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ORIGINAL ARTICLE

Magnetic *N*-succinyl chitosan/alginate beads for carbamazepine delivery

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Abstract

Context: Epilepsy is a chronic condition characterized by recurrent unprovoked seizures. The most optimal use of drugs was limited due to their widespread systemic and central side effects. In contrast, focal drug delivery to epileptogenic focus based on superparamagnetic carrier is considered to be a promising and safe alternative. This delivery system could arrive exactly at the targeted tissue and deliver the loaded drug there with the help of an external magnetic field. *Objective*: A new magnetic delivery system was established to inhibit paradoxical discharge once the onset of seizures. *Materials and methods*: Carbamazepine was incorporated into *N*-succinyl chitosan (NSC)/alginate hydrogel beads by ionic interaction. The characteristics of the beads including morphology, release behavior, and magnetic property were also investigated. *Results*: Acceptable spherical morphology, excellent slow-release property, and superparamagnetic property of the NSC/alginate hydrogel beads were observed. *Discussion and conclusion*: The magnetic NSC/alginate beads may be acted as a sustained-release formulation. The drugs exhibit the potential magnetic property owing to Fe_3O_4 particles. It is promising that the released drugs are induced by the weak magnetic field of epileptogenic zone and have the potential of locating them so as to inhibit paradoxical discharge once the onset of seizures.

Key words: *Carbamazepine; delivery properties; hydrogel; N-succinyl chitosan; superparamagnetic*

Introduction

Epilepsy is a chronic condition characterized by recurrent unprovoked seizures that may affect 2% of the population[1,2]. The goal of epilepsy management is to completely control the seizures with little or no adverse effects. Epilepsy is caused by paradoxical discharge from the diseased region. It has recently been noted that there is a weak magnetic field (MF) because of electromagnetic induction when epilepsy seizures occurs; the MF could induce magnetic nanoparticle directionally[3]. We focus our attention on this phenomenon and try to develop a magnetic drug delivery system. Based on this system, drugs can be induced to the diseased region and made to stay there.

Carbamazepine (CBZ) is widely used in the treatment of epilepsy and trigeminal neuralgia[4]. The drug has variable dissolution leading to irregular and delayed absorption[5–9]. In addition, widespread systemic and central side effects limit the most optimal use of the drugs[10–12]. Therefore, it is essential to prepare a drug-targeting formulation for the controlled release of CBZ.

N-succinyl chitosan (NSC) has unique characteristics in vitro and in vivo such as biocompatibility, low toxicity, and long-term retention in the body[13,14]. It is used to blend with alginate to prepare Ca^{2+} cross-linked hydrogel beads that generally exhibited pH-sensitive and ionic-sensitive swelling and drug release properties[15–17]. To date, there are only a few kinds of ionic cross-linked hydrogels reported.

Superparamagnetic material can be guided and aggregated more conveniently when external MF is added. Most of them are based on superparamagnetic Fe_3O_4 nanoparticles. These materials are considered to be potentially useful in drug delivery systems. They could arrive exactly

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at the targeted tissue and stay there with the help of external MF, and then deliver the loaded drugs[18,19].

This work presents a magnetic NSC/alginate beads. The nature of beads was also investigated. Under this premise, we look forward to establishing a magnetic nanoparticle for the controlled release of CBZ[20,21]. During ionic interaction, drugs were encapsulated into the gel network together with Fe_3O_4. They have the potential to exhibit magnetic property and could be induced to the diseased region because of the weak MF. Thus, local drug concentration increased, and paradoxical discharge is inhibited rapidly. The new delivery system would have a use-dependent mechanism, in which the drugs are dormant in the interictal state and disperse around while activated to gather at the diseased region by the epileptogenic process[22].

The aim of this study is to prepare magnetic NSC/alginate beads by dropping aqueous solution containing NSC and alginate into $CaCl_2$ solution[23]. The process is mild and simple. We studied not only the factors influencing swelling characteristics of the hydrogels but also the morphology, infrared spectrum, swelling characteristics, and release behaviors of the beads in HCl solution (pH 1.5) and phosphate buffer solution (pH 6.8).

Materials and methods

Materials

NSC (MW is 3×10^5, degree of deacetylation is 65%) was acquired from Lanzhou Institute of Chemical Physics, Chinese Academy of Sciences (Lanzhou, China). Sodium alginate of low viscosity (0.02 Pa s) for a 1% solution at 20°C was purchased from Shanghai Chemical Co. Ltd. (Shangai, China). Fe_3O_4 (average size is 20 nm) was purchased from Nanjing Emperor Nano Material Co. Ltd. (Nanjing, China). CBZ (purity is 99.76%) was provided by Suzhou Hengyi Pharmaceuticals Co. Ltd. (Suzhon, China). All the other chemicals and reagents used were of analytical grade.

