Indian Journal of Novel Drug Delivery

IJNDD

An Official Publication of Karnataka Education and Scientific Society

Research Article

A Novel Magnetic/pH Sensitive Chitosan/Alginate Hydrogel Bead for Controlled Carbamazepine Delivery

HUI-JUAN LIU [1, 2], PING LI [1, 2 *], YU-MIN LI [1, 2]

[1] Lanzhou University Second Hospital, Lanzhou, 730030, CHINA

[2] Key Laboratory of Digestive System Tumors, Gansu Province, Lanzhou, 730030, CHINA

ARTICLE DETAILS

Article history:
Received on 04 August 2011
Modified on 18 September 2011
Accepted on 24 September 2011

Keywords:
Carbamazepine,
Hydrogel,
Delivery properties,
Chitosan,
Superparamagnetic

ABSTRACT

A novel magnetic/pH sensitive chitosan/alginate（Chi/Alg） hydrogel bead was prepared by the $L_9(3^4)$ orthogonal Test（four factors:The alginate concentration, chitosan concentration, $CaCl_2$ concentration and weight ratio of Fe_3O_4 to polymer;three levels.）for controlled the delivery of carbamazepine（CBZ. Structure and surface morphology of the hydrogel were characterized by FTIR, SEM and magnetic property, respectively. In addition, the delivery behavior of carbamazepine from the hydrogel bead was studied.The CBZ cumulative release amount in pH 1.5 was smaller than in pH 6.8, the sequential release circumstance showed that the released amount of CBZ was 22.77% within 2 h and 91.63% after 24 h.The release of carbamazepine from the hydrogel bead at various pH values was analyzed by a semi-empirical equation,and it was found that the drug release mechanisms were either “anomalous transport” or “case-II transport”.The hydrogel bead possess magnetic property.The results clearly indicated that the hydrogel bead occupate magnetic/pH sensitivety, the magnetic/pH sensitive chitosan/alginate hydrogel bead may be a potential polymeric carrier for controlled the delivery of carbamazepine. This study may become an important experimental evidences of preparing an implantable magnetic nano-drug delivery system for treatment of the epilepsy.

© KESS All rights reserved

INTRODUCTION

Superparamagnetic carrier exhibit magnetic property, they can be guided and aggregated more conveniently only when external magnetic field is added. These carriers can release their contents at a desired rate, only when and/or where the release is needed, most are based on Fe_3O_4 nanoparticles. They could arrive exactly at the targeted tissue and deliver the loaded drug there with the help of an external magnetic field [1,2].

Alginates have ability to form gels by reaction with divalent cations such as Ca^{2+}, this network can entrap drugs[3]. The gelation of alginate can be carried out under an extremely mild environment with the help of non-toxic reagents.

Author for Correspondence:
Email: gsliping@163.com

Upon mixing, gel beads could be reinforced by chitosan[4], because the carboxyl residues of alginate and the amino groups of chitosan interact ionically to form polyelectrolyte complex, which is studied as a coating on alginate hydrogel beads. Complexation of chitosan and alginate reduces the porosity of alginate hydrogel beads and decreases the leakage of the encapsulated drugs[5,6].

Epilepsy is a chronic condition characterized by recurrent unprovoked seizures. It is caused by paradoxical discharge of diseased region. It has recently been noted that there is a weak magnetic field because of electromagnetic induction when epilepsy seizure. We focus our attention on this phenomenon and try to develop a magnetic drug delivery carrier. Based on this carrier, drugs can be induced to diseased region conveniently. Thus, epileptic discharge is able to be suppressed at the onset of seizures[7].

Carbamazepine is used primarily in the treatment of epilepsy and bipolar disorder, as well as trigeminal neuralgia. It has variable

dissolution leading to irregular and delayed absorption [8-13].About one third of all patients with epilepsy are resistant to treatment, and widespread systemic and central side effects limit the most optimal use of drugs. In contrast, drug delivery to epileptogenic focus is considered to be a promising and safe alternative [14-16].

