Drug Development and Industrial Pharmacy, 2010; 36(4): 371–378

informa
healthcare

ORIGINAL ARTICLE

Water uptake by substituted amylose tablets: experimentation and numerical simulation

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Abstract

Background: Substituted amylose (SA) has been developed as excipient for direct compression matrices in the formulation of sustained release solid dosage forms. *Method*: The gel performance of SA for controlling water diffusion was studied by measuring water content in SA tablets prepared by direct compression. *Results*: The SA gel was not freely swelling and results indicate that water content in equilibrium state was dependent on tablet size but not on compression force. The presence of electrolyte and hydrophobic lubricant played an effective role in adjusting water diffusion in SA gel. In addition, a numerical model based on finite difference method was developed that exhibits a high goodness of fit to experimental result. The output of the model was not only the macroscopic water content value but also the water distribution within SA tablets.

Key words: *Hydrogel; numerical simulation; substituted amylose; swelling; water uptake; tablet*

Introduction

Hydrogel, because of the swollen network of hydrophilic polymer[1], has played a crucial role in the development of controlled release drug delivery systems[2]. The most common mechanism of drug release from hydrogels is diffusion driven by the concentration gradient of drugs[3]. The physicochemical properties of hydrogel are therefore critical factors determining the drug-release profile from such systems.

A dry hydrophilic polymer is generally in the glassy state with a glass transition temperature (T_g) greatly higher than the temperature of the media. A system in such an unstable state will spontaneously absorb a large quantity of water from the surrounding media in order to reach an equilibrium state. During this process, the increase in system entropy and volume occurs and leads to an elongated configuration of polymer chains between network junctions. On the other hand, an inverse force develops in opposition to the swelling process. In equilibrium state, these two forces must be in balance[4]. Hence, their correlation determines the swelling degree of a polymer system. For example, a low-viscosity grade hydroxypropyl methyl cellulose can almost freely swell but a cross-linked amylose is partially swellable[5].

However, analysis of solute diffusion because of internal system stresses is not currently available because of a lack of sufficient knowledge on polymer microstructures. Instead, some models, most of which have been summarized in the literature, have been proposed to solve certain types of problems in the pharmaceutical field[6–8]. Nevertheless, application of published models is usually associated with some limitations, for example, validity has been demonstrated for only one specific polymer[9,10] or some special diffusion cases[11,12].

The solute diffusion in a polymer matrix obeys Fick's law for nonsteady state. For a solid cylinder as the normal tablet form (Figure 1), the mathematical form of this law is the following, as described by[6]

$$\frac{\partial C}{\partial t} = \frac{1}{r}\left[\frac{\partial}{\partial r}\left(rD\frac{\partial C}{\partial r}\right) + \frac{\partial}{\partial \theta}\left(\frac{D}{r}\frac{\partial C}{\partial \theta}\right) + \frac{\partial}{\partial z}\left(rD\frac{\partial C}{\partial z}\right)\right] \quad (1)$$

where C denotes solute concentration; t denotes time; r, z, and θ are related parameters of cylindrical coordinate system; and D is the diffusion coefficient.

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(Received 26 Feb 2009; accepted 9 Jul 2009)

ISSN 0363-9045 print/ISSN 1520-5762 online © Informa UK, Ltd.
DOI: 10.3109/03639040903173556