Preparation of carbamazepine magnetic NSC/alginate hydrogel beads

The NSC/alginate hydrogel beads were prepared by dropping aqueous NSC/alginate into calcium chloride solution. A series of NSC/alginate hydrogel beads with different compositions were prepared as shown in Table 1. CBZ and magnetite nanoparticles were mixed with 10 mL prepared aqueous NSC/alginate solutions adequately and sonicated until a uniform suspension was obtained. The suspension was introduced into a 10-mL syringe and then extruded through a needle with an internal diameter of 0.45 mm into a 40-mL calcium bath (1.5%, 2.0%, 2.5%) for 30 minutes under gentle magnetic stirring. The distance between the edge of the needle and the surface of the solution was 5 cm. The calcium-cross-linked beads were rinsed with distilled water for three times to remove unreacted calcium chloride on surface and subsequently dried in air overnight.

Scanning electron microscopy

Micrographs of the samples were taken using a scanning electron microscope (JSM-6380LV; Jeol, Akishima, Tokyo, Japan). Prior to observation, all samples were mounted on aluminum stubs, using double-sided adhesive tape, then hydrogel samples were coated with gold, and scanned at an accelerating voltage of 15 kV.

Table 1. Formulation of the magnetic *N*-succinyl chitosan/alginate beads utilizing single factor design.

Formulation	X_1 (%, w/v)	X_2 (%)	X_3 (mL)	X_4 (w/w)	X_5 (w/w)	Encapsulation efficiency (%)	Loading efficiency (%)
A_1	1:1	1.5	40	1:4	1:3	87.18	20.13
A2	1.5:1.5	1.5	40	1:4	1:3	94.84	17.87
A3	2:2	1.5	40	1:4	1:3	93.38	20.59
B1	1.5:1.5	2.0	40	1:8	1:3	88.65	7.15
B2	1.5:1.5	2.5	40	1:8	1:3	87.28	7.36
C1	1.5:1.5	2.0	30	1:4	1:3	91.33	15.75
C2	1.5:1.5	2.0	50	1:4	1:3	85.98	13.84
D1	1.5:1.5	2.0	40	1:6	1:3	89.17	10.32
D2	1.5:1.5	2.0	40	1:8	1:3	85.66	7.58
E1	1.5:1.5	2.0	40	1:4	1:2	92.00	13.50
E2	1.5:1.5	2.0	40	1:4	1:3	92.16	15.30
E3	1.5:1.5	2.0	40	1:4	1:4	92.67	15.69

*Distinct weight ratio of NSC to alginate (X_1), $CaCl_2$ concentration (X_2), the volume of $CaCl_2$ (X_3), the weight ratio of drugs to polymer (X_4), the weight ratio of Fe_3O_4 to polymer (X_5).

FTIR spectroscopy

Individual beads were crushed with pestle in an agate mortar, and the crushed material was mixed with potassium bromide in 1:100 proportions. The mixture was compressed to a 1 mm semitransparent disk by applying a pressure of 20 MPa (FW-4A pelleter) for 5 minutes. The Fourier transform infrared (FTIR) spectra over the wavelength range 4000–400 cm^{-1} were recorded using a FTIR spectrometer (Thermo Nicolet, Nexus, TM, Madison, Wisconsin, USA).

Calibration curves

Stock solutions of CBZ were prepared by dissolving and diluting the drug in ethanol at a concentration of 1.001 mg/mL. CBZ stock solution was further diluted with ethanol to obtain the different working solutions at concentrations of 4.004, 6.006, 8.008, 10.010, 12.012, 14.014, 16.016, and 18.018 μg/mL. The standard solutions were determined by UV-spectrophotometry (UV-2401PC, Shimadzu Corporation, Shimadzu, Japan) at 285 nm. The equation of calibration curves is as follows:

$$C = 19.39A - 0.170 (r = 0.99990). \quad (1)$$

Determination of encapsulation efficiency and loading efficiency

After preparation of CBZ magnetic NSC/alginate hydrogel beads, the mixture of calcium chloride solution and deionized water-rinsed CBZ magnetic NSC/alginate hydrogel beads was transferred into a 50-mL volumetric flask, and deionized water was added to scale. The resulting solution was diluted 12.5 times with deionized water before filtering. The amount of free CBZ in the filtrate was determined by UV-spectrophotometry (UV-2401PC) at 285 nm, deionized water was taken as control. The encapsulation efficiency is the percentage of contained CBZ within the hydrogel bead in relation to the initial amount employed. The loading efficiency (%) is defined as the weight percentage of loaded drugs based on the weight of drug-loaded hydrogel bead.