To optimize the preparation technology, this work presented a magnetic alginate-chitosan hydrogel bead through the $L_9(3^4)$ orthogonal Test, followed our previous work preparation [17-19], drugs were encapsulated within the gel network together with Fe_3O_4. Thus, drugs possess potential magnetic property, it is promising that anticonvulsant could respond to the neuromagnetic fields and move to the epileptogenic focus so as to suppress the paradoxical discharges. Accordingly, side effects and teratogenic effect are reduced. The nature of beads was also been investigated, the influence of magnetic Fe_3O_4 nanoparticle on the CBZ delivery system including loading efficiency, swelling characteristic and release behavior were definite. Under this premise, we look forward to establishing a new magnetic sustained-release implant for the controlled release of CBZ. This kind of implant could be given by subcutaneous injection. Therefore, it is more convenient to take medicine. In addition, the implants would have excellent sustained release function, and they could target to the epilepsy focus under the effect of magnetic Fe_3O_4 nanoparticle.

MATERIALS AND METHODS

Materials

Chitosan (MW is 8.0 $\times 10^5$, degree of deacetylation is 89%) 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 (Shanghai, 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. (Suzhou, China). All the other chemicals and reagents used were of analytical grade.

Preparation of carbamazepine magnetic alginate-chitosan hydrogel beads

The experiment of carbamazepine magnetic alginate-chitosan hydrogel beads was arranged by $L_9(3^4)$orthogonal design (Table 1 and 2). Alginate solution (w/v) was prepared by dissolving sodium alginate (1.5 g, 2.0 g, 2.5 g) in 100 mL of deionized water. Chitosan solution (w/v) was prepared by dissolving chitosan (0.5 g, 1.0 g, 1.5 g) in 100 mL 1% acetic acid solution. CBZ (0.075 g, 0.1 g, 0.125 g) and magnetic Fe_3O_4 nanoparticles (wt% = 1:1, 1:2, 1:3) were mixed with 10 mL alginate solution 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 40 mL of calcium bath (1.5%, 2.0%, 2.5%) for 30 min under gentle magnetic stirring. The distance between the edge of the needle and the surface of the solution was 5 cm. Then the magnetic calcium-alginate hydrogel beads were prepared by ionic polymerization. The wet magnetic calcium-alginate beads were rinsed with deionized water before being transferred into chitosan solution (0.5%, 1.0%, 1.5%). After stirring for 30 min, the resulting magnetic alginate-chitosan hydrogel beads were collected and rinsed with deionized water. The optimization (2.5%, alginate; 1.0%, chitosan; 2.5%, $CaCl_2$; 1:3, Fe_3O_4) chosen by the results of orthogonal design (Table 2) was used for testing the performance of magnetic hydrogel beads.

Scanning electron microscopy

Micrographs of the samples were taken using a SEM (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.

FTIR spectroscopy

Individual beads were crushed with pestle in an agate mortar, 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 min. The 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 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, 18.018 μg/mL. The standard solutions were determined by UV-spectrophotometry (UV-2401PC, Shimadzu Co., Japan) at 285 nm, ethanol alone was taken as control.

Determination of encapsulation efficiency and loading efficiency

After preparation of CBZ magnetic calcium-alginate hydrogel beads, the mixture of calcium chloride solution and deionized water-rinsed CBZ magnetic calcium-alginate hydrogel beads was transferred into 50 mL volumetric flask, and deionized water was added to scales. The resulting solution was diluted 12.5 times with deionized water after filtering. The amount of free CBZ in the filtrate was determined by UV-spectrophotometry at 285 nm, deionized water was taken as control because there is no absorption of blank magnetic hydrogel beads at 285nm. 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 drug based on the weight of drug loaded hydrogel bead.

Encapsulation efficiency (%) =
[(the amount of initial carbamazepine-the amount of free carbamazepine)/the amount of initial carbamazepine]×100 (1)

Loading efficiency (%) =
[(the amount of initial carbamazepine-the amount of free carbamazepine)/weight of drug loaded beads]×100 (2)

Swelling analysis

Accurately weighed amounts of dried gel beads 10 mg were respectively dipped in 15 mL hydrochloric acid solution (pH 1.5) and phosphate buffer solutions (pH 6.8) prepared according to the Chinese Pharmacopoeia (2005) at 37±0.5°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:

$$SR = (W-W_0)/W_0 \quad (3)$$

Where W is the weight of the beads in the swollen state and W_0 is the initial weight of the beads.