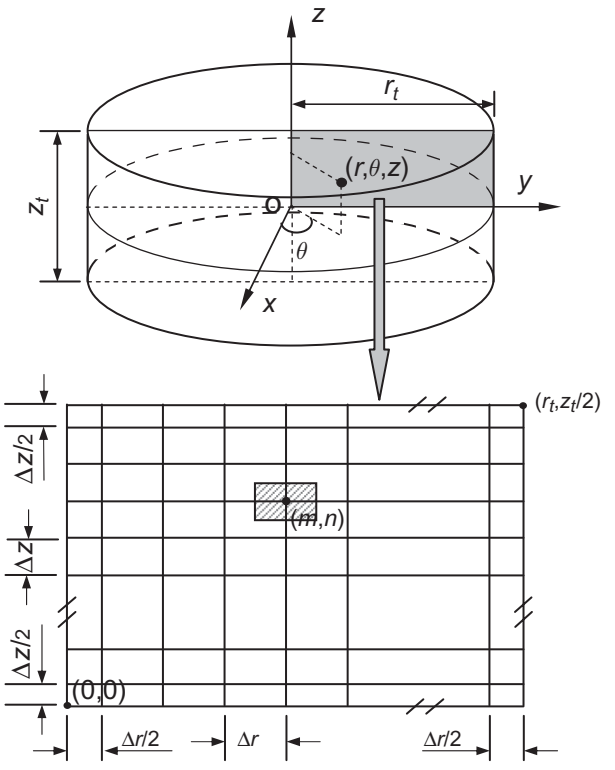

Figure 1. Schematic representation of tablet structure and grids dividing for finite difference treatment.

If there is no concentration gradient between angles θ, Equation (1) will be transformed into

$$\frac{\partial C}{\partial t} = \frac{\partial}{\partial r}\left(D\frac{\partial C}{\partial r}\right) + \frac{D}{r}\frac{\partial C}{\partial r} + \frac{\partial}{\partial z}\left(D\frac{\partial C}{\partial z}\right) \qquad (2)$$

According to Stokes–Einstein's law[13], the solute diffusibility is system viscosity dependent and is therefore polymer concentration dependent. As a result, the diffusion coefficient D is the critical term for resolving the partial differential equations (PDEs), Equations (1) and (2). However, Stokes–Einstein's law is not available for most of polymer systems. On the contrary, the free volume theory is effective and widely accepted. The model proposed by Fujita[14] based on this theory is often cited[10,15] but is not universally suitable for aqueous systems. Masaro et al.[16] have fitted three models, proposed by Yasuda[17], Phillies[18], and Petit[19], to self-diffusion coefficients of water and poly(ethylene glycol) in aqueous polymer systems. Their results have demonstrated that these models can be used for evaluating the diffusion capacity of solute in aqueous systems, but the equation proposed by Phillies provided good fits to the diffusion data over the whole range of polymer concentrations, for all the diffusants and matrix polymers tested. Moreover, this model has a quite concise form as shown below:

$$D = D_0 \exp(-\alpha C_{\mathrm{p}}^{\upsilon}) \qquad (3)$$

where D denotes solute self-diffusion coefficient in polymer-solvent mixture; D_0 is solute self-diffusion coefficient in the same solvent but in the absence of polymer; C_{p} is polymer concentration; α and υ are constant physical parameters for a defined polymer-solvent system, in which υ equals to 0.5 and 1 for macro and small molecules, respectively.

The polymer used in this work is an ether of amylose, prepared in a one-step reaction in a basic medium with suitable substituent(s) such as glycidol (1,2-epoxypropanol), leading to substituted amylose (SA), SA,G–*n*, where SA stands for SA, G for glycidol, and *n* the degree of substitution (DS) expressed as mole of substituent per kilogram of amylose.

Previous works have shown that SA,G polymers have remarkable compressibility, gel physicochemical properties, and drug-release controlling potential[20–22]. Drug-release profile from SA,G matrices was characterized as including three regions. The first region presents high release rates, typical of a so-called burst effect because of drug dissolution on the tablet surface. Furthermore, in the very early stage, as no gel layer is yet formed, the drug in this external layer dissolves without any interference from the polymer. The second region is not representative of a hydrophilic matrix system as it exhibits a quasi-constant-release rate, whereas the third region is associated with a first-order-like decline of the release rate. These two regions are more typical of a reservoir system, obtained after coating a tablet with an insoluble polymer-controlling drug diffusion. In that case, driven by a drug concentration gradient, the drug is constantly released through a membrane[23].

The aim of this work was to study the water diffusion kinetics within SA,G tablets using both experimentation and numerical simulation methods to better understand the polymer performance in controlling drug release as water penetration and drug release are two related processes occurring in opposite direction.

Materials and methods

Materials

Hylon VII, high amylose cornstarch that contains 70% of amylose chains and 30% of amylopectin, was obtained from the National Starch and Chemical Company

(Bridgewater, NJ, USA) and glycidol from Sigma Chemical Company (St. Louis, MO, USA). Potassium chloride and magnesium stearate were from Laboratoires Denis Giroux Inc. (Saint-Hyacinthe, QC, Canada) and sodium chloride (crystals, lab-grade) from Anachemia Ltd. (Montreal, QC, Canada).

