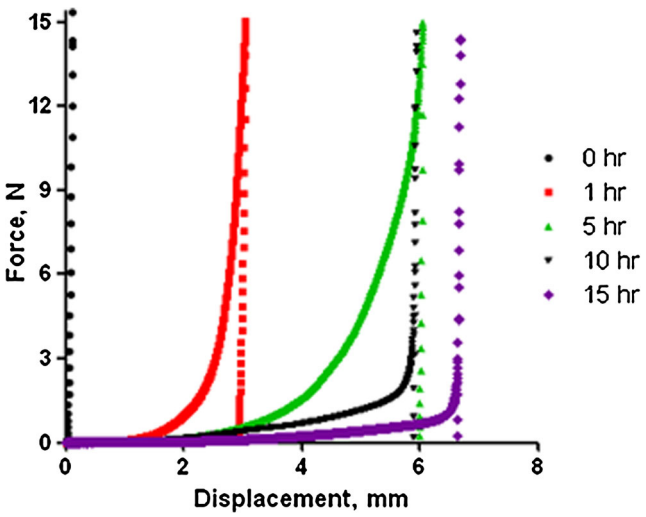

Fig. 4. A typical force-displacement profile for swelling sodium alginate matrix tablets

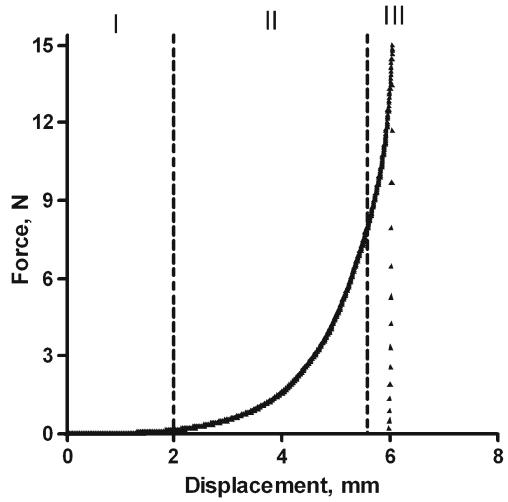

Fig. 5. A schematic illustration of different regions in the polymer matrix due to water penetration: *I* swollen gel layer; *II* hydrated but not swollen region; *III* dry core

proportional to the apparent viscosity of the polymer solutions in the diffusion layer. Previous study (13) revealed that grades A and B have critical concentrations (C_d=8%) similar to that for grade C (C_d=8%) but lower apparent viscosities in the diffusion layer (solutions with low sodium alginate concentrations, *e.g.*, 2%) than grade C (Fig. 3). It is very likely that the lower apparent viscosities of solutions of grades A and B in the diffusion layer lead to a larger D_{ave} of polymer in the diffusion layer and hence faster erosion rates for grades A and B.

Although grade D has a higher critical concentration (C_d=10%) than the other grades, it has higher apparent viscosities in the diffusion layer than the other grades (Fig. 3). It appears that the high apparent viscosities of grade D at low concentrations (*e.g.*, 2% *w*/*w*) substantially influence the erosion process, resulting in an erosion rate slower than that for the other grades. Therefore, the rheological properties of sodium alginate at both low and high concentrations could be important parameters for predicting the swelling and erosion behavior of sodium alginate in matrix tablets. Grades with higher apparent viscosities at low solution concentrations and higher viscoelasticity at high solution concentrations (lower C_d) tend to form matrix tablets with slower rates of erosion and higher rates of swelling.

Table IV. Porosity of APAP-Sodium Alginate Matrix Tablets Prepared from Four Different Grades

APAP-sodium alginate tablet	Porosity
Grade A	0.14±0.003
Grade B	0.15±0.004
Grade C	0.14±0.002
Grade D	0.15±0.005

Hydrated Polymer Layer Dynamics

A representative force-displacement profile for the swelling sodium alginate tablets at different time points is depicted in Fig. 4. Based on the force-displacement profile, a typical schematic illustrates the changing phases due to water penetration into the polymer matrix (Fig. 5). An overall increase in hydrated polymer layer thickness of sodium alginate tablets is observed with respect to swelling time. The hydrated polymer layer thickness as a function of swelling time for the four grades of sodium alginate is illustrated in Fig. 6. Although similar after 1 h, the hydrated layer thickness of grades C and D increase to a higher plateau than grades A and B by the 5 h time point. There is little if any change in thickness beyond 5 h.