Moreover, swelling characteristic of the beads in different intensity of magnetism (0 Oe, 60 Oe, 1000 Oe, 3200 Oe) was also determined.

Magnetic property

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

Magnetic responsibility of the beads can be clarified by the response time to a given magnetic field of about 3200 Oe.

Drug release studies

Accurately weighed amounts of 60 mg CBZ magnetic 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 taken 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 being filtered through 0.45 μm hydrophilic millipore filter membrane, the drug release percent was determined using Eq. (4).

$$\text{Drug release (\%)} = [R_t / L] \times 100 \quad (4)$$

Where L and R_t represent the initial amount of drug loaded and cumulative amount of drug 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 hydrochloric acid solution (pH 1.5) for 2 h. At predetermined time points, the percentage of cumulative amount of released CBZ was determined as previously described. The statistical analysis was also done on release data of the magnetic hydrogel beads in pH 1.5 and 6.8 with the one-way analysis of variance.

Release kinetics

The mathematical models Higuchi $M_t/M_\infty = kt^{1/2}$ equations was fitted to individual dissolution data with linear regression. The drug release mechanisms of hydrogel beads were described by a semi-empirical equation.

Table 1: Factors and Levels Table of $L_9(3^4)$ Orthogonal Test

Levels	A[%]	B[%]	C[%]	D[w/w]
1	1.5	0.5	1.5	1:1
2	2.0	1.0	2.0	1:2
3	2.5	1.5	2.5	1:3

The alginate concentration (A), the chitosan concentration (B), the $CaCl_2$ concentration (C), the weight ratio of Fe_3O_4 to polymer (D)

Table 2: The Results of $L_9(3^4)$ orthogonal Test Design

Formulation	A	B	C	D	Encapsulation efficiency[%]	Loading efficiency[%]	Comprehensive score[%]
1	1	1	1	1	24.71	94.37	53.54
2	1	2	2	2	26.04	90.12	58.05
3	1	3	3	3	24.81	93.05	59.93
4	2	1	2	3	27.81	94.04	60.93
5	2	2	3	1	20.12	94.64	57.38
6	2	3	1	2	24.12	93.94	59.03
7	3	1	3	2	28.25	96.70	62.48
8	3	2	1	3	29.10	96.25	62.68
9	3	3	2	1	20.47	96.17	58.32
k_1	56.840	58.983	58.417	56.413			
k_2	59.113	59.370	59.100	59.853			
k_3	61.160	58.760	59.597	60.847			
R	4.320	0.610	1.180	4.434			

Mean value(k) and range(R)

Table 3: The Results of Variance Analysis

Factors	Sum of squares	Freedom	Mean square	F	Difference significance
A	28.019	2	49.070	19.000	*
B	0.571	2	1.000	19.000	
C	2.106	2	3.688	19.000	
D	32.457	2	56.874	19.000	*

$F_{0.05}(2, 2)=19.0$; $F_{0.01}(2, 2) = 99.0$

Table 4: Estimated Parameters and Drug Release Mechanism of Magnetic Alginate-Chitosan Beads in Media of pH 1.5 and 6.8

pH	n	k	r	Drug Transport Mechanism
1.5	0.4289	2.8609	0.9836	Fickian Diffusion
6.8	0.4711	3.7136	0.9838	Anomalous transport

Kinetic constants (k), diffusional exponents (n), and correlation coefficients (r), by linear regression of log (M_t/M_∞) vs. 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.