Substituted amylose synthesis

First, 300 g of Hylon VII was added to 1.8 L of 1 N NaOH at 50°C; then, the system was homogenized for 15 minutes in a Hobart planetary mixer at its slowest speed. To obtain SA,G-2.7, 50 mL of glycidol was added gradually and mixing continued for another 15 minutes at the same speed. The well-mixed mass was then neutralized as follows: First, 1.5 L of distilled water (heated to 50°C) was added, followed by the addition of the necessary volume of acetic anhydride to obtain a pH of 7.0, and homogenization was continued for another 5 minutes at the same speed. The resulting gel was filtered through a Büchner funnel and washed with water and acetone. The powder product was air-dried overnight at ambient temperature.

Preparation of tablets

SA,G-2.7 tablets were prepared by direct compression, that is, dry mixing of drug and excipient(s) followed by compression. The SA,G-2.7 and other excipients, if any, were mixed manually in a mortar and compressed on an IR 30-ton press (C-30 Research & Industrial Instruments Company, London, UK) with a dwell time of 30 seconds (flat-faced punch die set). The diameter of all the tablets was 1.28 cm.

To evaluate the influence of compression force (CF) and tablet weight on the water uptake, tablets weighing from 50 to 1000 mg were compressed at various CFs ranging from 1.5 to 5.0 tons/cm^2 pressure.

Tablets containing 0.2% of magnesium stearate and 99.8% of SA,G-2.7 and the polymer content ranging from 50 to 1000 mg were prepared at CF 2.5 tons/cm^2 to evaluate the combined effect of the presence of hydrophobic lubricant on water uptake. Similar test with 5%, 10%, and 15% of sodium chloride was made for the same goal but with addition of electrolytes.

Polymer-swelling study

The swelling behavior of the polymer was characterized by measuring gravimetrically the water uptake of matrix tablets (n = 3). SA tablets were suspended in a phosphate buffer solution, pH 7.4, at 37°C, in a dissolution tester equipped with a rotating paddle (50 rpm) on a metal mesh in such a way that swelling could occur three-dimensionally with water penetrating all sides of the tablets. After 24 hours of immersion, each tablet was removed from the aqueous medium with forceps, briefly patted with lint-free cleaning tissues to remove the solution wetting its surface, and weighed. The measurements were made in triplicate.

Numerical simulation

Currently, there is no suitable mathematical function for the treatment of solute diffusibility gradient within a polymer-solvent system. It is therefore difficult to find analytical solution(s) of Equation (2). However, the numerical analysis method, such as finite difference (FD), is capable of offering approximate solution with varying precision.

With FD method, the considered object is divided into grids limited in number. Continuous derivatives in a PDE are replaced by the ratio of the differences at each junction point, in order to approach its real solution[24]. As shown in Figure 1, the mathematical treatment can be made at only one-fourth of vertical section crossing the center of the tablet because of the symmetry of the cylindrical tablet structure. With FD method, the object will be divided into numerous small elements in a length of Δr in the radial direction and Δz in axial direction. A $(r_t/\Delta r)$ by $(z_t/2/\Delta z)$ matrix is hence obtained (Δr and Δz are radial and axial step lengths; r_t and z_t denote the radius and the thickness of tablet, respectively). A random junction point (m, n) is the representative of a rectangular element taking the junction point as its center and having a surface area $\Delta r \times \Delta z$. For this reason, side lengths of the peripheral grids have been set as one-half of Δr and Δz for the purpose of minimizing calculation errors[25].

In dry state, water concentration C_w being equal to 0 within the entire tablet, the initial condition is therefore as follows:

$$t = 0 \quad C_w = 0 \quad 0 \le r_t \le r_t \quad 0 \le z \le z_t$$

We suppose that as soon as the water enters into contact with the media, water concentration at the tablet surface will immediately be equal to that in equilibrium state C_{weq}. Consequently, we have the following boundary conditions:

$$t > 0 \quad C_w = C_{weq} \quad 0 \le r \le r_t \quad z = \frac{z_t}{2};$$

$$t > 0 \quad C_w = C_{weq} \quad 0 \le z \le \frac{z_t}{2} \quad r = r_t.$$

In the experimental section, the methods for determining C_{weq} and tablet swelling, that is, Δr and Δz at

each time step have been explored. As a result, water concentration at each junction point and each time step can be calculated with Equations (2) and (3).