The hydrated polymer layer thickness profile for sodium alginate tablets is similar to the water uptake profile as shown in Fig. 2. For the first 4 or 5 h, hydrated layer thickness increases with increasing water uptake into the matrix tablets. After 5 h, the hydrated layer thickness stays relatively constant for grades C and D while the weights of the hydrated tablets do not change. The hydrated layer thickness for grades

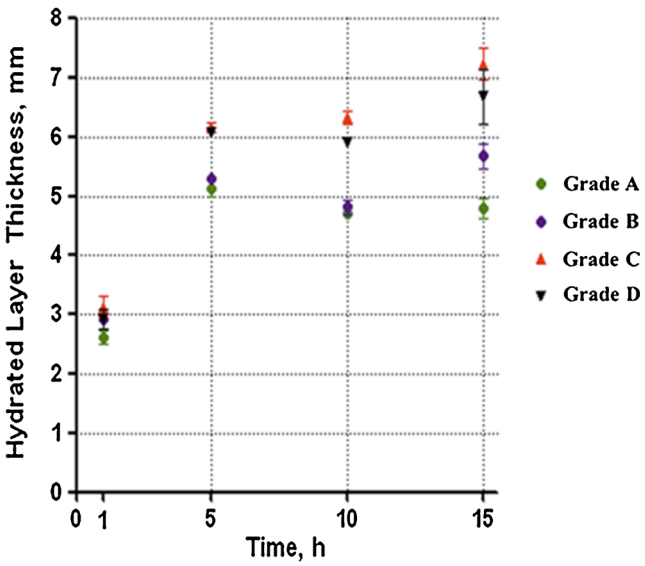

Fig. 6. Hydrated polymer layer thickness as a function of swelling time for matrix tablets of four grades of sodium alginate after exposed to water

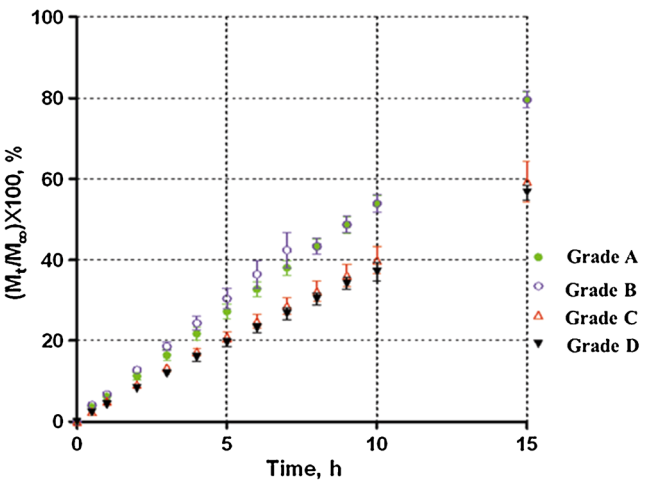

Fig. 7. Acetaminophen release profile from sodium alginate matrix tablets prepared from four different grades of sodium alginate

Table V. The Constant, k (Reported as Mean ± Standard Deviation, Based on Three Replicates), and Coefficient of Determination (R^2) of the Linear Regression Fitting of the Zero-Order Drug Release Data from Sodium Alginate (Four Grades) Matrix Tablets

Sodium alginate	k	R^2
Grade A	5.41±0.04	0.993
Grade B	5.65±0.08	0.973
Grade C	4.07±0.05	0.981
Grade D	3.80±0.03	0.990

C and D is larger than that of grades A and B, which is in accordance with the higher amount of water uptaken by tablets prepared from grades C to D. The thickness of the hydrated layer is expected to affect the rate of transport of drug molecules away from the tablet core.