$$\text{encapsulation efficiency (\%)} = \left[\frac{\text{the amount of initial carbamazepine} - \text{the amount of free carbamazepine}}{\text{the amount of initial carbamazepine}} \right] \times 100. \quad (2)$$

$$\text{loading efficiency (\%)} = \left[\frac{\text{the amount of initial carbamazepine} - \text{the amount of free carbamazepine}}{\text{weight of drug loaded beads}} \right] \times 100. \quad (3)$$

Swelling analysis

Accurately weighed amounts of dried gel beads 10 mg were dipped in 15 mL HCl solution (pH 1.5) and phosphate buffer solutions (pH 6.8) prepared according to the Chinese Pharmacopoeia 2005 at 37°C. The beads were separated from the swelling medium at fixed time intervals. Immediately, they were wiped gently with filter paper and weighed. The dynamic weight change of the beads with respect to time was calculated according to the formula

$$\text{SR}(\%) = \frac{W - W_0}{W_0}, \quad (4)$$

where W is the weight of the beads in the swollen state and W_0 is the initial weight of the beads. Moreover, swelling characteristics of the beads in different intensity of magnetism (0 Oe, 60 Oe, 1000 Oe, 3200 Oe) were also determined.

Magnetic property

A vibrating-sample magnetometer (VSM) (735 VSM, Model 7304; Lake Shore, Westerville, OH, USA) was used at room temperature to characterize the magnetic properties of pure Fe_3O_4 nanoparticles and magnetic beads.

Magnetic responsibility of the NSC/alginate beads can be evaluated by the response time to a given MF of about 3200 Oe.

In vitro release properties of carbamazepine

Accurately weighed amounts of 60 mg NSC/alginate hydrogel beads were suspended in 900 mL solution and maintained at 37 ± 0.5°C under 100 rpm. The solutions were hydrochloric acid solution (pH 1.5) and phosphate buffer solutions (pH 6.8). At predetermined time intervals, 10 mL solution was withdrawn and the dissolution medium was supplied with 10 mL fresh buffer solution to maintain the total volume. The content of CBZ in 10 mL sample was determined spectrophotometrically at 285 nm after

filtration. The drug release percent was determined using Equation (5).

$$\text{Drugs release}\,(\%) = \left[\frac{R_t}{L}\right] \times 100, \qquad (5)$$

where L and R_t represent the initial amount of drugs loaded and cumulative amount of drugs released at time t.

The sequential release properties of CBZ was determined by transferring the gel beads into phosphate buffer solutions (pH 6.8) after being immersed in HCl solution (pH 1.5) for 2 hours. At predetermined time points, the percentage of cumulative amount of released CBZ was determined as previously described.

Results and discussion

Characterization of magnetic NSC/alginate beads

The wet magnetic NSC/alginate hydrogel beads were spherical, smooth, and dark brown because of the presence of Fe_3O_4 nanoparticles. After drying in air, the beads had a rough structure on surface and volume decreased (Figure 1a and b). Detailed examination of the surface structure reveals that dried CBZ magnetic NSC/alginate hydrogel beads had a large surface area with the presence of many pores and also some cracks on the surface (Figure 1d–f). The cracks were caused by partial collapsing of the polymer network during dehydration. The dehydration of the NSC membrane surrounding the beads leads to corrugations and loss of the spherical shape. These results indicated that the integrity of NSC/alginate membrane was seriously destroyed in the drying process[24].

It is known that complex formation occurs in alginate and chitosan solution in the presence of a cationic polymer for alginate is an anionic polymer. Gel formation was also observed upon addition of aqueous NSC into a calcium chloride solution indicating that ionic cross-link between the carboxylate ($-COO^-$) of NSC can also be established by Ca^{2+}. Thus, in the preparation of the NSC/alginate beads, alginate was encapsulated through the NSC network, resulting in the formation of interpenetrating polymeric network. Meanwhile, Fe_3O_4 magnetic nanoparticle and drugs mixing with sodium alginate were also encapsulated into the gel network.

FTIR spectroscopy

The FTIR spectra of NSC, sodium alginate, CBZ, magnetic NSC/alginate blank beads, and CBZ magnetic NSC/alginate beads are shown in Figure 2. The FTIR spectrum of NSC showed stretching vibration of –OH

