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A Sustained Release of Model Drug from a Novel Polyacrylic Acid-polyaluminium Chloride Superabsorbent

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ABSTRACT

A new kind of drug loaded superabsorbent polymer was prepared and the properties of drug delivery performance are reported in the current study. The superabsorbent polymer was prepared via a process in which polyacrylic acid (PAA) was cross-linked via complex formation with polyaluminium chloride (PAC) through $AlCl_3$ hydrolysis under alkaline conditions followed by freeze drying. The drugs were loaded into the network structure of the superabsorbent during the complex formation of cross-linking process. The new drug loaded superabsorbents were prepared aiming to overcome the drawbacks of those prepared via conventional method. The loading as well as the sustained release of the model drug acetaminophen (AMP) using the prepared superabsorbent has been studied by UV-absorption spectroscopy, and compared with superabsorbent prepared via conventional free radical polymeri-zation method. It was found that the AMP loaded before complex formation of cross-linking process and showed a much better loading performance and drugs sustained release properties compared to the product with which AMP was added during the process of complex formation of cross-linking process. The drug release mechanism has been analyzed for the polymers with different cross-linking densities via numerical simulation based on different kinetic models as well as the Ritger-Peppas equation. At the same time, it is found that the AMP release rate at pH 4 is initially greater than that at pH 10 and release rate increases as temperature is increased.

Key Words:

polyacrylic acid;
polyaluminium chloride;
cross-linking;
drug loading;
sustained release.

INTRODUCTION

As excellent properties of water absorption and water retention, superabsorbent polymers have been extensively applied as sorbents in the fields of infant diapers and feminine hygiene products [1,2]. Meanwhile, the superabsorbent polymers with sustained release functions also attract world attention for a variety of morespecialized applications, such as the controlled release devices for fertilizers in agricultural field and for druggery in intelligent cure [3-6].

Polyacrylate superabsorbents or hydrogels have shown promising applications as matrices for sustained release drug delivery [7]. However, conventional polyacrylate superabsorbents are usually prepared via free radical polymeri-zation and the structures of the drugs are easily destroyed during this process. Therefore, the drug-loaded polyacrylate super-

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absorbents specifically employed in sustained release of drugs are often prepared first via synthesizing polyacrylate hydrogels and subsequently loading the drugs into the prepared hydrogel networks by absorption [8,9]. However, the efficiency of the above loading method depends crucially on the specific interactions between the hydrogels and drug molecules. As a consequence, the amount of loaded drug is usually rather limited, and the drug molecules are often concentrated near the exterior surface of the hydrogels.

In the last few years, the pharmaceutical and medical applications of superabsorbents, and in particular, as direct skin contact materials for body fluid absorption, have been extensively studied in our research group [10,11]. To promote the body fluid absorption properties ulteriorly, our group has recently employed different methods for preparing superabsorbent polymers with porous structures, such as solvent precipitation method [12], foaming method [13] and freeze-drying method [14], etc., and the absorption velocity of the polymers to water or body fluid are noticeably promoted. Particularly, the efficiency of superabsorbents as body liquid absorbing materials can be enlarged by loading and sustained release of anti-bacterial, anti-inflammatory, haemostatic, pain-relieving and promoting wound healing compounds.

Recently we have explored a novel method to prepare the superabsorbent polymers via complex formation of cross-linking reaction of polyacrylic acid (PAA) and polyaluminium chloride (PAC) through $AlCl_3$ hydrolysis under basic conditions and further processed through freeze-drying method to form porous structures [15]. The prepared polymers can absorb over 600 g/g distilled water and the properties of water retention and gel strength are satisfactorily met. The exothermicity of the above complex formation is low, the corrosive of the acrylate monomer is non-existent and the oxidation effects of the initiator to the loaded molecule are absent. On the whole, the above method is a promising process for loading functional molecules into the networks and is able to overcome the disadvantages of the traditional loading method.

In this research work, to explore a novel method for preparing the drug-loaded superabsorbent polymers, we have conducted the loading and sustained release of the model drug acetaminophen (AMP) from the superabsorbent polymers prepared by complex formation of cross-linking reaction of polyacrylic acid (PAA) and polyaluminium chloride (PAC) through $AlCl_3$ hydrolysis at basic conditions. Then, the performance of these superabsorbent polymers are compared with the drug-loaded superabsorbent polymers prepared through free radical polymerization in aqueous solution.