Because of the rather large tablet size (r = 12.8 mm) and the long diffusion period (more than 20 hours for tablets heavier than 400 mg), an acceptable precision has been presented when the step lengths of space and time (Δr, Δz, and Δt) have been set as 0.2 mm, 0.06 mm, and 0.1 second, respectively.

In this work, a program based on mathematical tool Matlab® V.6 (The MathWorks Inc., Natick, MA, USA) was developed for the numerical model mentioned above. By compiling the Matlab functions (.m files) into executable (.exe) files, a reasonably high operating speed has been obtained.

Results and discussion

Water uptake by pure SA tablets: effect of compression force and tablet size

Figure 2 shows the combined effect of CF and tablet size on water uptake by pure SA,G-2.7 tablets. Clearly, water content in equilibrium state decreases in function of tablet size. The polymer swelling is a process in which the internal system stresses are seeking equilibrium. In a swollen matrix, polymers behave as 'bridges' by cross-linking and form a network. But most of the polymers are visco-elastic materials[26], and pure plastic deformation is rarely observed during matrix swelling. Thus, in such a matrix, an increase in the amount of polymer leads to more numerous and firmer 'bridges' and hence to an increase of the force opposing polymer chain extension. Consequently, a decrease of the permeated water ratio occurs, except for some special polymer gels with weak strength as low-viscosity grade hydroxypropyl methyl cellulose.

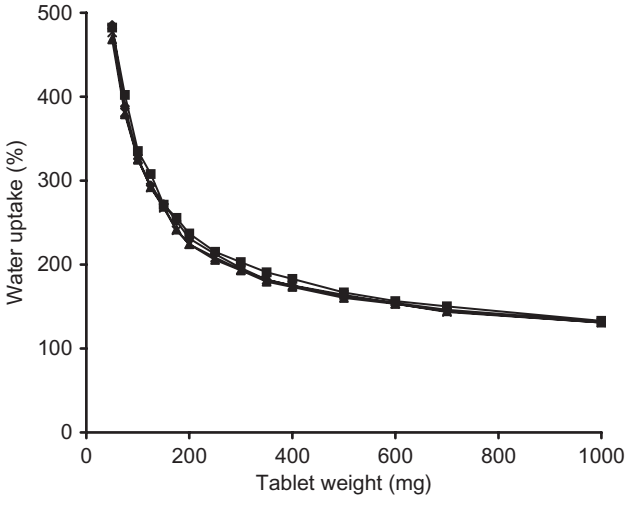

Figure 2. Effect of tablet size and compression force (CF) on water uptake of SA tablets in equilibrium state (◆, CF = 1.5 tons/cm^2; ■, CF = 2.5 tons/cm^2; ▲, CF = 3.5 tons/cm^2; ×, CF = 5.0 tons/cm^2). Arithmetic means (n = 3) are shown (RSD less than 5%).

Water absorption and swelling of SA,G-2.7 tablets decrease asymptotically in function of tablet weight. The polymer has therefore good characteristics to form a rigid gel, which implies good control over the release of the active ingredient in tablets having the required thicknesses.

On the other hand, the CFs ranging from 1.5 to 5.0 tons/cm^2 did not have significant effect on water uptake. In another part of our work, the same CF range did not cause tablet size variation either[23]. Evidently, SA,G-2.7 has a good compressibility as tablets prepared at such CFs have an identical structure. The porosity and polymer chain elongation in these tablets are similar. There is, therefore, no additional free volume introduced into the system.

Consequently, a low CF as 1.5 tons/cm^2 can seemingly be employed in tablets manufactured with SA,G-2.7, in order to increase the production capacity and to reduce the cost. Moreover, slight variations in CFs, regularly encountered during tabletting, will not affect the mechanical properties or the swelling and release characteristics of the tablets[22].