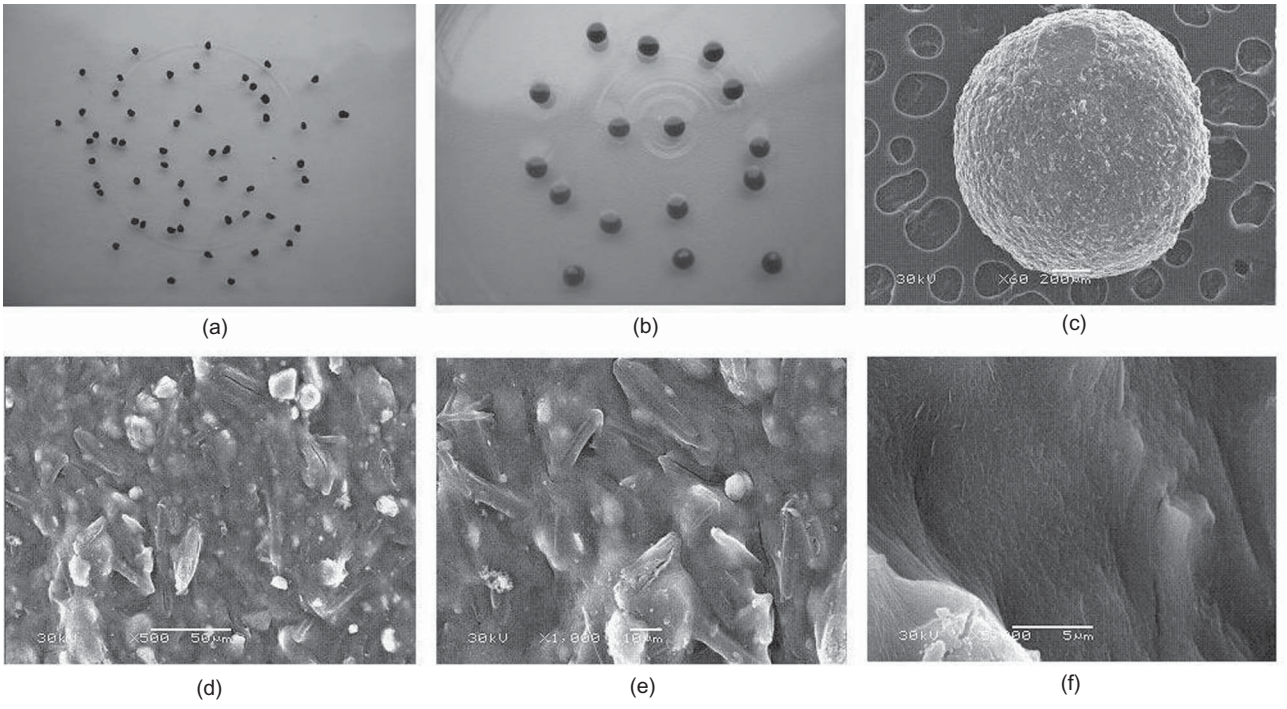

Figure 1. (a) Dry CBZ magnetic NSC/alginate beads, (b) wet CBZ magnetic NSC/alginate beads. Scanning electron microscope micrographs of surface morphology of CBZ magnetic NSC/alginate beads: magnification (c) ×60, (d) ×500, (e) ×1000, (f) ×5000.