EXPERIMENTAL

Materials

Polyacrylic acid (PAA) with average molecular weight of 1.05×10^6 was supplied by Beijing Chemical Reagents Company (China). Aluminium chloride hexahydrate ($AlCl_3.6H_2O$) was purchased from Sinopharm Chemical Reagent Co., Ltd. (China). Acrylic acid (AA, A.R.) was purchased from Tianjin Chemical Reagent Institute (China) and purified through distillation under reduced pressure before polymerization. *N,N′*-Methylene bisacrylamide (MBAM A.R.) was used as cross-linking agent and ammonium persulphate (APS, A.R.) was used as initiator for the superabsorbent prepared via free radical polymerization. Acetaminophen (AMP) was used as the model drug and supplied by Sinopharm Chemical Reagent Co., Ltd. (China). NaOH was analytical grade and used as received.

Loading of AMP in the Superabsorbent Polymers Prepared via PAA-PAC Complexation (Method A)

A volume of 150 mL deionized water and 2.5 g PAA were added into a triple-necked flask, which was equipped with a stirring apparatus and a reflux condenser. Then, the polymer was dissolved by quick stirring and 0.2 mol/L NaOH aqueous solution was added to adjust the pH of the solution around 9.65. An amount of 0.125 g AMP was added into the flask and stirred for 20 min. Then $AlCl_3$ solution was dripped into the flask via a constant pressure funnel. A moderate amount of de-ionized water was supplied and the total volume of water in the system was kept at 200 mL. After for 4 h reaction, the reactant was poured into a petri dish of Φ 90×10 mm and then was

frozen in the refrigerator of -20°C for 12 h. The frozen sample was freeze-dried on FD-1E lyophilizer (Beijing Detianyou Technology Development Co., Ltd., China) under the temperature of -56°C and pressure of 5 Pa.

Loading of AMP in the Superabsorbent Polymers during the Process of Free Radical Polymerization (Method B)

Acrylic acid (12 g) was dissolved in 150 mL de-ionized water and neutralized by NaOH to neutralization degree of 50%, and then the solution was added into a triple-necked flask, which was equipped with a stirring apparatus and a reflux condenser. The solution was stirred for 20 min and heated in a water bath of 70°C under nitrogen protection. Then, 0.15 g MBAM and 0.60 g AMP were added into the flask at the same time and the solution was stirred incessantly. An amount of 0.45 g APS, dissolved in 30 mL de-ionized water, was slowly added into the flask to initiate the polymerization process after 30 min. The reaction was stopped after 4 h. The prepared hydrogel was poured into a petri dish of Φ 90×10 mm and was then frozen in the refrigerator of -20°C for 12 h. The frozen sample was freeze-dried on a FD-1E lyophilizer at -56°C and pressure of 5 Pa.

Analysis and Characterization

The accumulative release amount of AMP through the network structure of the hydrogel was measured as follows. An appropriate amount of AMP-loaded superabsorbent was first weighed and put into a nylon mesh bag. Then, the superabsorbent along with the nylon mesh bag was immersed into the test aqueous solution. The entire system was kept at a definite temperature by being placed into a super thermostat water bath and stirred magnetically. The AMP concentration in the solution was measured at every fixed time interval by taking 5 mL absorption solution and subsequently determining its AMP concentration through measuring its UV-absorbance strength at 243 nm by using a Pgeneral TU-1810 UV-vis spectrophotometer (Beijing Purkinje General Instrument Co., Ltd., China). Meanwhile, 5 mL of original aqueous solution was supplied into the solution to maintain a constant solution volume.

Specifically, the accumulative release amount of AMP after the nth sampling can be calculated by:

$$Q_n = C_n V + V_1 \sum_{i=1}^{n} C_{n-1} \quad (1)$$

In which Q_n is AMP accumulative release amount after the nth sampling (mg); C_n is the sample concentration at the nth sampling (mg/mL); V is the volume of the solution (mL); and V_1 is the volume of each sampling (mL).