Effect of the presence of electrolytes and hydrophobic lubricant on water uptake

The study of water absorption of a polymer in the presence of electrolytes is essential to evaluate its performance for pharmaceutical applications. The effects of electrolytes and hydrophobic lubricant on water uptake are presented in Figures 3 and 4, respectively. Water absorption of SA,G-2.7 tablets can slightly increase after addition of electrolytes. Moreover, as much as 15% of sodium chloride will not cause significant erosion of the gel, confirming the stability and rigidity of the gel.

The addition of electrolytes leads to a more complex system because of the two diffusion processes that are in opposite directions[27]. The increase in water content is seemingly because of the following factors: First, NaCl molecules occupy a certain volume and water will fill the cavities left by released electrolytes. Such excipient is often referred to as a channeling agent. Second, NaCl molecules separate polymer chains and the latter will be more difficult to be physically cross-linked. The polymer gel will exhibit a weaker structure. Third, the presence of electrolytes can decrease the contact angle between liquid and polymer particles. Finally, the increase in the osmotic pressure of the electrolyte solution may cause additional gel swelling.

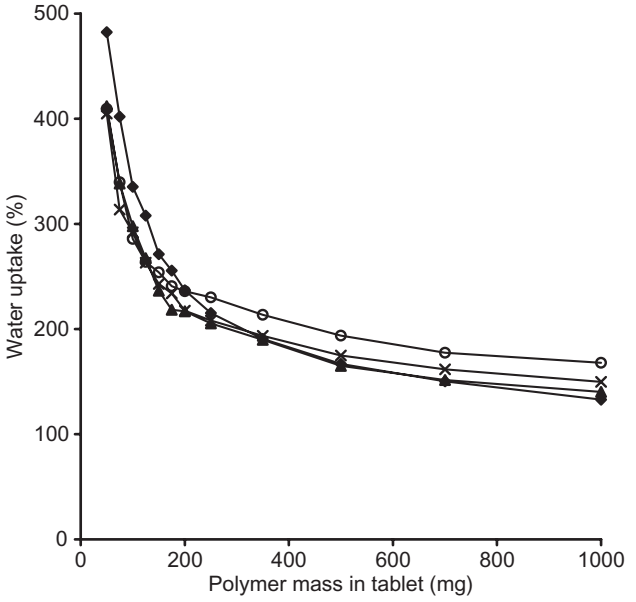

Figure 3. Effect of the presence of electrolyte on water uptake of SA tablets (◆, pure SA; ▲, SA with 5% of NaCl; ×, SA with 10% of NaCl; ❍, SA with 15% of NaCl). Arithmetic means (n = 3) are shown (RSD less than 4%).

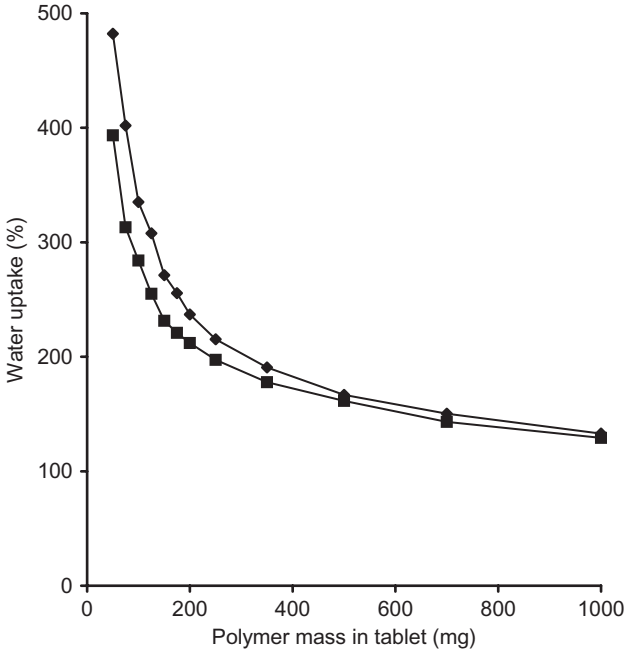

Figure 4. Effect of the presence of hydrophobic lubricant on water uptake of SA tablets (◆, pure SA; ■, SA with 0.2% of magnesium stearate). Arithmetic means (n = 3) are shown (RSD less than 4%).

In summary, the presence of electrolytes can affect the continuity and the homogeneity of the matrix structure and as a result cause a weakness in the gel because of a decrease in the degree of physical cross-linking. The consequence is an increase in the drug-release rate.