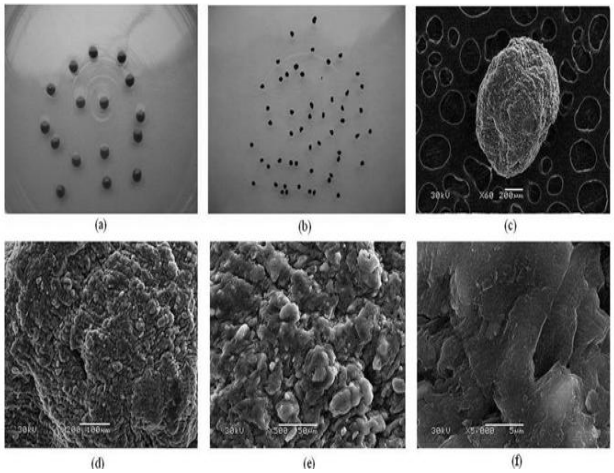

Figure 1. Wet beads (a); dried beads (b). SEM micrographs of the surface morphology of CBZ magnetic alginate-chitosan hydrogel beads: magnification(c×60), (d×500), (e×1000), (f×5000)

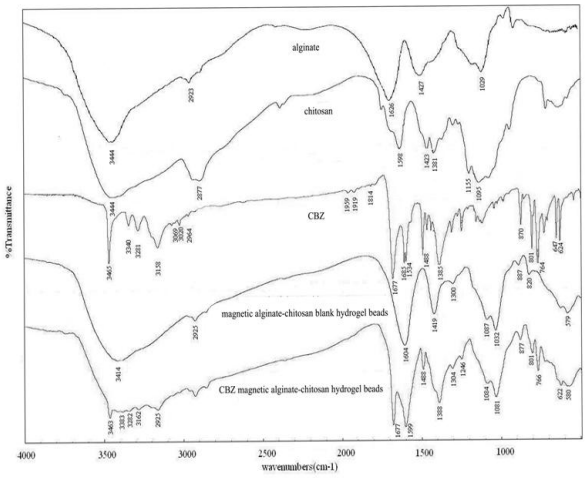

Figure 2. The FTIR spectra of chitosan, sodium alginate, magnetic alginate-chitosan blank hydrogel beads, CBZ, and CBZ magnetic alginate-chitosan hydrogel beads

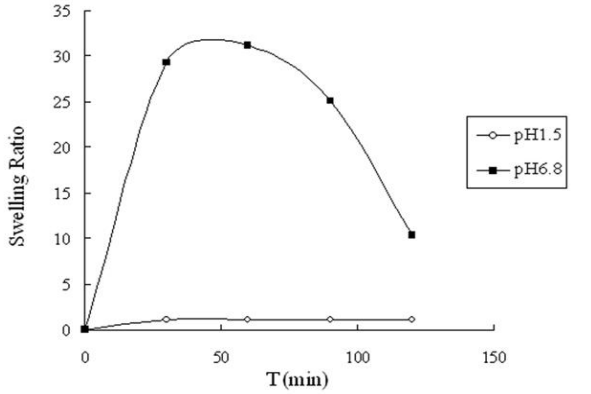

Figure 3. Swelling profiles of dry CBZ magnetic alginate-chitosan hydrogel beads in hydrochloric acid solution (pH 1.5) and phosphate buffer (pH 6.8) at 37 ± 0.5°C