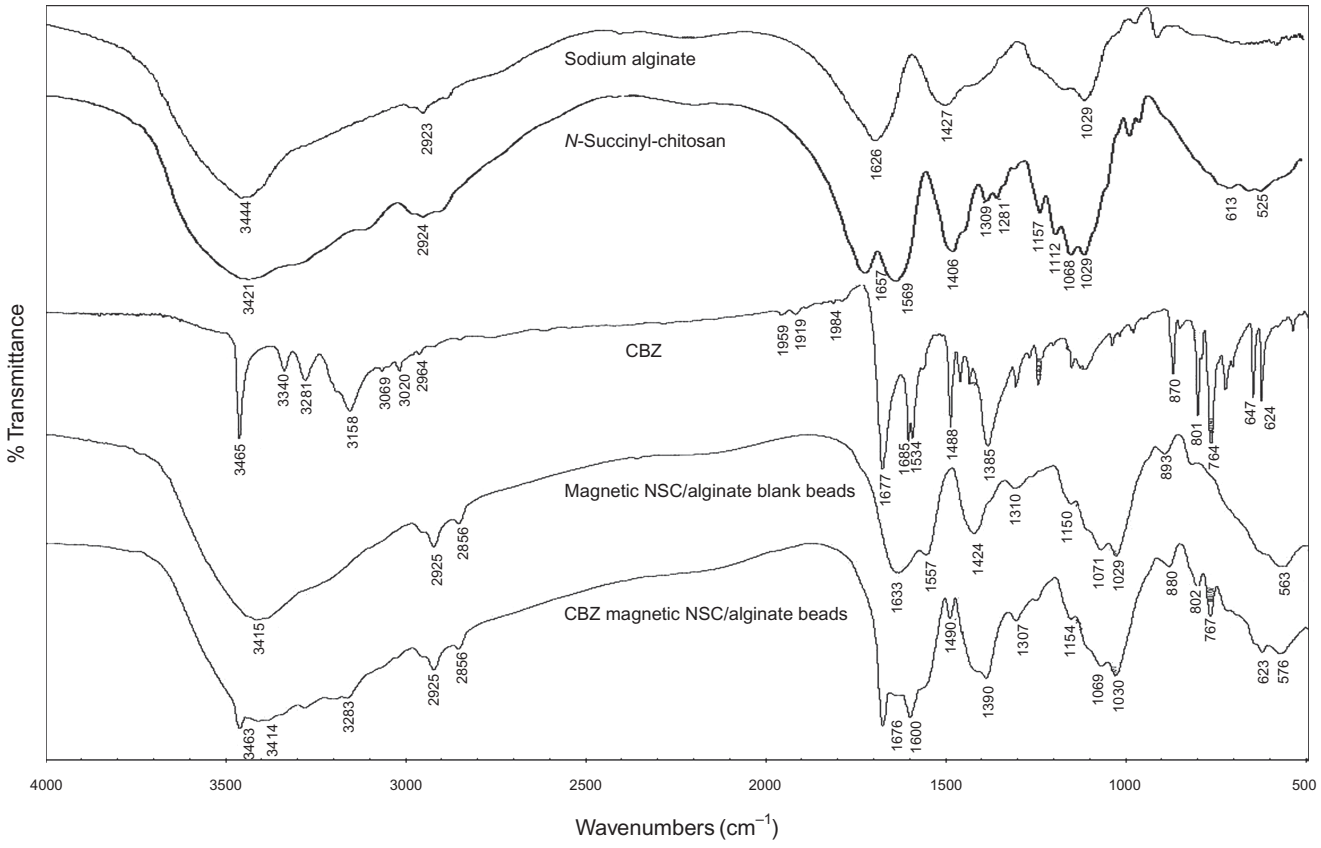

Figure 2. The FTIR spectra of sodium alginate, NSC, magnetic NSC/alginate blank beads, CBZ, and CBZ magnetic NSC/alginate beads.

and –NH_2 at 3421 cm^{-1}, the weak band of –CH_2 stretching at 2924 cm^{-1}, the C=O stretching of amide I band at 1657 cm^{-1}, and the amide II band at 1569 cm^{-1} [25]. The peak at 1406 cm^{-1} belongs to –COOH symmetric stretching vibration, the peaks observed at 1068 and 1029 cm^{-1} were the secondary hydroxyl group (characteristic peak of –CH–OH in cyclic alcohols, C–O stretching) and the primary hydroxyl group (characteristic peak of –CH_2–OH in primary alcohols, C–O stretching)[26]. Sodium alginate showed the following distinct peaks: (1) strong absorption bands at 1626 and 1427 cm^{-1} due to carboxyl anions (asymmetric and symmetric stretching vibrations); (2) the bridge oxygen (C–O–C, cyclic ether) stretching bands at 1029 cm^{-1}. To the magnetic NSC/alginate blank beads, the absorption band at 1569 cm^{-1} of NSC shifts to 1557 cm^{-1} after the reaction with alginate, the stretching vibration of –OH and –NH_2 at 3421 cm^{-1} became broad, indicating that intramolecular and intermolecular hydrogen bonds are formed and enhanced between NSC and alginate.

In the FTIR spectra of CBZ characteristic bands were found at 3465, 3158 cm^{-1} (–NH valence vibration), and 1677 cm^{-1} (–CO–R vibration)[7]. For the CBZ magnetic NSC/alginate beads, –CO–R was detected at the same position as that of drug. The N–H valence vibrations were seen at 3463 cm^{-1}. The band at 3463 cm^{-1} corresponding to the symmetrical and asymmetrical N–H stretching vibrations of CBZ primary amide groups was seen in the CBZ magnetic NSC/alginate beads, which indicated that CBZ was physically filled in the polymeric network.

The swelling behaviors of beads

The swelling behavior of dried beads was shown in Figures 3–7. The swelling characteristic in HCl solution (pH 1.5) was hardly observed. In phosphate buffer solutions (pH 6.8), the swelling behavior was influenced mainly by the weight ratio of NSC to alginate, $CaCl_2$ concentration, the weight ratio of drugs to polymer, and the weight ratio of Fe_3O_4 to polymer. As can be seen, the swelling ratio of test beads (NSC:alginate = 1.5:1.5%) was higher than the other two groups in pH 6.8, the beads eroded slowly. The swelling degree increased with the increase of Ca^{2+} concentration. But above 2%, the swelling degree did not increase anymore. With the growing weight ratio of CBZ to polymer, swelling degree decreased significantly. But considering the loading efficiency of the magnetic beads, we finally took 1:4 as