As for hydrophobic lubricant like magnesium stearate, a content of 0.2% is not enough to elicit a significant change in tablet structure. The decrease in water uptake is mainly because of the increase in the contact angle between liquid and polymer particles. In tablets including some other polymers, by improving CF distribution and a more homogeneous porosity as well as by decreasing the extent of stress relaxation, the lubricant can decrease the porosity and therefore water diffusibility[28]. This effect is, however, not observed with SA,G-2.7.

Numerical model: water content and water distribution

As shown in Figure 5, by transforming the curve of tablets prepared at CF 2.5 tons/cm^2 into logarithmic coordinate system, two straight lines crossing at 175 mg were obtained. Considering the fewer applications of controlled release formulations including a polymer amount below 175 mg, as well as the greater risk of errors in measurement for smaller tablets (as it is more difficult to remove water at their surface), the following equation is proposed to estimate water content in equilibrium state:

$$\frac{W_w}{W_p} = \frac{m}{W_p{}^n} \tag{4}$$

where W_w denotes water weight in equilibrium state (mg); W_p is polymer weight (mg); m and n are the slopes of the straight lines and are equal to 14.5 and 0.35, respectively, for pure SA,G-2.7.

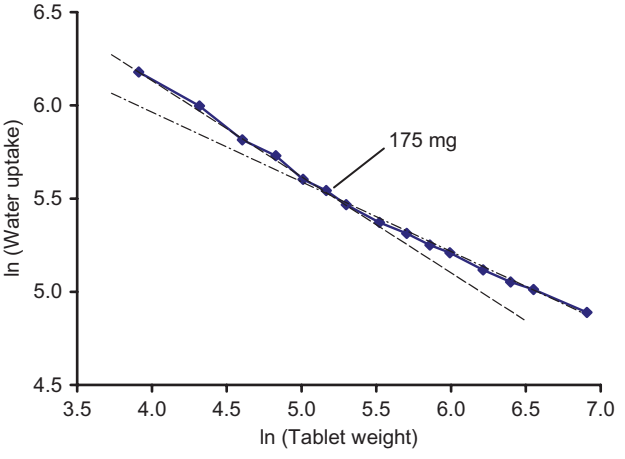

Figure 5. Logarithmic representation of water uptake curve (◆, experimental result; dash line, fitting curve for the tablets lighter than 175 mg; dot and dash line, fitting curve for the tablets heavier than 175 mg, r^2 = 0.999).

The tablet volumes in equilibrium state V_{eq} have been also measured in this work and obeyed approximately the following equation:

$$V_{eq} = V_0 \exp\left(k_\nu \frac{W_w}{W_p}\right) \quad (5)$$

where V_0 denotes initial tablet volume and the constant k_ν equals to 0.67 for pure SA,G-2.7.

Many polymers are not freely swellable and there should be swollen limits for both diameter and thickness[29]. In this work, a maximum diameter for all tablets has been observed and was equal to 17 mm. If we assume that the polymer-swelling degree is proportional to water concentration, the following equations can be employed to calculate Δr and Δz at each time step:

$$V_t = V_0 + \frac{C}{C_{eq}}(V_{eq} - V_0) \quad (6)$$

$$r_t = r_0 + (r_{max} - r_0)\left(\frac{C}{C_{eq}}\right)^{\frac{1}{3}} \quad (7)$$

where V_t and r_t denote tablet volume and radius, respectively, at time t; r_0 and r_{max} are initial and maximum tablet radii (6.4 and 8.5 mm in this work); C is water concentration at same time t; and C_{eq} is that in equilibrium state.

As a result, water concentration at each intersection point shown in Figure 1 can be calculated at a given time with Equations (2)–(7).

Figure 6 shows a comparison between calculated and experimental results on water content, in pure SA,G-2.7 400-mg tablets, in function of operating time. The corresponding values are listed in Table 1. Hence, our numerical model can be used for simulating water diffusion kinetics with a relatively high goodness of fit (determination coefficient r^2 = 0.998). In this case, the following parameters of Equation (3) were determined: $D_0 = 2.06 \times 10^{-5}$ cm^2/s, $\alpha = 5.9$, and $\upsilon = 1$.