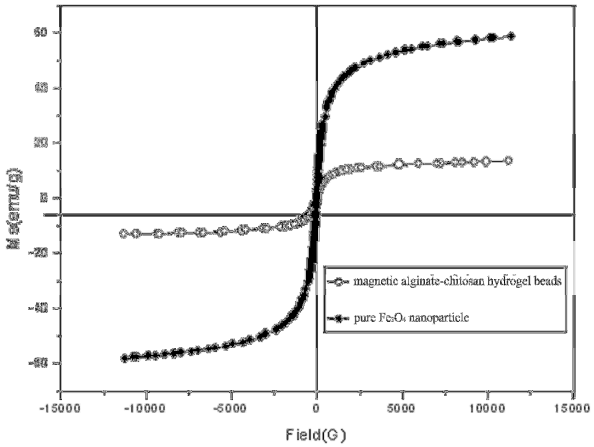

Figure 4. Magnetization curve of magnetic alginate-chitosan hydrogel beads

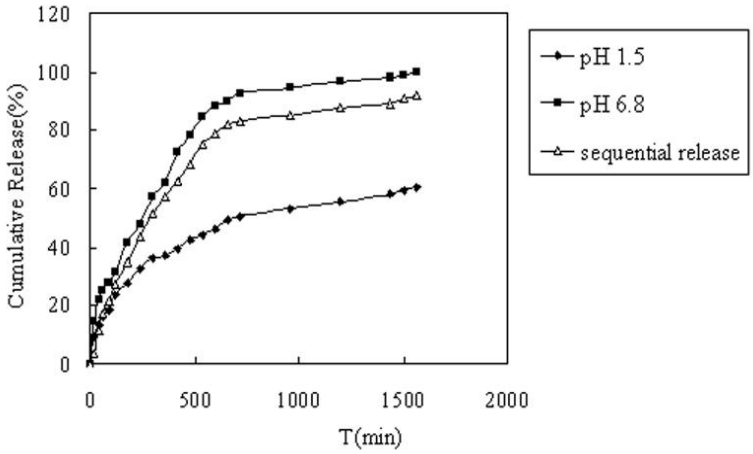

Figure 5. The cumulative release profiles of CBZ magnetic alginate-chitosan hydrogel beads in media of pH 1.5 and 6.8 at 37±0.5°C

RESULTS

Morphology of the beads

As in Figure 1, the wet CBZ magnetic alginate-chitosan hydrogel bead was spherical, smooth and dark brown. The diameter was about 3.5-4.5 mm. After drying in air, the beads had a rough structure and decreased volume, the diameter was about 1-2 mm (Figure 1 a and b). Detailed examination of the surface structure revealed that dried CBZ magnetic alginate-chitosan hydrogel beads had a large surface area with the presence of many pores and some cracks (Figure 1 d-f).

FTIR spectroscopy

The FTIR spectra of chitosan, sodium alginate, magnetic alginate-chitosan blank hydrogel beads, CBZ, CBZ magnetic alginate-chitosan hydrogel beads are shown in Figure 2. The characteristic absorption bands of chitosan and alginate were observed in the FTIR spectra of magnetic alginate-chitosan blank hydrogel beads. The absorption band at 1598 cm^{-1} of chitosan shifted to 1604 cm^{-1}, 3444 cm^{-1} shifted to 3414 cm^{-1} and came broad. The characteristic absorption peak of magnetic Fe_3O_4 also appeared at round 579 cm^{-1}.

The absorption band of CBZ at 1677 cm^{-1} was detected at the same position of CBZ magnetic alginate-chitosan hydrogel beads. The absorption bands at 3465 and 3158 cm^{-1} shifted to 3463 and 3162 cm^{-1}.

Swelling behaviors of bead

Figure 3 shows the swelling behavior of the magnetic beads. The test beads exhibited higher swelling rates when exposed to the slightly alkaline environment of phosphate buffer solutions (pH 6.8). The swell ratio of the magnetic hydrogel beads was 38.67 in phosphate buffer solutions (pH 6.8), it was nearly 40 times higher than in hydrochloric acid solution (pH 1.5). In addition, magnetic intensity had no effect on swelling ratio of magnetic hydrogel beads.

Magnetic property

Figure 4 shows the magnetization curve of magnetic alginate-chitosan hydrogel beads. Comparing with the reference value of the pure magnetic Fe_3O_4 nanoparticles (58.57 emu/g), the saturation magnetization (*Ms*) of the magnetic alginate-chitosan hydrogel beads was relatively small (13.24 emu/g), no remanence was observed.

Response time of the beads to magnetic field decreased quickly with the increasing of the weight ratio of magnetic Fe_3O_4 nanoparticles. The higher the weight ratio of magnetic Fe_3O_4 to polymer, the shorter the response time and the better the magnetic response property.

Drug release study

Figure 5 shows CBZ release profiles of the magnetic hydrogel beads in various media (pH 1.5 and 6.8) at 37 ± 0.5°C. The release characteristics in two media were obviously different from each other. During 24 h, cumulative release percentage of CBZ in pH 1.5 and 6.8 was respectively 60.45 and 100%. The sequential release circumstance was also shown in Figure 5, the released amount of CBZ was 22.77% within 2 h and 91.63% after 24 h. The one-way analysis of variance showed the release of the magnetic hydrogel beads had statistics difference (p<0.05). That is to say, there was significant difference between pH 1.5 and 6.8.

