CARRIER STRUCTURE, DRUG CARRIER, AND MANUFACTURING METHOD AND USE THEREOF

FIELD OF THE INVENTION

[0001] The present invention relates to a carrier structure, a drug carrier applying the carrier structure, and manufacturing methods and use thereof, more particularly to the drug carrier for inhibiting helicobacter pylori, and the manufacturing methods and use thereof.

BACKGROUND OF THE INVENTION

[0002] In a human body, the gastric acid and pepsin secreted by the stomach can be used for not only decomposing and digesting food but also removing harmful bacteria in the system from the mouth. However, after a human body is infected with helicobacter pylori, the helicobacter pylori can convert urea into alkaline ammonia by its secreted urease to avoid damage by the gastric acid. In the resistance of bacteria by a human immune system, the protection mechanism of stomach may be damaged due to the gastric acid and pepsin, thus causing chronic inflammation or peptic ulcer (damage of the gastric wall or duodenal wall). If no appropriate treatment is taken, complications such as gastrointestinal bleeding, perforation, outlet obstruction, or even gastric cancer may occur. The infection rate of the helicobacter pylori is 100% for chronic gastritis, 90 to 95% for duodenal ulcer, 60 to 80% for gastric ulcer, 80% for gastric lymphoma, and 90% for gastric cancer.

[0003] In general, the infection rate of the helicobacter pylori increases with age, and the prevalence rate varies slightly with the level of development of regions. Almost all adults in developing countries carry such microorganism (The infection rate is approximately 90%), but the infection rate in developed countries drops significantly (The infection rate is approximately 11%).

[0004] In general, a so-called “three-in-one treatment” or “four-in-one treatment” is mainly

used to eradicate the helicobacter pylori. In other words, a combination of proton pump inhibitor and antibiotic is used for the treatment. However, the treatment for eradicating the helicobacter pylori takes time, and the number of pills taken in a single dose is up to about ten. The drugs used to eradicate the helicobacter pylori usually cause dizziness, diarrhea, tongue coating, slow sense of taste, allergies, and other side effects. Thus, patients become unwilling to cooperate, which leads to failure of treatment.

[0005] In the prior art, a technique related to the nanoparticles of cross-linked polyglucosamine and amoxicillin has been disclosed. An anionic surfactant and oil are added and mixed to form a water-in-oil emulsion to encapsulate the cross-linked polyglucosamine by the amoxicillin. In this technique, the average particle size is 100-600 nm, and the total weight of nanoparticles encapsulated by the amoxicillin is at least 5% (w/w). When orally administrated, the residence time of the nanoparticles in stomach is longer than that of the free amoxicillin or micron-scale particles.

[0006] Further, a technique related to a shell-core drug structure has been disclosed. Alginate is used as a base substance to encapsulate a drug to form microspheres, and then a chitin membrane is provided to encapsulate the microspheres to form the shell-core drug structure. A slow-relief effect can be achieved with the help of the alginate in a colloidal state. Such a drug structure may help protect the drug from damage in gastric acid, but when used in the treatment of gastric ulcer, it cannot overcome the shortcomings of having to use a plurality of drugs for the treatment.

[0007] Further, a technique related to a drug structure combining the use of alginate and chitosan has been disclosed. In the drug structure, calcium pantothenate is added to promote the formation of sodium alginate into colloidal particles to encapsulate a drug. The drug structure has an instant release feature and releases the drug within two hours, but this drug structure still cannot overcome the shortcomings of having to use a plurality of drugs for the clinical treatment of gastric ulcer.

[0008] In summary, an improved drug structure may be one of the feasible solutions to break through the bottleneck of the clinical treatment of gastric ulcer. The drugs indicated in the aforementioned techniques relate to the use of alginate and chitosan, but they differ in their effectiveness and all need further improvements. Although alginate and chitosan are promising materials for the preparation of a drug carrier, their relative composition ratio, combining method, carrier size, and other parameters still substantially and significantly affect the efficiency and feature of the manufactured medical structure. Exploring composition ratios and methods with the finest effect is the most critical and has the most creative feature in the related fields of techniques.

[0009] In view of the aforementioned shortcomings in the prior art, the inventor of the present invention based on years of experience to conduct extensive research and experiment, and finally provided a feasible solution to overcome the drawbacks of the prior art.