Drug Release Studies

The porosity of acetaminophen (APAP)-sodium alginate matrix tablets prepared from four different alginate grades is listed in Table IV. Tablets from all four grades have similar porosities.

Release profile of APAP from sodium alginate matrix tablets is depicted in Fig. 7. The APAP release data from sodium alginate matrix tablets in this study can be adequately described by the zero-order equation,

$$\frac{M_t}{M_\infty} = kt, \tag{6}$$

with R^2>0.97 (the constants and R^2 are listed in Table V). Grades A and B are similar in their k values as are grades C and D. However, the k values of grades C and D are smaller than those of grades A and B.

The differences among the four grades in their drug release behavior could be partly explained by their solution rheological properties. Drug release from sodium alginate matrix tablets is expected to be influenced by both sodium alginate gel erosion rate and the viscosity of sodium alginate solutions in the diffusion layer. Grades C and D demonstrate much higher apparent viscosity values (greater than three times) than grades A and B at low concentrations from 1 to 3% *w*/*w*. Since grade C has similar viscoelasticity with grades A and B at high concentrations, it is very likely that the substantial differences in apparent viscosity at low concentrations contribute to the slower drug release from matrix tablets prepared from grade C than matrix tablets prepared from grades A to B. Although grade D shows slightly lower viscoelasticity than other grades at high concentrations, it has substantial higher apparent viscosity than grades A and B at low concentrations. This result suggests that the substantial differences in apparent viscosity at low concentrations could be the main factors determining sodium alginate's functionality in matrix tablets. On the other hand, despite the fact that grades A and B (or grades C and D) do exhibit significant differences in their apparent viscosities at lower concentration according to previous study (13), the absolute differences between these two grades in apparent viscosities are usually within 50%. This result indicates that grades with <50% difference in their apparent viscosities at low concentrations may not show any substantial differences in their performance in matrix tablets.

Additionally, sodium alginate matrix tablets prepared from grades C to D demonstrate a thicker hydrated polymer layer than those tablets prepared from grades A to B. A thicker polymer layer would decrease the amount of drug diffusing through the hydrated polymer layer per unit time.

Inter-Batch Variability

Porosity of the pure sodium alginate matrix tablets prepared from batches II to III is almost the same (0.16), while the porosity of batch I tablets is slightly higher (0.21) (Table VI). The water uptake and erosion behavior of matrix tablets prepared from the three batches of grade B is depicted in Fig. 8. All three batches show increasing water uptake during the first 4 h. The swelling matrix of batch I has a relative constant weight from 4 to 15 h, while batches II and III show a substantial drop in % increase-in-total-weight from 7 to 15 h. Batches I and II exhibit similar water uptake behavior in the first 5 h with % increase-in-total-weight slightly but not significantly higher than that of batch III. After 6 h, the differences in % increase-in-total-weight among the three batches become more substantial, with the batch rank order Batch I>II>III. Batch I is significantly (P<0.05) higher in % increase-in-total-weight than batches II and III after 10 h, while batch II becomes significantly (P<0.05) higher in % increase-in-total-weight than batch III at 15 h. This

Table VI. True Density, Matrix Tablet Porosity and Tensile Strength for the Three Batches of Sodium Alginate

Sodium alginate	Matrix tablet porosity[a]	Matrix tablet tensile strength[a] (MPa)
Batch I	0.21±0.001	5.26±0.23
Batch II	0.16±0.002	6.21±0.14
Batch III	0.16±0.008	4.63±0.46