DISCUSSION

Characterization of magnetic alginate-chitosan hydrogel beads

Calcium-alginate hydrogel beads were obtained by dropping aqueous solution of sodium alginate into $CaCl_2$. Meanwhile, magnetic Fe_3O_4 nanoparticles and drugs mixed with sodium alginate were encapsulated into the gel network. Next, strong ionic interactions between the carboxyl residues of the alginate and the amino terminals of the chitosan occurred to form a polyelectrolyte complex. This complex can be used to stabilize the hydrogel and reduce the porosity of the alginate beads[20].

The orthogonal experiment analysis (Table 3) indicated that the concentration of alginate and the weight ratio of Fe_3O_4 to polymers are the most remarkable influencing factors on the magnetic hydrogel beads preparation. The surface morphology variation of magnetic alginate-chitosan hydrogel beads was caused by the dehydration. It is indicated that the integrity of alginate-chitosan bead was seriously destroyed in the drying process[21].

FTIR spectroscopy

In Figure 2, the FTIR spectra of chitosan, sodium alginate, magnetic alginate-chitosan blank hydrogel beads, CBZ, CBZ magnetic alginate-chitosan hydrogel beads were shown. The FTIR spectrum of chitosan showed a weak band of -OH stretching at 2877 cm^{-1}, the absorption band of

the carbonyl (C=O) stretching of the secondary amide (amide I band) at 1655 cm^{-1}, and the bending vibrations of the N-H (N-acetylated residues, amide II band) at 1598 cm^{-1}[22]. The peaks at 1423 and 1381 cm^{-1} belong to the N-H stretching of the amide, ether bonds and N-H stretching (amide III band) respectively. The peaks observed at 1095 and 1033 cm^{-1} were the secondary hydroxyl group (characteristic peak of -CH-OH in cyclic alcohols, C-O stretch) and the primary hydroxyl group (characteristic peak of -CH_2-OH in primary alcohols, C-O stretch)[23]. 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}. For the magnetic alginate-chitosan blank hydrogel beads, the peaks at 1604, 1419, 1087, and 1032 cm^{-1} were the characteristic absorption band of chitosan and alginate, the stretching vibration of -OH and -NH_2 at 3444 cm^{-1} shifted to 3414 cm^{-1} and came broad after the reaction with alginate, indicating the polyelectrolyte complexes formed between chitosan and alginate. The characteristic absorption peak of Fe_3O_4 at 579 cm^{-1} revealed that magnetic Fe_3O_4 nanoparticle was encapsulated into the hydrogel beads.

In the FTIR spectra of CBZ, 1677 cm^{-1} belongs to the -CO-R vibration, characteristic bands of 3465 and 3158 cm^{-1} correspond to the symmetrical and asymmetrical N-H stretching vibrations of primary amide groups[9].Also, the absorption band of -CO-R and N-H stretching vibrations were detected in the FTIR spectra of CBZ magnetic hydrogel beads. It is indicated that CBZ was successfully encapsulated into the hydrogel network.

Swelling behaviors of beads

As in Figure 3, the swelling degree of dried gel beads in pH 1.5 was small, that is because magnetic alginate-chitosan hydrogel beads were stable in pH 1.5. The beads tended to shrink when exposed to the acidic environment, because the carboxylate groups of alginate were protonated at low pH values (<4) and hence the electrostatic repulsion among these groups lessened and shrinkage was favored[3,24]. With the increase of pH, carboxyl groups of alginate that were not cross linked by Ca^{2+} or disrupted from calcium-alginate cross linking network were ionized and absorbed water, which resulted in higher swelling degree. On the other hand, due to the chelating action of phosphate ions, the affinity of phosphate to calcium was stronger than that of alginate[25]. So the disruption of gel matrix occurred faster in pH 6.8 than in 1.5.