SUMMARY OF THE INVENTION

[0010] Accordingly, the present invention aims to provide a manufacturing method of a carrier structure including the following steps: providing an aqueous solution of a negatively charged polymer having 100 parts by weight and a pH value from 6 to 8; providing an aqueous solution of sodium tripolyphosphate having 330 to 1000 parts by weight and a pH value from 6 to 8; providing an aqueous solution of chitosan having 830 to 2500 parts by weight and a pH value from 3 to 5; mixing the aqueous solution of the negatively charged polymer, the aqueous solution of sodium tripolyphosphate, and the aqueous solution of chitosan to form a starting mixture; and making the starting mixture react from 5 to 60 minutes to allow the negatively charged polymer, the sodium tripolyphosphate, and the chitosan to self-assemble to form the carrier structure.

[0011] Preferably, the carrier structure has a particle size from 90nm to 150nm.

[0012] Preferably, the carrier structure in the aqueous solution has a surface potential from

15mV to 30mV.

[0013] Preferably, the negatively charged polymer includes an alginic acid salt, heparin, polyacrylic acid, polystyrene sulfonate, polymalic acid, hyaluronic acid, or any combination thereof.

[0014] By the carrier structure manufactured according to the manufacturing method of the present invention, the ingredients thereof not only have excellent biocompatibility, but also improve the pharmaceutical effect with the help of the release of the drug or the residence time of the drug in a body of a patient.

[0015] The present invention further provides a manufacturing method of a drug carrier including the following steps: providing an aqueous solution of a negatively charged polymer having 100 parts by weight and a pH value from 6 to 8; providing an aqueous solution of sodium tripolyphosphate having 330 to 1000 parts by weight and a pH value from 6 to 8; providing an aqueous solution of an active substance having 2000 to 3000 parts by weight and a pH value from 6 to 8; mixing the aqueous solution of the negatively charged polymer, the aqueous solution of sodium tripolyphosphate, and the aqueous solution of the active substance; adding an aqueous solution of chitosan having 830 to 2500 parts by weight and a pH value from 3 to 5 to form an active mixture; and making the active mixture react from 5 to 60 minutes to allow the negatively charged polymer, the sodium tripolyphosphate, the active substance and the chitosan to self-assemble to form the drug carrier.

[0016] Preferably, the drug carrier structure has a particle size from 110nm to 160nm.

[0017] Preferably, the drug carrier structure in the aqueous solution has a surface potential from 15mV to 25mV.

[0018] Preferably, the active substance inhibits the activity of the helicobacter pylori.

[0019] Preferably, the active substance includes amoxicillin, clarithromycin, omeprazole, penicillin or any combination thereof.

[0020] Preferably, the negatively charged polymer is selected from a group consisting of

free alginic acid salt and polyacrylic acid.

[0021] Preferably, the drug carrier encapsulating the active substance has an encapsulation rate from 55% to 75%.

[0022] Preferably, the active ingredient in the drug carrier has a weight equal to 32% to 38% of the weight of the drug carrier.

[0023] By the drug carrier manufactured according to the manufacturing method of the present invention, and the design of the composition ratio and solvent selection, the drug effect can be improved to provide a better treatment effect. In addition, not only is the preparation method of the drug carrier of the present invention simple, but the manufactured drug carrier is also capable of providing higher drug encapsulation rate and stable particle size and surface charge with high biocompatibility.

[0024] In addition, the present invention provides a use of a drug carrier for the manufacture of a medicament for treatment of a gastrointestinal disease, including: providing said drug carrier; and applying an effective dose of the drug carrier to the helicobacter pylori in a body of a host.

[0025] Preferably, the effective dose falls within a range from 1 mg/kg of body weight daily to 10 mg/kg of body weight daily.

[0026] Preferably, the host is a human body.

[0027] Preferably, the gastrointestinal drug further includes an adjuvant, an excipient, a medically acceptable carrier, or any combination thereof.

[0028] Preferably, the gastrointestinal disease is a disease caused by the helicobacter pylori.

[0029] Preferably, the gastrointestinal disease includes chronic gastritis, duodenal ulcer, gastric ulcer, gastric lymphoma, gastric cancer, gastric cancer, gastric mucosal atrophy, gastric intestinal metaplasia or any combination thereof.