[a] n=3

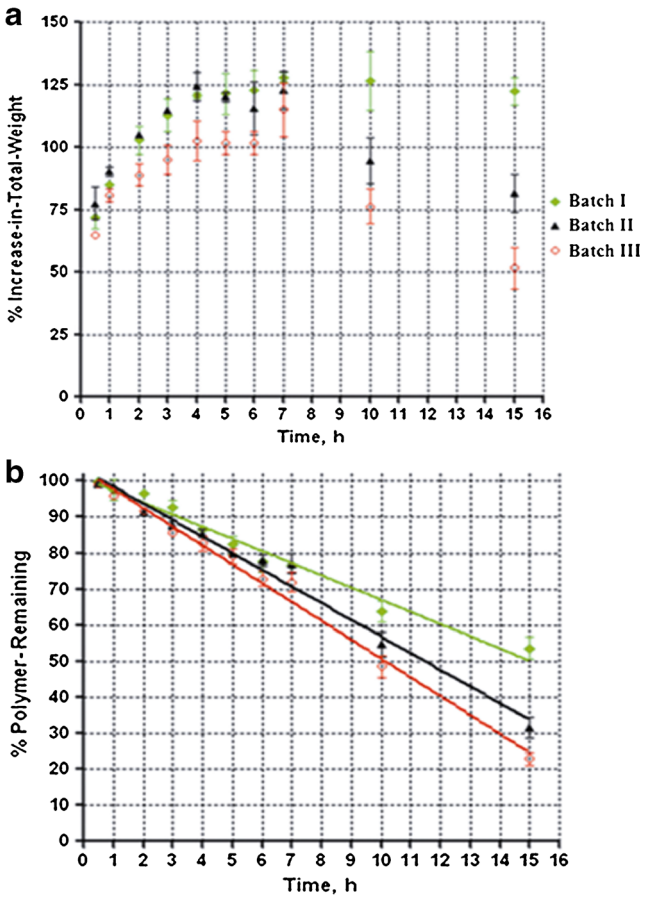

Fig. 8. The % increase-in-total-weight (**a**) and % polymer remaining (**b**) of three batches of one grade (LF120M) of sodium alginate matrix tablets in deionized water at 37°C. Data are shown as mean and standard deviation of three replicates

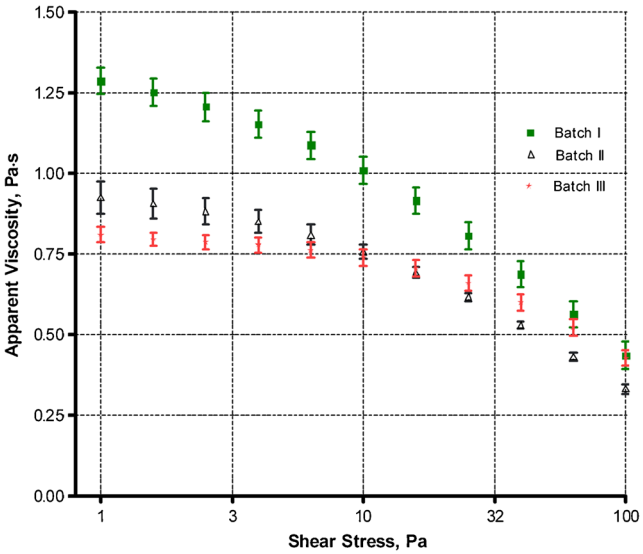

Fig. 9. Apparent viscosity of three batches of sodium alginate grade LF120M solutions at 2% *w/w* (13)

phenomenon reflects the differences in the erosion behavior of the three batches as shown in Fig. 8. All three batches show similar % polymer remaining at the first 7 h. After 10 h, the rank order of % polymer remaining for the three batches is as follows: batch I>II>III. The % polymer remaining as a function of time data for the three batches of sodium alginate (as shown in Fig. 8) were fitted to Eq. 4 by linear regression. The slopes and R^2 values are listed in Table VII. The rank order of the slopes of the equations for the three batches differ from one another with Batch III>Batch II>Batch I, indicating that Batch III gel layer has the fastest erosion rate among the three batches. Batches with slower polymer erosion/dissolution rate also show higher weight gain in deionized water.

The erosion behavior of these three batches of sodium alginate may be explained in part by their rheological properties in solution. Previous study (13) indicated that Batch I has significantly higher apparent viscosities (2% *w/w* solution, Fig. 9) and viscoelasticity (8% *w/w*, Fig. 10) than batches II and III. As a result, batch I exhibits slower erosion rate and higher extent of water uptake than batches II and III. Batch II is not significantly different from batch III in apparent viscosity at low concentration (2% *w/w*) but is significantly higher in viscoelasticity at high (8% *w/w*) concentrations than batch III. The higher viscoelasticity of batch II leads to a slower erosion rate than batch III. At 15 h, batch II shows significantly higher % increase-in-total-weight and % polymer remaining than batch III. Thus, those batches showing no significant differences in their apparent viscosities at low solution concentration could still differ in their swelling and erosion behavior due to their differences in viscoelasticity.