In addition, AMP accumulative release percentage can be determined by:

$$y = \frac{Q_n}{q} \quad (2)$$

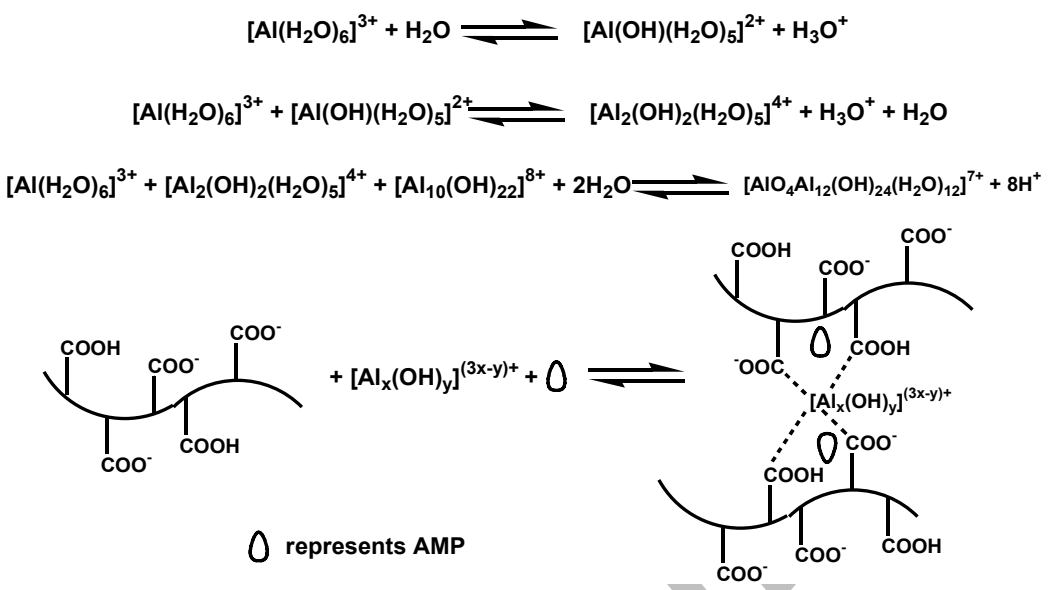
where y is the accumulative release percentage of AMP at the nth sampling (%); Q_n is AMP accumulative release amount after the nth sampling (mg); and q is the total AMP amount loaded in the superabsorbent (mg).

RESULTS AND DISCUSSION

Preparation of Superabsorbent

The hydrolysis products of $AlCl_3$ have been analyzed by Akitt et al. using 27Al NMR at several basic conditions [16]. Meanwhile, the absorption spectra of Al-Ferron complex have been measured by Stumm et al. [17] as a function of time during the hydrolysis of $AlCl_3$. All the results show that $AlCl_3$ can be hydrolyzed to polyaluminium chloride (PAC) polycations carrying multiple hydroxyl groups, as shown in Scheme I [18,19]. These PAC polycations can form complexes with the carboxyl groups of PAA through the electrostatic interaction, and ultimately lead to the formation of superabsorbent possessing cross-linked network structure.

The structural changes between PAA and PAA-PAC complexation were observed by FTIR spectroscopy (Figure 1). After PAA was complexed with $AlCl_3$ hydrolysis at basic conditions, the absorption peak at 1715 cm^{-1} that attributed to the extension vibration of C=O was transferred to 1625 cm^{-1}, confirming that the C=O groups of PAA had been



Scheme I. Hydrolysis of $AlCl_3$ and complex formation of cross-linking reaction of hydrolysis products with PAA.

complexed with PAC formed through the hydrolysis of $AlCl_3$ and the network structures could be produced. The swelling ratio of PAA-PAC complexation polymer was tested. The results show that the polymer can absorb over 450.95 g/g distilled water and over 68.43 g/g normal saline (NaCl 0.9% aqueous solution) in 1 h.

The Standard Curve of AMP Aqueous Solutions

As shown in Figure 2, the solution of AMP has a strong UV-absorption peak at 243 nm, whereas absorption solution in which PAA-PAC superabsorbent polymer is swollen shows no UV-absorption around this wavelength. Therefore, the release amount of AMP can be quantitatively determined by UV-absorption strength at 243 nm and then the standard curve of AMP aqueous solution may be tested.