[0030] In summary, the type and proportion of the ingredients contained in the carrier structure and the drug carrier of the present invention help the release of the active ingredient

in a living organism and extend the residence time, thus enabling the drug effect to be exerted effectively. In addition, the drug structure of the present invention is designed to combine the ingredients by their mutually attracted static charges, so as to achieve a higher encapsulation rate of the active ingredient. In other words, the drug structure of present invention is a mixed structure of the contained ingredients, but not a shell-core structure, nor a structure that adds and mixes an anionic surfactant and oil to form the water-in-oil emulsion. As a result, the preparation method is much simpler than that of the drug with the conventional shell-core structure or water-in-oil structure.

[0031] Furthermore, when the drug structure of the present invention is adhered to mucosal tissues and near a neutral environment of a cell layer of a gastric wall, the nanostructure of the drug carrier breaks down gradually due to the change of the charge property of chitosan and alginic acid salt or polyacrylic acid, so that the active ingredient in the drug carrier is released. This release property allows the drug to be released at a position where pathogens are gathered and helps improve the treatment effect of the active ingredient.

BRIEF DESCRIPTION OF THE DRAWINGS

[0032] FIG. 1 is a flow chart of a manufacturing method of a carrier structure in accordance with an embodiment of the present invention.

[0033] FIG. 2 is a flow chart of a manufacturing method of a drug carrier in accordance with an embodiment of the present invention.

[0034] FIG. 3 is a graph showing the relation between the particle size, surface potential, and pH value of a sample of a drug carrier of the present invention.

[0035] FIG. 4 is a photo showing the sample of FIG. 3 observed by a transmission electron microscope.

[0036] FIG. 5 is a graph showing the relation between the particle size, surface potential, and pH value of another sample of a drug carrier of the present invention.

[0037] FIG. 6 is a photo showing the sample of FIG. 5 observed by a transmission electron microscope.

[0038] FIGS. 7 and 8 show the in vitro experimental results of a drug carrier of the present invention.

DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0039] The technical contents of the present invention will become apparent with the detailed description of preferred embodiments accompanied with the illustration of related drawings as follows. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0040] The carrier structure and drug carrier of the present invention are prepared by selecting specific type and ratio of ingredients and their mixing sequence. Compared with the prior art, it is more helpful for the present invention to improve the treatment effect of a drug. Specifically, the use of the carrier structure of the present invention together with the drug carrier obtained by an active substance achieves an excellent effect of inhibiting helicobacter pylori by using a single dose and breaks through the technical bottleneck of the conventional gastric ulcer treatment that has to use a multiple of active ingredients simultaneously and the hydrogen proton pump inhibitor.

[0041] In the disclosure of the present invention, the effect of “inhibiting helicobacter pylori” macroscopically refers to the capability of “controlling the size of a helicobacter pylori group”, “shrinking a helicobacter pylori group” and/or “eliminating a helicobacter pylori group” and microscopically refers to the capability of “reducing the physiological effect of helicobacter pylori”, “reducing the contagion of helicobacter pylori” and/or “killing helicobacter pylori”.

[0042] “A substance capable of inhibiting helicobacter pylori” refers to the aforementioned substance having the aforementioned effect of “inhibiting helicobacter pylori” such as

antibiotic, amoxicillin, clarithromycin, omeprazole, or penicillin, etc. Specifically, an “active ingredient” refers to a substance capable of inhibiting helicobacter pylori.

[0043] “A substance capable of assisting the inhabitation of helicobacter pylori” refers to a substance having the capability of “inhibiting helicobacter pylori” indirectly to help the aforementioned substance “capable of inhibiting helicobacter pylori” to exert its effects. More specifically, it is necessary to add the hydrogen proton pump inhibitor to the three-in-one or four-in-one in the current drug administration for the treatment of gastric ulcer antibiotic. The hydrogen proton pump inhibitor does not have the capability of inhibiting helicobacter pylori directly, but just helps improve the effect of antibiotic only. Specifically, a substance “capable of helping inhibiting substance” may be the aforementioned hydrogen proton pump inhibitor, bismuth, etc.

[0044] “A substance capable of helping the inhabitation of helicobacter pylori” does not include any substance that is designed in the pharmacology to assist the application of a drug, improve the taste of a drug, or extend the expiration date of a drug. In other words, it does not include any additive commonly used in a drug structure such as a medical carrier, a flavoring agent, or a preservative, etc.