The overall hydrated polymer layer thickness as a function of time for sodium alginate matrix tablets prepared from three batches was plotted in Fig. 11. The hydrated polymer layer increased at the beginning and kept almost constant after 5 h. Among the three batches, batch I has the largest hydrated layer thickness after 5 h. Batch II has similar thickness to batch I at 5 and 10 h, but smaller thickness at 15 h. Batch III has the smallest thickness after 5 h. The hydrated polymer profile could be explained by the swelling and erosion behavior of these three batches. Batches with higher water uptake and slower erosion rate would show thicker hydrated layer thickness. However, the differences among the batches in hydrated layer thickness are not as pronounce as in water uptake profile.

Table VII. Slope and R^2 Values of the Linear Regression Fit for the Erosion Profile of the Three Batches of Sodium Alginate

Sodium alginate	Slope ± s.e.[a]	R^2
Batch I	−3.38±0.12	0.9640
Batch II	−4.62±0.13	0.9771
Batch III	−5.23±0.12	0.9846

[a] $n=3$

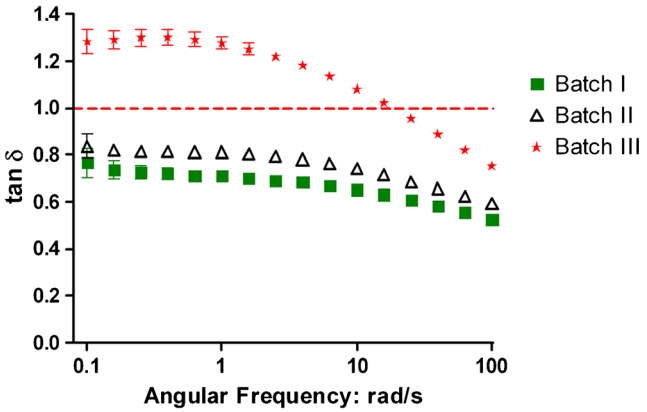

Fig. 10. Viscoelasticity of three batches of sodium alginate grade LF120M solutions at 8% *w/w* (tan $\delta = G''/G'$: tan $\delta > 1$, liquid state; tan $\delta \leq 1$: gel state) (13)

The porosity of APAP-sodium alginate matrix tablets prepared from three batches is almost the same, varying from 0.15 to 0.16. The APAP release profile from sodium alginate matrix tablets prepared from three batches is shown in Fig. 12.

ANOVA test shows that batches I and II are not significantly different in their drug release profile ($P > 0.05$ at each time point). Batch III has higher percentage of drug released at each time point than batches I and II after 1 h ($P < 0.01$).

APAP release from sodium alginate matrix tablets prepared from three batches is adequately described by Eq. 6 with $R^2 > 0.992$ (Table VIII).

The k values of batches I and II are almost the same, while the k value of batch III is higher than those of batches I and II. It is not surprising that tablets prepared from batch III shows the fastest drug release since matrix tablets of batch III has the highest erosion rate in water among the three batches. Although batch I matrix shows slower erosion than batch II matrix, the drug release profiles are the same between the two batches. The differences in apparent viscosity among the three batches are less than 50% (Fig. 9), while the viscoelasticity of batch II in solution is between batch III and batch I, and is closer to batch I than to batch III (Fig. 10) (13). The results suggest that, for multiple batches within a relatively narrow range of apparent viscosity, viscoelasticity of sodium alginate solutions could be more indicative than the apparent viscosity of drug release behavior from sodium alginate-based matrix tablets. An abstract submitted to Society of Rheology also demonstrated that the viscoelastic properties of hypromellose gels are correlated with the dissolution profile from hypromellose matrix tablets prepared from multiple lots of hypromellose with similar viscosity and chemical substitution (20).