A series of AMP aqueous solutions with concentrations at 5×10^{-4} g/L, 1×10^{-3} g/L, 2×10^{-3} g/L, 5×10^{-3} g/L, 8×10^{-3} g/L, 1×10^{-2} g/L and 1.5×10^{-2} g/L were confected. The UV-absorbance of AMP aqueous

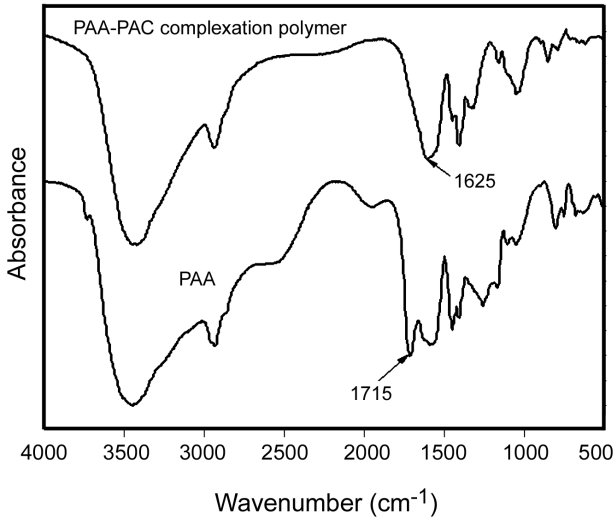


Figure 1. FTIR Spectra of PAA and PAA-PAC complexation polymer.

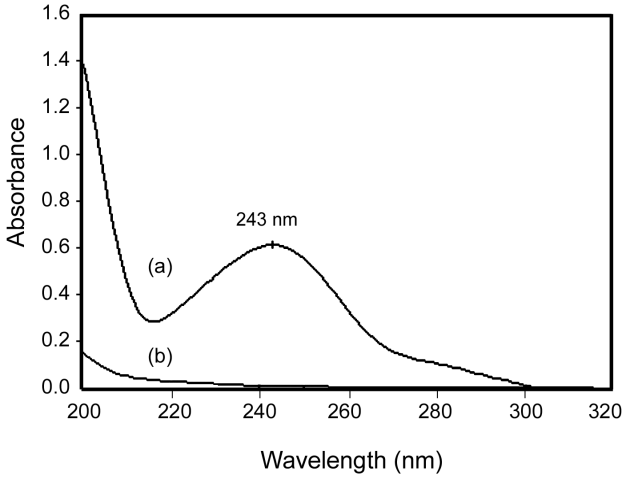


Figure 2. UV-Absorption spectra of: (a) AMP and (b) the absorption solution in which PAA-PAC superabsorbent polymer was swollen.

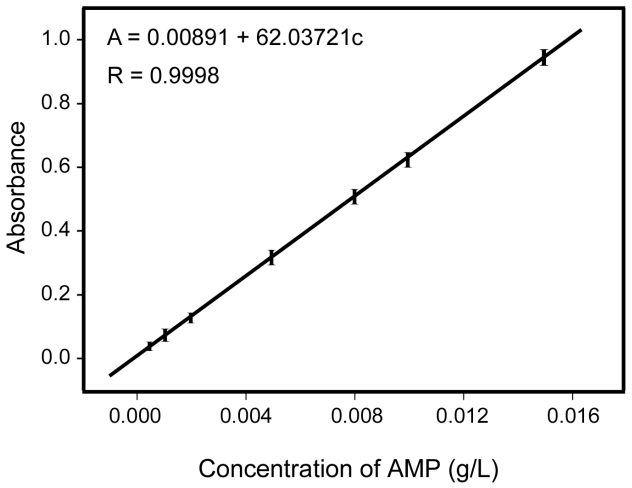


Figure 3. The calibration curve of AMP aqueous solutions.