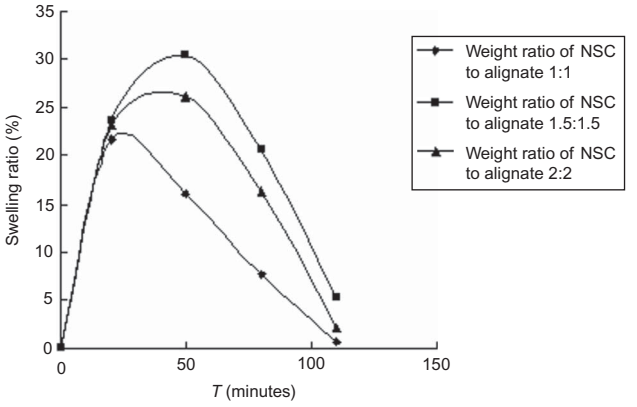

Figure 3. The influence of the weight ratio of NSC to alginate on the swelling characteristic from magnetic NSC/alginate beads (the weight ratio of drugs to polymer, 1:4; $CaCl_2$ concentration, 1.5%; the volume of $CaCl_2$, 40 mL).

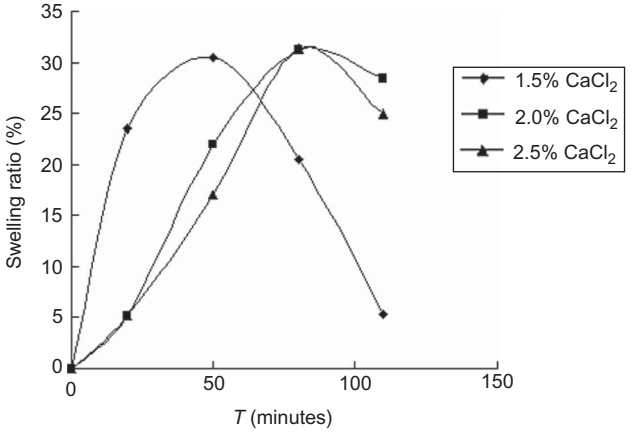

Figure 4. The influence of $CaCl_2$ concentration on the swelling characteristic from magnetic NSC/alginate beads (the weight ratio of NSC to alginate, 1.5:1.5; the weight ratio of drugs to polymer, 1:4; the volume of $CaCl_2$, 40 mL).

the optimal ratio. Likewise, the weight ratio of Fe_3O_4 to polymer could also affect swelling ratio to a great extent, 1:3 is appropriate taking into account magnetic responsivity. In addition, magnetic intensity had no effect on swelling ratio of magnetic beads.

The swelling behavior of the dry beads is mainly attributed to the hydration of the hydrophilic groups of alginate and NSC[27]. NCS is an amphoteric macromolecule containing both carboxyl and amino groups. In pH 1.5, intermolecular and intramolecular hydrogen bonds were formed between alginate and NSC. Additionally, a repulsive force within the hydrogel is created because of protonation of primary amino groups ($-NH^{3+}$) of NSC. Because the force of hydrogen bond is greater than the repulsive force, the beads are kept in a shrunk state. In pH 6.8, the swelling ratios of test beads increased significantly

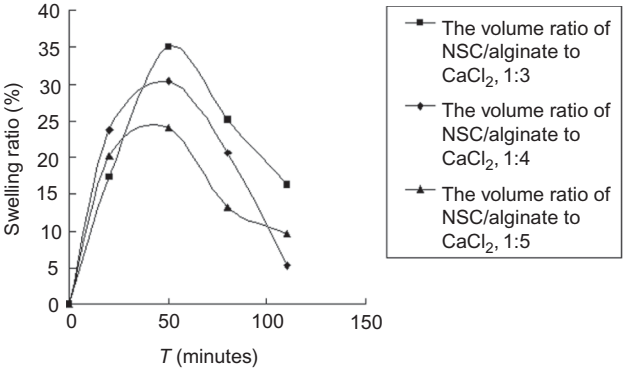

Figure 5. The influence of volume of $CaCl_2$ on the swelling characteristic from magnetic NSC/alginate beads (the weight ratio of NSC to alginate, 1.5:1.5; the weight ratio of drugs to polymer, 1:4; $CaCl_2$ concentration, 2%).