Figure 7 presents the water distribution profiles within tablets at 1, 5, and 12 hours. This can be employed for analyzing drug-release process because solute diffusibility is polymer concentration dependent.

Our work confirms previous results obtained by our team where diffusion was shown to be the main mechanism in controlling drug release from SA,G-2.7 matrices. The gel of this polymer is firm enough to oppose osmotic pressure and offers high performance in controlling drug release, even at drug loading as high as 40% (acetaminophen) or for tablet weight as low as 75 mg. In the case of high drug loading (i.e., 50% acetaminophen), gel erosion is slightly observed, but the polymer still maintains its performance in controlling drug release. In that case, the SA,G matrices show a typical drug-release profile observed in many polymeric system, that is, the drug release is controlled by both dissolution and diffusion[30].

Furthermore, it has been shown that dry coated tablets containing 300 mg of SA,G-2.7 show a quasi-linear drug release for more than 30 hours and that drug-release rate can be increased by augmenting porosity of the polymer shell with the addition of electrolytes[20,21,23,30,31].

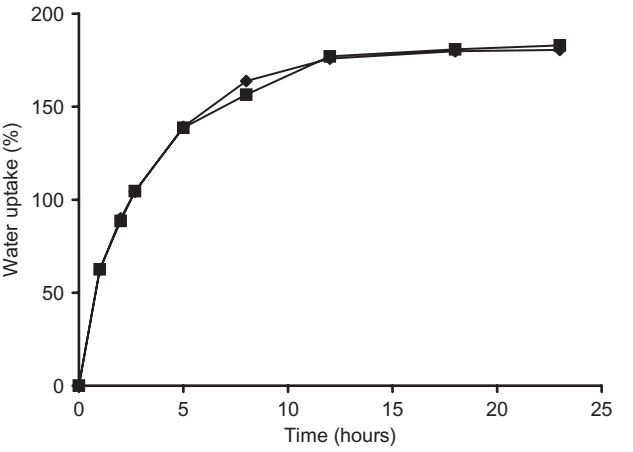

Figure 6. Water uptake result fitting with numerical model (◆, experimental result; ■, calculated result with numerical model, r^2 = 0.998).

Table 1. Water uptake by pure SA tablets (400 mg).

	Water uptake (%)	
Time (hours)	Experimental	Calculated
0.00	0.00	0.00
1.00	62.30	62.50
2.00	89.90	88.60
2.68	104.30	104.60
5.00	139.10	138.70
8.00	163.80	156.50
12.00	175.90	177.10
18.00	179.90	180.90
23.00	180.50	183.00

Conclusion

SA,G-2.7 polymer has a high compactibility. The polymer achieves a nearly absolute plastic deformation even at CF as low as 1.5 tons/cm^2. The hydrogel of this polymer

presents a high strength for controlling matrix swelling and water penetration, which increases in function of the amount of polymer. Tablet CFs ranging from 1.5 to 5.0 tons/cm^2 have no significant effect on SA gel swelling.

The water uptake by mass unit of SA,G-2.7 decreases in function of tablet mass. Hence, the gel of this polymer does not freely swell and exerts a high resistance to water penetration. However, the SA gel performance in controlling solute diffusion can be adjusted by the presence of electrolytes or hydrophobic additives. Moreover, the numerical method can be used for simulating water diffusion process in SA gel and offers some information as to water distribution, which cannot be easily determined by experimental method. The physicochemical properties of SA,G-2.7 indicate a good potential of this polymer as tablet excipient for controlled drug-release applications.

Declaration of interest

The authors report no conflicts of interest. The authors alone are responsible for the content and writing of this paper.