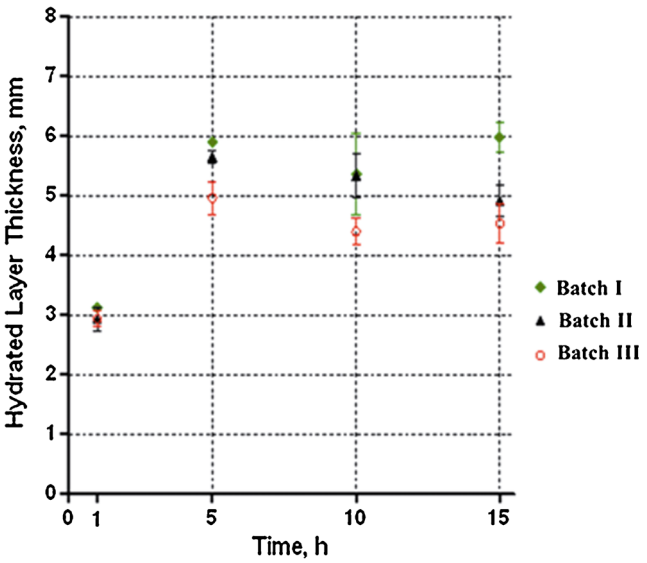

Fig. 11. Hydrated polymer layer thickness as a function of time for sodium alginate matrix tablets of three batches of grade B during swelling

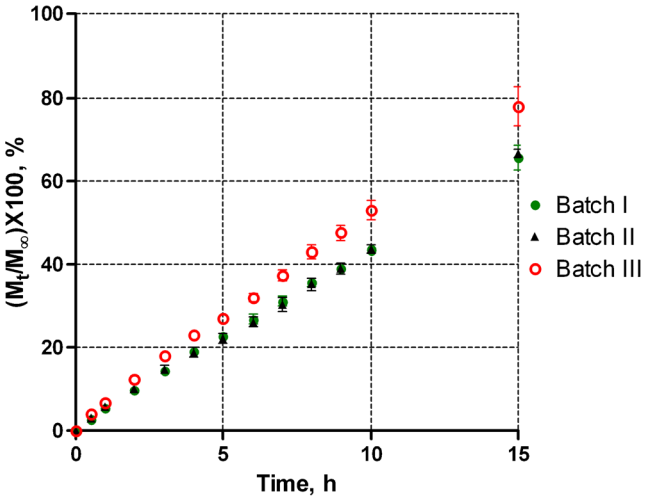

Fig. 12. The APAP release profile from sodium alginate matrix tablets prepared from three batches

CONCLUSION

Significant differences in swelling and erosion behavior of sodium alginate matrix tablets were evident among different viscosity grades of sodium alginate. Even different batches of the same grade of sodium alginate exhibit significant differences in the swelling and erosion behavior of their matrix tablets. The differences in swelling behavior observed among matrix tablets prepared from different sodium alginate grades may be attributed to their significant differences in erosion behavior, which can be partly explained by sodium alginate rheological properties (both apparent viscosity and viscoelasticity) in solution. Sodium alginate with higher apparent viscosity and viscoelasticity in solution show slower erosion rate and higher swelling

Table VIII. The Constant, k (Reported as Mean ± Standard Deviation Based on Three Replicates) and R^2 Values of the Zero-Order Fitting of Drug Release Data from Sodium Alginate Matrix Tablets Prepared from Three Batches

Sodium alginate	k	R^2
Batch I	4.41±0.03	0.996
Batch II	4.41±0.03	0.995
Batch III	5.30±0.04	0.992

rate. Compacts prepared from grades or batches with higher viscosity and higher viscoelasticity show slower drug release. For grades or batches with similar apparent viscosities, apparent viscosities of sodium alginate solution at low concentration alone are not sufficient to predict the functionality of sodium alginate in matrix tablets. Viscoelastic properties of sodium alginate solutions at a high concentration corresponding to the polymer gel state are suitable indicia of the controlled release behavior of these matrix tablets.

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