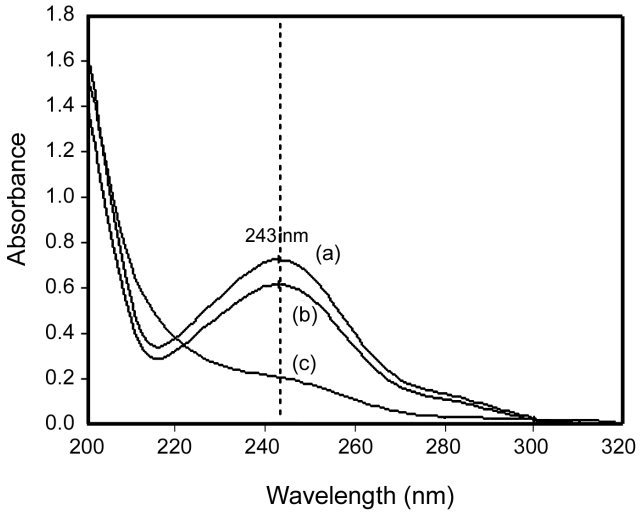


Figure 4. UV-Absorption spectra of the release solution for the polymers prepared through different methods: (a) AMP standard aqueous solution, (b) method A, and (c) method B.

solutions was tested with de-ionized water used as blank control. Then, the standard curve of AMP can be deduced as: A = 0.00891+62.03721c, R = 0.9998 (Figure 3).

AMP Loading Efficiency Through Different Superabsorbent Preparation Methods

The AMP loading efficiency of superabsorbents prepared through PAA-PAC complexation and free radical polymerization have been studied and compared together. Specifically, the drug-loaded superabsorbents were immersed into distilled water for 4 h, and the UV-absorbance of AMP released into the solutions was recorded as a function of time. Particularly, as shown in Figure 4, a strong absorption band at 243 nm appeared in the release aqueous solution of the drug loaded superabsorbent prepared via method A (PAA-PAC complexation), which was consistent with that of AMP standard solutions. However, such absorption band has not been observed in the release aqueous solution of the superabsorbent prepared via method B (acrylic acid polymerization) during the entire 4 h drug releasing period. This indicates that the superabsorbent prepared by method B may exert some undesired effects on AMP and eventually lead to some structural changes. This may be deduced by many explanations. First, the radical polymerization is the exothermic reaction and the heat produced during polymerization cannot be removed promptly due to the poor thermal transport properties of the hydrogels, which leads to a severe thermal accumulation inside the networks, and therefore the AMP as model drug is easily destroyed. Meanwhile, the persulphate salts used as the initiator in the polymeri-zation may destroy the structure and performance of the drugs loaded by inducing undesired oxidation reactions. Finally, the acrylate used as monomers for polymerization is strongly corrosive and AMP is easily decomposed. Overall, the structure and function of the model drug AMP are easily destroyed and at the same time the poly-merization process (method B) is not fit for AMP loading. In contrast, the reaction process of PAA-PAC complexation (method A) is mild, the exothermicity is low, the corrosive of the acrylate is non-existent and the oxidation effects of the initiator to the molecules loaded are absent, then the structure of loaded drug can be protected from damage and the drug is also release from the networks properly. Method A is an ideal process for drug loading.

Effects of Drug Loading Procedure on AMP Release

In this study, AMP was loaded into the PAA-PAC superabsorbent polymers through two procedures. In procedure A, 5% AMP (relative to the superabsorbent mass) was added before the complex cross-linking between PAA and Al(III), while in procedure B, the

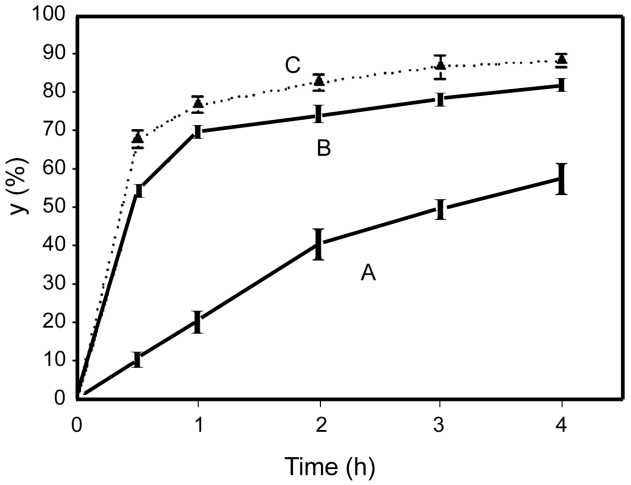


Figure 5. UV-Absorption spectra of the release solution for the polymers prepared through different procedures.