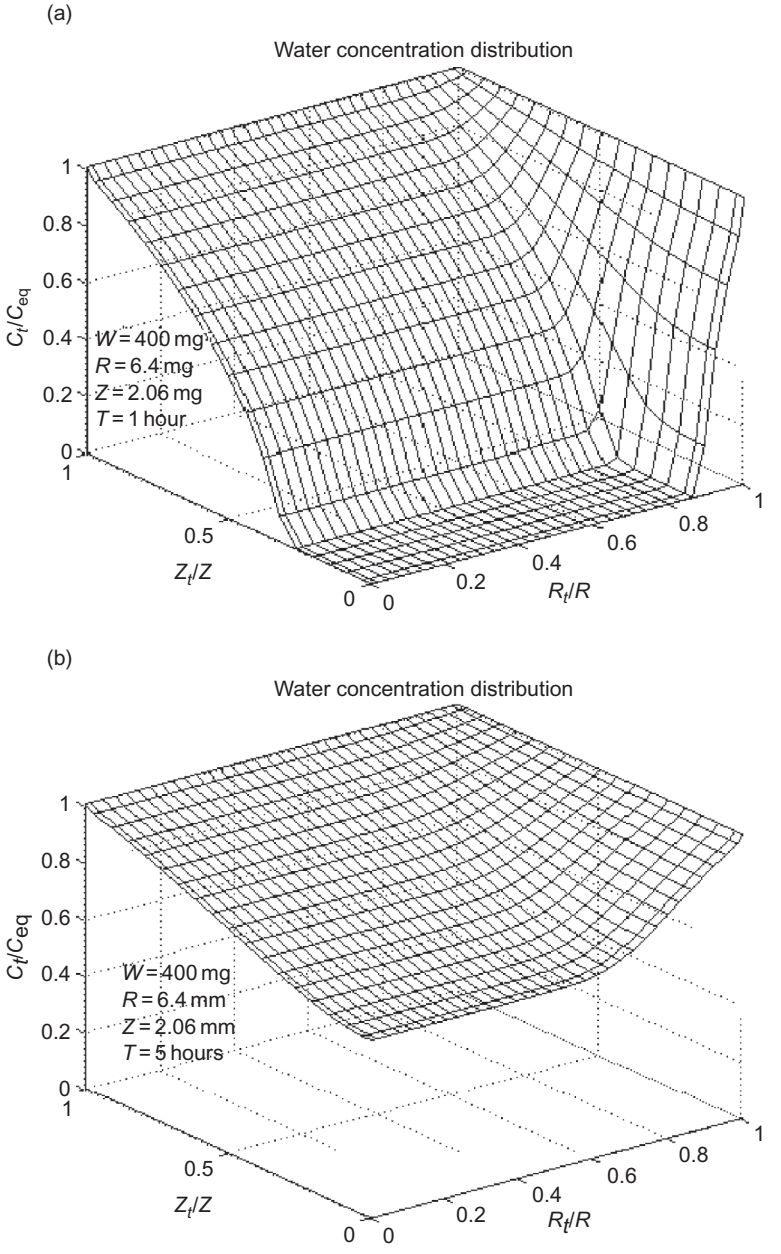

Figure 7. Numerical simulation of water distribution within SA tablets. (a) 1 hour, (b) 5 hours, and (c) 12 hours.

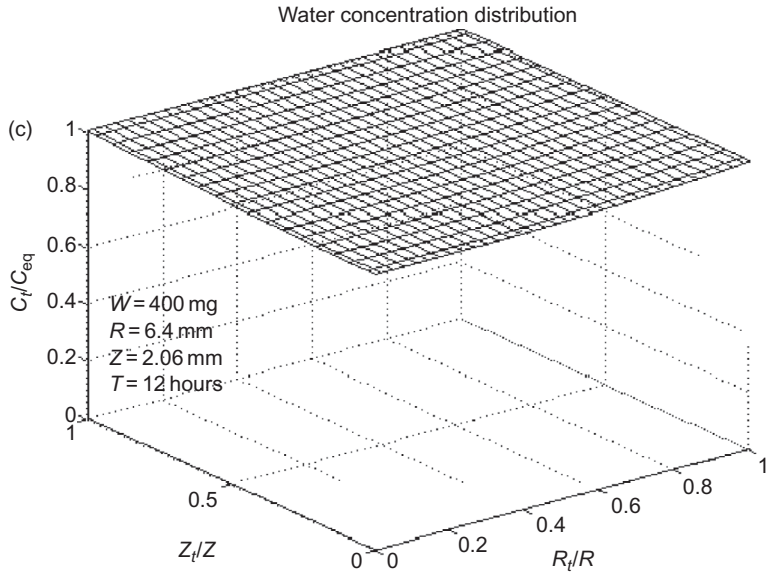

Figure 7. (*Continued*).

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