[0045] In the manufacturing method of the present invention, chitosan is used, which is a natural polymer that has drawn much attention in recent years. The source of chitosan comes from a high-concentration hot alkaline treatment of chitin to conduct deacetylation in order to convert an acetyl group of the chitin into an amino group. Since chitosan molecules carry a positive charge and has a mucoadhesive property in an acidic environment, it can be widely used in the medical field. A commercial chitosan generally has a molecular weight from 3,800 to 20,000 kDa, a deacetylation percentage of 66 to 95%, and a highly reactive group such as the amino group and hydroxyl group. Thus, it can be manufactured into other derivatives and dissolved in weakly acidic aqueous solution and made in form of films, balls, fibers, or gels.

[0046] The chitosan used in the present invention has a molecular weight of 4,000 kDa,

5,000 kDa, 6,000 kDa, 7,000 kDa, 8,000 kDa, 9,000 kDa, 10,000 kDa, 11,000 kDa, 12,000 kDa, 13,000 kDa, 14,000 kDa, 15,000 kDa, 16,000 kDa, 17,000 kDa, 18,000 kDa, 19,000 kDa, 20,000 kDa or any molecular weight falling within this range. The chitosan used in the present invention has a deacetylation percentage of 66%, 68%, 70%, 72%, 74%, 76%, 78%, 80%, 82%, 84%, 86%, 88%, 90%, 92%, 94% or any deacetylation percentage falling within this range. However, the chitosan preferably has a molecular weight around 15,000 Da and a deacetylation percentage of 84%.

[0047] The negatively charged polymer used in the present invention refers to the negatively charged polymer in a neutral or acidic environment, such as a negatively charged polymer in an environment with a pH value from 1 to 8, or a negatively charged polymer in an environment with a pH value from 2 to 8 preferably. The negatively charged polymer includes but not limited to alginic acid salt, heparin, polyacrylic acid, polystyrene sulfonate, polymalic acid, and hyaluronic acid. Preferably, the negatively charged polymer is alginic acid salt or polyacrylic acid.

[0048] The active ingredient refers to a compound intended for achieving the effects of treatment, prevention, and detection. In the present invention, the active ingredient is a compound used for the treatment of gastric ulcer, which is the aforementioned active substance that inhibits the activity of the helicobacter pylori. The active ingredient of this invention includes amoxicillin, clarithromycin, omeprazole, or penicillin. The drug structure of the present invention may contain several different substances capable of inhibiting the helicobacter pylori. Preferably, the drug structure of the present invention only uses a single substance as the active ingredient for inhibiting helicobacter pylori.

[0049] Preferably, chitosan, negatively charged polymer, sodium tripolyphosphate, and/or active ingredient are in a solution state which can help control the pH value of the aforementioned ingredients and keep each ingredient in an appropriate charged state.

[0050] The present invention will become clearer in light of the following detailed

description of an illustrative embodiment of this invention described in connection with the drawings. It is intended that the embodiments and figures disclosed herein are to be considered illustrative rather than restrictive.

[0051] In a manufacturing method of a carrier structure in accordance with an embodiment of the present invention, the manufacturing method includes the steps S11 to S13. In the step S11, an aqueous solution of a negatively charged polymer having 100 parts by weight and a pH value from 6 to 8, an aqueous solution of sodium tripolyphosphate having 330 to 1000 parts by weight and a pH value from 6 to 8, and an aqueous solution of chitosan having 830 to 2500 parts by weight and a pH value from 3 to 5 are prepared.

[0052] In other words, when the aqueous solution of the negatively charged polymer has 100 parts by weight, the aqueous solution of sodium tripolyphosphate may be 330, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 100 parts by weight or any other part by weight falling within this range, and the aqueous solution of chitosan may be 830, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, 1800, 1850, 1900, 1950, 2000, 2050, 2100, 2150, 2200, 2250, 2300, 2350, 2400, 2450, 2500 parts by weight or any other value falling within this range.

[0053] Wherein, the aqueous solution of the negatively charged polymer may have a concentration of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20 mg/ml or any other value falling within this range and a pH value of 6.0, 6.2, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0 or any other value falling within this range. The aqueous solution of sodium tripolyphosphate may have a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 mg/ml or any other value falling within this range; and a pH of 6.0, 6.2, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0 or any other value falling within this range. The aqueous solution of chitosan may have a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 mg/ml or any other value falling within this range and a pH of 3.0, 3.2, 3.4, 3.6, 3.8,

4.0, 4.2, 4.4, 4.6, 4.8, 5.0 or any other value falling within this range.