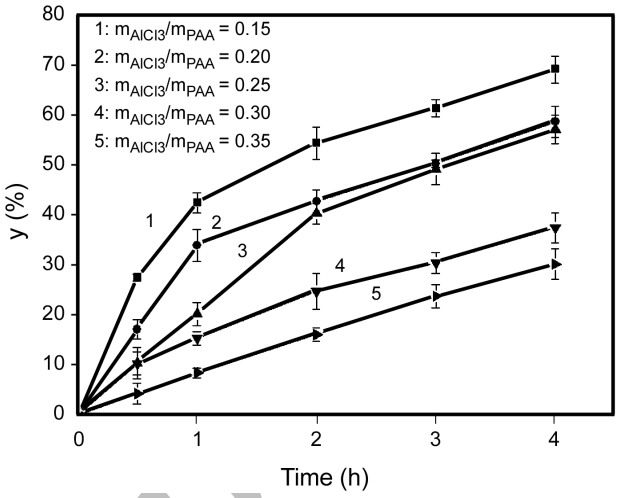


Figure 6. Effects of m_{AlCl3}/m_{PAA} on releasing rate of AMP.

same amount of AMP (5%) was added during the process of complex forming cross-linking reaction. The time course of AMP releasing from the super-absorbents prepared through these two procedures are shown in Figure 5. Specifically, the accumulative release percentage of AMP loaded via procedure B was already above 50% after only 0.5 h, and became about 80% after 4 h. Particularly, the temporal release profile of AMP loaded by procedure B was quite similar to that of the control, in which AMP was just physically mixed with cross-linked PAA-PAC superabsorbent, indicating that procedure B is not satisfactory in terms of its poor loading as well as sustained release performance. In contrast, the AMP loaded via procedure A showed a much better loading performance as well as more satisfactory sustained release performance (Figure 5). In this figure, procedure C represents physical mixture of AMP with cross-linked PAA-PAC superabsorbent.

Effects of $AlCl_3$ Amount on AMP Release

The effects of mass ratio of $AlCl_3$ cross-linking agent to PAA (m_{AlCl3}/m_{PAA}) on AMP release have been studied at a fixed AMP loading level, i.e., 5% (relative to the superabsorbent mass). As shown in Figure 6, the AMP releasing rate is decreased significantly with the increase in the amount of cross-linking agent, which can be attributed to the increase of AMP diffusion resistance in the interior of the super-absorbent as well as the decreased dissolution rate due to enhanced network cross-linking structure. Generally, the efficiency of sustained release would be promoted as the releasing rate decreases. However, increasing the cross-linking agent amount can lead to a significant decrease in water absorbency due to water being more difficult to enter the interior of superabsorbent, which is usually undesirable from the practical viewpoint. The swelling ratio for m_{AlCl3}/m_{PAA} = 0.25 was 450.95 g/g, while decreased to 268.46 g/g at m_{AlCl3}/m_{PAA} = 0.35. Therefore, the amount of cross-linking agent should be carefully selected through comprehensive considerations between loading capacity, release rate and the swelling capacity of the superabsrbent polymer.

The experimental AMP release rates of the polymers prepared with different amounts of cross-linking agent have been fitted by theoretical rates calculated under an assumption of the zero-order kinetics, the first-order kinetics, and the Higuchi model, respectively. The results are summarized in Table 1. The corresponding coefficients (r) of the curves stimulated by different models are compared and the one with the highest r value has been considered to be the best corresponding model. Specifically, the drug transport can be well described by the Higuchi model at low cross-linking densities, in which the transport resistance experienced by drug molecules is small and consequently drug molecules are easy to leave the network. Particularly, drug molecules on the exterior surface of superabsorbent can directly dissolve into the solution phase; and simultaneously, the drug

Table 1. The fitting results of release curves of the polymer with different amounts of cross-linking agent.