Magnetic property

It can be seen from figure 4 that the hysteresis and coercivity were almost undetectable (no remanence effect), that is the magnetic beads remain satisfactory superparamagnetism at room temperature. The *M*s of the magnetic alginate-chitosan hydrogel beads was about 13.24 emu/g. Comparing with the reference value of the pure magnetic Fe_3O_4 nanoparticles (58.57 emu/g), the reduced *M*s could be attributed to the low content of Fe_3O_4 nanoparticles in the beads. Although the beads exhibited relatively low *M*s, they showed satisfactory magnetic-responsive aggregation and redispersion property in deionized water. That is, the prepared bead possess satisfactory magnetic responsive ability, they can be readily guided with the help of external magnetic field[1].

Drug release study

The CBZ cumulative release amount in pH 1.5 was smaller than in pH 6.8, because only drug adsorbed at beads dissolved in release media. And in phosphate buffer (pH 6.8), drugs encapsulated into the hydrogel beads released and dissolved continuously with the swelling and disruption of magnetic beads. For the sequential release, after being transferred into pH 6.8, the drugs encapsulated inner of the beads began to release with swelling of the hydrogel network, so cumulative amount of CBZ increased quickly.

Drug release 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 and 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

$$M_t/M_\infty = k_1 t^n \text{ or } \log (M_t/M_\infty) = \log k_1 + n \log t \qquad (5)$$

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.

Kinetic parameters *n* and k_1 were calculated from the plot of log (M_t/M_∞) versus log *t*. 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 drug release from polymer was due to Fickian diffusion [6]. 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 alginate-chitosan hydrogel beads in different pH is shown in Table 4. In pH 1.5, values of *n* was 0.4289, the release was because of Fickian diffusion. Meanwhile, values of *n* in pH 6.8 (0.4711) was between 0.43 and 0.85, the release mechanism was because of anomalous transport (both diffusion and erosion mechanisms). CBZ release was controlled both by diffusion and disintegration of the magnetic alginate-chitosan gel matrix in pH 6.8.

CONCLUSIONS

This study demonstrated that Magnetic/pH Sensitive alginate-chitosan hydrogel beads with satisfactory shape could be prepared by electrostatic interaction. The Magnetic/pH Sensitive alginate-chitosan hydrogel beads showed excellent superparamagnetism and controlled release property.Drugs could have potential superparamagnetism because of the presence of Fe_3O_4 nanoparticle.They could be induced by the weak neuromagnetic fields and locate at the epileptogenic zone. Thus, paradoxical discharge is able to be controlled rapidly. Further study on a magnetic nano-drug delivery system is carrying out. We look forward to establishing a target controlled preparation, which can be implanted by subcutaneous injection. Consequently, drugs could be released at the condition of physiological pH, and localize at the epileptogenic zone under the action of neuromagnetic fields,drug concentration at epileptogenic focus increased in time, paradoxical discharge could be inhibited effectively.

ACKNOWLEDGEMENTS

This study was supported by the medical subject fund of Lanzhou University Second Hospital (Grant No: YJ2010-08).

DECLARATION OF INTEREST

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

REFERENCES

[1] Yang WC, Xie R, Pang XQ, Ju XJ, Chu LY.Preparation and characterization of dual stimuli-responsive microcapsules with a superparamagnetic porous membrane and thermo-responsive gates. J Membr Sci 2008;321:324-30.

[2] Liu XQ, Kaminski MD, Chen HT, Torno M, Taylor LT, Rosengart AJ.Synthesis and characterization of highly-magnetic biodegradable poly (d, l-lactide-co-glycolide) nanospheres. J Control Release 2007; 119:52-8.

[3] Bouropoulos PG.Swelling studies and in vitro release of verapamil from calcium alginate and calcium alginate-chitosan beads. Int J Pharm 2006;323:34-42.

[4] Murata Y, Miyamoto E, Kawashima S.Additive effect of chondroitin sulfate and chitosan on drug release from calcium-induced alginate gel beads. J Control Release 1996;38: 101-8.

[5] George M, Abraham T.Polyionic hydrocolloids for the intestinal delivery of protein drugs: Alginate and chitosan-a review. J Control Release 2006;114:1-14.

[6] Wong TW, Chan LW, Kho SB, Heng PWS.Design of controlled-release solid dosage forms of alginate and chitosan using microwave. J Control Release 2002;84:99-114.