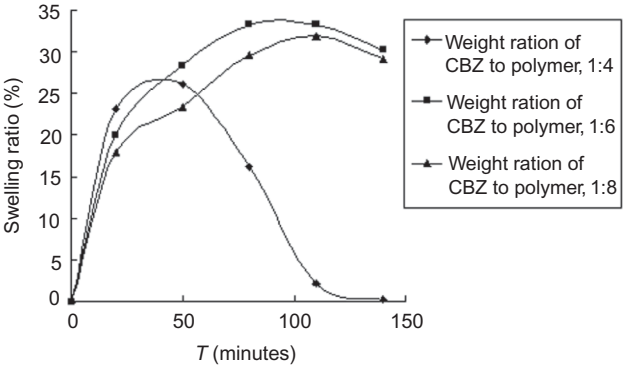

Figure 6. The influence of weight ratio of drugs to polymer on the swelling characteristic from magnetic NSC/alginate beads (the weight ratio of NSC to alginate, 1.5:1.5; $CaCl_2$ concentration, 2%; the volume of $CaCl_2$, 40 mL).

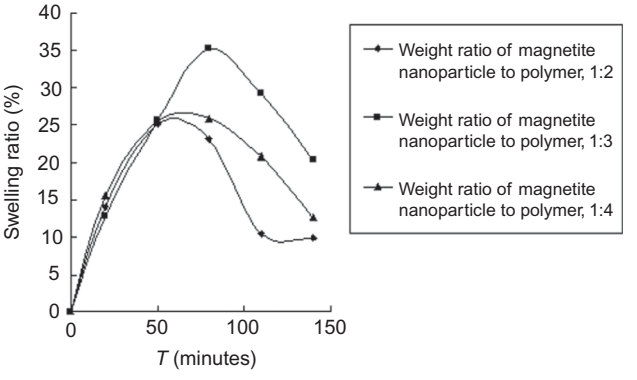

Figure 7. The influence of weight ratio of magnetite nanoparticles to polymer on the swelling characteristic from magnetic NSC/alginate beads (the weight ratio of NSC to alginate, 1.5:1.5; the weight ratio of drug to polymer, 1/4; $CaCl_2$ concentration, 2%; the volume of $CaCl_2$, 40 mL).

because of ionization of carboxyl groups in neutral pH. Carboxyl groups of alginate that were not cross-linked by Ca^{2+} and disrupted from calcium–alginate network were ionized and absorbed water, which resulted in higher swelling degree. After swelling for 1–2 hours in pH 6.8, the swelling ratios began to decline because of the disintegration of beads[28].

Magnetic property

The magnetic properties of the beads are measured using a VSM. Figure 8 shows the magnetization curve of magnetic NSC/alginate beads. It can be seen that the hysteresis and coercivity are almost undetectable (no remanence effect), suggesting that the magnetic beads can remain satisfactory; superparamagnetic property results from Fe_3O_4 nanoparticles at room temperature. Comparing with the reference value (58.57 emu/g) of the pure magnetite nanoparticles, the saturation magnetization (M_s) of the magnetic NSC/alginate beads was 8.74 emu/g. The reduced M_s (8.74 emu/g) can be attributed to the low content of Fe_3O_4 nanoparticles in the beads. Although the beads exhibit relatively low M_s, they show satisfactory magnetic-responsive aggregation and redispersion property in deionized water by adding or removing the MF, respectively. That is to say, the prepared beads possess satisfactory time-independent magnetic responsive ability and can be readily guided and collected with the help of external MF.

Drug release study

The release characteristics of magnetic beads in both HCl (pH 1.5) and phosphate buffer solutions (pH 6.8) were investigated. The cumulative release percentage of CBZ from magnetic beads is depicted in Figure 9. The

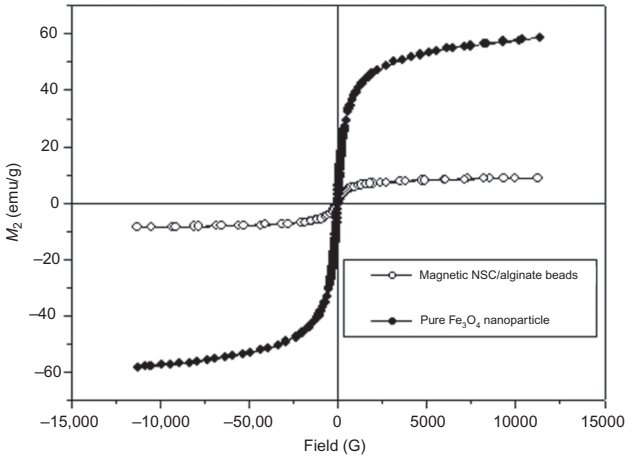

Figure 8. Magnetization curve of CBZ magnetic NSC/alginate beads.