m_{AlCl3}/m_{PAA}	Model for fitting	Fitting equation	r
0.15	Zero-order equation	y = 0.1515t+0.1602	0.9161
	First-order equation	ln(1-y) = -0.2712t-0.1575	0.9708
	Higuchi equation	$y = 0.3458t^{1/2}+0.0302$	0.9922
	Ritger-Peppas equation	lny = 0.4278lnt-0.9344	0.9888
0.25	Zero-order equation	y = 0.1450t+0.0422	0.9806
	First-order equation	ln(1-y) = -0.2172t-0.0166	0.9944
	Higuchi equation	$y = 0.3057t^{1/2}-0.0533$	0.9809
	Ritger-Peppas equation	lny = 0.8346lnt-1.6209	0.9922
0.35	Zero-order equation	y = 0.0758t+0.0054	0.9991
	First-order equation	ln(1-y) = -0.0902t+0.0014	0.9999
	Higuchi equation	$y = 0.1544t^{1/2}-0.0383$	0.9652
	Ritger-Peppas equation	lny = 0.9412lnt-2.4835	0.9998

molecules in the interior networks can gradually migrate out towards the solution phase with the influence of the concentration gradient. As the amount of cross-linking agent is increased, the transport resistance increases accordingly, and the rate of drug release begins to be controlled by the effects of surface dissolution-diffusion. Consequently, the drug release behaviour starts to deviate from the Higuchi model and instead follows the zero-order or the first-order kinetics. Moreover, as shown in Table 1, the slope of the fitting curve of each model is decreased as the amount of cross-linking agent increases, indicating a decrease in AMP release rate as the cross-linking density is increased.

Ritger et al. put forth a simplified semi-empirical equation ($y = kt^n$) to describe the release properties of the drug from the matrice [20-23], while the diffusion exponent, n, indicates the characteristic parameter related to release mechanism. The value of n below 0.45 corresponds to a pure Fickian diffusion mechanism, while n bigger than 0.89 indicates a release controlled by matrix erosion. $0.45<n<0.89$ indicates a combined release mechanism consisting of both matrix erosion and Fickian diffusion.

The dynamics of AMP release is investigated by using the Ritger-Peppas equation at various amounts of a cross-linking agent. The results are also listed in Table 1. Specifically, the migration of AMP follows the Fickian diffusion with a low amount of cross-linking agent (m_{AlCl3}/m_{PAA} = 0.15, n = 0.3458). However, with the increase in the amount of cross-linking agent, the value of n is increased (m_{AlCl3}/m_{PAA} = 0.25, n = 0.8346), indicating a release controlled simultaneously by both matrix erosion and Fickian diffusion. With further increase in the amount of cross-linking agent and consequently increased n value (m_{AlCl3}/m_{PAA} = 0.35, n = 0.9412), AMP transport is predominated by matrix erosion. These results are consistent with those of model fitting results based on the Higuchi model, the zero-order and the first-order kinetics.

Effects of pH on AMP Release

The AMP release rates of the superabsorbent prepared via PAA-PAC complexation have been measured at pH around 4 and 10, respectively, as shown in Figure 7. Particularly, the AMP release rate at pH 4 has initially been larger than the release rate at pH 10, however, finally close to it as time passes. This may be explained as follows: under basic conditions, $AlCl_3$, as discussed in the above reaction mechanism, can be hydrolyzed to form polyaluminium chloride polycations carrying multiple hydroxyl groups, which can form stable complexes with PAA and lead to a network structure of high cross-linking density, consequently, a slow AMP release. On the other hand,

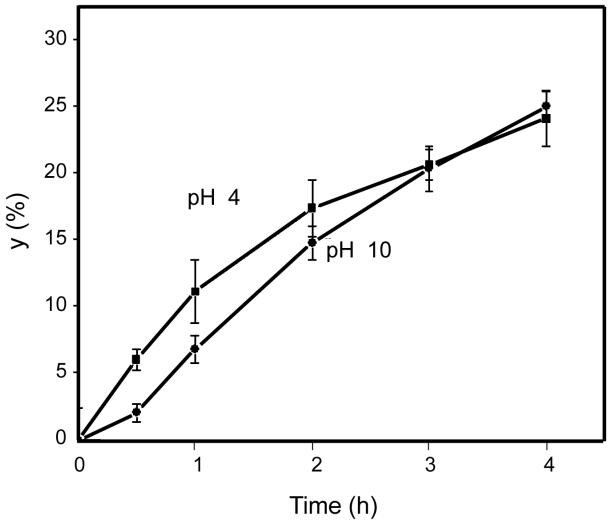


Figure 7. The AMP release curves at pH 4 and pH 10.