[7] Ceon Ramon, Mark D. Holmes, Jens Haueisen, Paul H. Schimpf, Walter J. Freeman. Scalp potentials and magnetic fields of a fully and partially activated central sulcus. International Congress Series. 2007; 1300:157-160

[8] Sethia S, Squillante E.Physicochemical characterization of solid dispersions of carbamazepine formulated by supercritical carbon dioxide and conventional solvent evaporation method. J Pharm Sci 2002;91:1948-57.

[9] Sethia S, Squillante E.Solid dispersion of carbamazepine in PVP K30 by conventional solvent evaporation and supercritical methods. Int J Pharm 2004;272:1-10.

[10] Rustichelli C, Gamberini G, Ferioli V, Gamberini MC, Ficarra R, Tommasini S. Solid-state study of polymorphic drugs:

carbamazepine. J Pharm Biomed Anal 2000;23: 41-54.
[11] Bertillson L. Clinical pharmacokinetics of carbamazepine.Clin Pharmacokinet 1978;3: 128-43.
[12] Dong WY, Maincent P, Bodmeier R.In vitro and in vivo evaluation of carbamazepine-loaded enteric microparticles. Int J Pharm 2007; 331:84-92.
[13] Machiste EO, Giunched P, Setti M, Conte U.Characterization of carbamazepine in systems containing a dissolution rate enhancer. Int J Pharm 1995;126: 65-72.
[14] Boison D. Engineered adenosine-releasing cells for epilepsy therapy: Human mesenchymal stem cells and human embryonic stem cells. Neurotherapeutics 2009; 6: 278-83.
[15] Vajda FJE.Pharmacotherapy of epilepsy: New armamentarium, new issues.J Clin Neurosci 2007;14:813-23.
[16] Nilsen KE, Cock HR.Focal treatment for refractory epilepsy: Hope for the future? Brain Res Brain Res Rev 2004; 44:141-53.
[17] Dai YN, Li P, Zhang JP, Wang AQ, Wei Q.A novel pH sensitive N-succinyl chitosan/alginate hydrogel bead for nifedipine delivery. Biopharm Drug Dispos 2008; 29:173-84.
[18] Dai YN, Li P, Zhang JP, Wang AQ, Wei Q.Swelling characteristics and drug delivery properties of nifedipine-loaded pH sensitive alginate-chitosan hydrogel beads. J Biomed Mater Res B Appl Biomater 2008;86B:493-500.
[19] Liu HJ, Li P,Wei Q. Magnetic N-succinyl chitosan/alginate beads for carbamazepinedelivery. Drug Dev Ind Pharm, 2010; 36(11): 1286–1294
[20] Albarghouthi M, Fara DA, Saleem M, El-Thaher T, Matalka K, Badwan A.Immobilization of antibodies on alginate-chitosan beads. Int J Pharm 2000; 206:23-34.
[21] Shu XZ, Zhu KJ.The release behavior of brilliant blue from calcium-alginate gel beads coated by chitosan: the preparation method effect. Eur J Pharm Biopharm 2002;53: 193-201.
[22] Sankalia MG, Mashru RC, Sankalia JM, Sutariya VB.Reversed chitosan-alginate polyelectrolyte complex for stability improvement of alpha-amylase: Optimization and physicochemical characterization. Eur J Pharm Biopharm 2007;65:215-32.
[23] Chen SC, Wu YC, Mi FL, Lin YH, Yu LC, Sung HW.A novel pH-sensitive hydrogel composed of N, O-carboxymethyl chitosan and alginate cross-linked by genipin for protein drug delivery. J Control Release 2004;96:285-300.
[24] Ouwerx C, Velings N, Mestdagh MM, Axelos MAV.Physicochemical properties and rheology of alginate gel beads formed with various divalent cations. Polym. Gels Networks 1998;6:393-408.
[25] Sankalia MG, Mashru RC, Sankalia JM, Sutariya VB. Reversed chitosan-alginate polyelectrolyte complex for stability improvement of alpha-amylase: Optimization and physicochemical characterization. Eur J Pharm Biopharm. 2007; 65: 215–232.