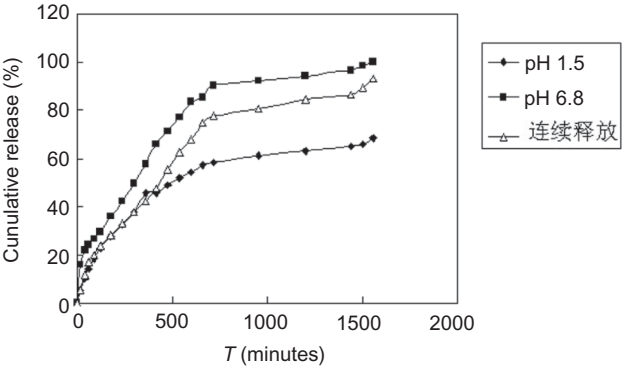

Figure 9. The cumulative release profiles of CBZ magnetic NSC/alginate beads in media of pH 1.5 and 6.8 at 37 ± 0.5°C.

release characteristics in the two media were obviously different from each other. It seems that there is a little CBZ released from magnetic beads in HCl (pH 1.5) because only drugs adsorbed at beads would dissolve in releasing media. On the contrary, in phosphate buffer (pH 6.8), drugs encapsuled within the beads released and dissolved continuously when magnetic beads swell and degrade, almost all the drugs dispersed in the medium. So, sequential release studies showed that initial release was 23.81% nearly during the first 2 hours in pH 1.5. After being transferred into pH 6.8, with swelling of the hydrogel network, the drugs encapsulated within the beads began to release. The cumulative amount of CBZ was 93.41% after 24 hours. Thus, CBZ seems not be released in stomach until arriving at intestinal tract if CBZ-loaded beads are given by oral administration. So the magnetic beads could be used as a kind of sustained-release preparation for therapy of epilepsy.

Drug release carbamazepine kinetics

The mechanism of drug release was investigated by fitting the drug release data into Korsmeyer–Peppas equation. This equation was used to explain the drug release mechanism to compare the release profiles. An approximation of the equation can be obtained by plotting the fraction of drug released versus square root of time as expressed by

$$\frac{M_t}{M_\infty} = k_1 t^n \quad \text{or} \quad \log\left(\frac{M_t}{M_\infty}\right) = \log k_1 + n \log t, \qquad (6)$$

where M_t/M_∞ is the fractional amount of the drug released at time t, n is a diffusion exponent that indicates the release mechanism, and k_1 is a characteristic constant of the system. From the slope and intercept of the plot of $\log(M_t/M_\infty)$ versus $\log t$, kinetic parameters n and

Table 2. Estimated parameters and drug release mechanism of magnetic *N*-succinyl chitosan/alginate beads in media of pH 1.5 and 6.8.

pH	*n*	*k*	*r*	Drug transport mechanism
1.5	0.4214	2.9161	0.9623	Fickian diffusion
6.8	0.4878	3.0789	0.9643	Anomalous transport

Kinetic constants (k), diffusional exponents (n), and correlation coefficients (r) by linear regression of log (M_t/M_∞) versus log t; k is the constant related to the structural and geometric characteristic of the device; n is the diffusional exponents, indicative of the drug release mechanism.

k_1 were calculated. For spheres, values of n between 0.43 and 0.85 are an indication of both diffusion-controlled drug release and swelling-controlled drug release (anomalous transport). Values above 0.85 indicate case-II transport which relate to polymer relaxation during gel swelling. Values below 0.43 indicate that drugs release from polymer was because of Fickian diffusion[14,29]. The release rate constant was calculated by fitting the experimental drug release data into the dissolution models and the goodness-of-fit of the drug release data was evaluated by linear regression.

CBZ release kinetics from magnetic NSC/alginate beads at different pH is shown in Table 2. In pH 1.5, values of n were 0.4214, and the release was because of Fickian diffusion. Meanwhile, value of n (0.4878) was between 0.43 and 0.85 in pH 6.8, and the release mechanism was because of anomalous transport (both diffusion and erosion mechanisms). CBZ release was controlled both by diffusion and by disintegration of the magnetic NSC/alginate gel matrix.

Conclusion

In conclusion, the magnetic NSC/alginate beads containing anti-epileptic drug CBZ was successfully prepared by a novel non-toxic method. Acceptable spherical morphology was observed. The swelling and release behaviors were also studied. The magnetic NSC/alginate beads showed excellent slow-release property and would be a suitable polymeric carrier for the controlled drug delivery. CBZ exhibits potential magnetic property owing to Fe_3O_4 within the beads. It is potential that CBZ could be induced by the weak magnetic field of epileptogenic zone and concentrated there to inhibit paradoxical discharge effectively. In addition, this delivery system has a practically clinical meaning to reduce the times of administration, narrow the blood concentration fluctuation, and reduce the side effects of CBZ. Furthermore, we look forward to establishing a magnetic delivery system containing CBZ that can be implanted by injection.

Declaration of interest

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