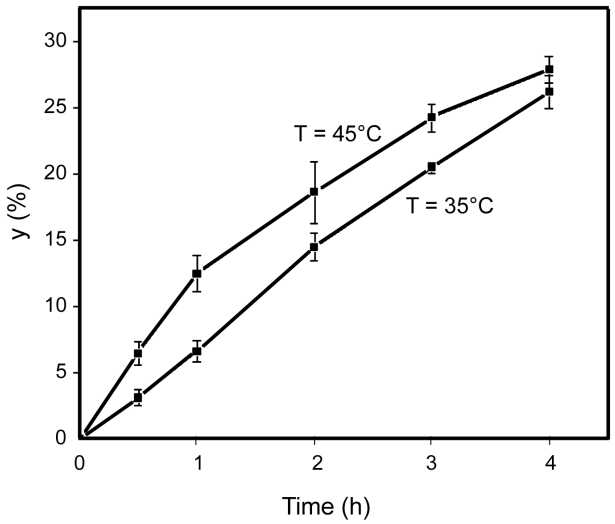


Figure 8. The AMP release curves at different temperatures.

some -COOH groups may lose their proton and become $-COO^-$ at acidic pH, which would reduce the swelling degree of the hydrogel and lead to limited release of AMP. Under acidic conditions, the hydrolysis of $AlCl_3$ can be reversed to such an extent that Al^{3+} ions exist in the solution primarily in the form of $[Al(OH)(H_2O)_5]^{2+}$, resulting in a significant decrease in cross-linking effects occurring between Al(III) and C=O; secondly, acetaminophen may be partially converted to phenolate and increases its water solubility; finally, $-COO^-$ groups may be formed from COOH groups, leading to an increase of the swelling degree. Consequently, AMP can be released from the network more quickly at the initial stage.

Effects of Temperature on AMP Release

Effects of temperature on the release rate of AMP have also been examined in this study. As shown in Figure 8, the AMP release rate is increased with temperature, which can be attributed to the increase of the diffusivity as well as the solubility of loaded AMP molecules inside the superabsorbent. Meanwhile, the increase in the degree of swelling of the superabsorbent as a result of temperature increases may also be at least partly responsible for the increase of AMP release rate through enlarging the diffusion pathways throughout the superabsorbent. Both two factors are believed to contribute to the increase of AMP release rate as the temperature is increased.

CONCLUSION

A novel AMP-loaded PAA-PAC complexation superabsorbent polymer was prepared. The drug was loaded during the process that polyacrylic acid (PAA) entered complex formation via cross-linking reaction with polyaluminium chloride (PAC) through $AlCl_3$ hydrolysis under basic conditions. It is found that drug-loaded superabsorbent prepared via the above method can effectively protect the structure of the loaded drug from damage for its mild reaction conditions. The sustained release properties of the prepared PAA-PAC complexation superabsorbent polymers to the model drug AMP have been studied. The procedure of the loading process has been studied and the results indicate that the AMP loaded before the complex formation of cross-linking reaction shows a much better loading performance and drugs sustained release properties compared to the product with which AMP was added during the process of complex forming of cross-linking reaction. The AMP releasing rate is decreased significantly with increased amount of cross-linking agent and the releasing models are transferred from controlled state by Higuchi model to follow the zero-order or the first-order kinetics. The study results from the Ritger-Peppas equation which reveals that the migration of AMP follows Fickian diffusion model at low level of cross-linking agent. With increased levels of cross-linking agent, the release is controlled by

both matrix erosion and Fickian diffusion. With the further increase of cross-linking agent, AMP transport is predominated by matrix erosion. It has been found that the AMP release rate at pH 4 is initially greater than its release rate at pH 10 and release rate increases as temperature is increased.

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