[0054] In the step S12, the aforementioned aqueous solutions of the negatively charged polymer, sodium tripolyphosphate, and chitosan are mixed to form a starting mixture. After the reaction has taken place for a period of time, the aforementioned aqueous solutions self-assemble to form the carrier structure of the present invention. Preferably, the reaction time is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31, 32, 33, 34, 35, 36, 37, 38, 39, 40, 41, 42, 43, 44, 45, 46, 47, 48, 49, 50, 51, 52, 53, 54, 55, 56, 57, 58, 59, 60 minutes or any other value falling within this range. Preferably, the reaction temperature is 4℃, 5℃, 6℃, 7℃, 8℃, 9℃, 10℃, 11℃, 12℃, 13℃, 14℃, 15℃, 16℃, 17℃, 18℃, 19℃, 20℃, 21℃, 22℃, 23℃, 24℃, 25℃, 26℃, 27℃, 28℃, 29℃, 30℃ or any other value falling within this range.

[0055] The carrier structure manufactured according to the aforementioned method can maintain a stable charged state and a stable structure during storage. Moreover, the aforementioned method does not include the steps related to the uniformity of the particle size and the minimization of carrier structure in order to manufacture the carrier structure with the required particle size. To maintain an appropriate charged state in each ingredient of the carrier structure and maintain the carrier structure, the carrier structure is preferably maintained and/or used in a solution state. Preferably, the pH value of the solution is adjusted during the storage and/or use to maintain the charge state of each ingredient more stably. For example, the appropriate pH value is 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, or any value falling within this range.

[0056] In the carrier structure of this embodiment, chitosan, negatively charged polymer, and sodium tripolyphosphate are combined with each other through the electrostatic attraction to self-assemble into particles of a specific size, thus having a fine biocompatibility. Preferably, the particle size of the assembled carrier structure is in a nanoscale such as 80 nm, 85 nm, 90nm, 95 nm, 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm,

140 nm, 145 nm, 150 nm, 155 nm, 160 nm, or any value falling within this range. The aforementioned nanoparticle is beneficial to the absorption efficiency of a drug in a living organism, which enhances the function and use of the drug carried by the carrier structure.

[0057] The surface potential at the surface of the assembled carrier structure is a positive value. Preferably, the surface potential is 15 mV, 16 mV, 17 mV, 18 mV, 19 mV, 20 mV, 21 mV, 22 mV, 23 mV, 24 mV, 25 mV, 26 mV, 27 mV, 28 mV, 29 mV, 30 mV, or any value falling within this range. The structure with the aforementioned surface charge is beneficial to the residence time of the carrier structure in stomach.

[0058] In a manufacturing method of a drug carrier in accordance with another embodiment of the present invention, the manufacturing method includes the steps S21 to Step S24. In the step S21, an aqueous solution of a negatively charged polymer having 100 parts by weight and a pH value from 6 to 8, an aqueous solution of sodium tripolyphosphate having 330 to 1000 parts by weight and a pH value from 6 to 8, and an aqueous solution of an active substance having 2000 to 3000 parts by weight and a pH value from 6 to 8 are provided; and the aqueous solutions of the negatively charged polymer, sodium tripolyphosphate, and the active substance are mixed.

[0059] In other words, the aqueous solution of the negatively charged polymer has 100 parts by weight, the aqueous solution of sodium tripolyphosphate may have 330, 350, 400, 450, 500, 550, 600, 650, 700, 750, 800, 850, 900, 950, 100 parts by weight, or any value falling within this range; and the aqueous solution of the active substance may have 2000, 2050, 2100, 2150, 2200, 2250, 2300, 2350, 2400, 2450, 2500, 2550, 2600, 2650, 2700, 2750, 2800, 2850, 2900, 2950, 3000 parts by weight, or any value falling within this range.

[0060] Wherein, the aqueous solution of the negatively charged polymer may have a concentration of 0.01, 0.02, 0.03, 0.04, 0.05, 0.06, 0.07, 0.08, 0.09, 0.10, 0.11, 0.12, 0.13, 0.14, 0.15, 0.16, 0.17, 0.18, 0.19, 0.20mg/ml, or any value falling within this range and a pH value of 6.0, 6.2, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0, or any value falling within this range. The

aqueous solution of sodium tripolyphosphate may have a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 mg/ml, or any other value falling within this range and a pH value of 6.0, 6.2, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0 or any other value falling within this range. The aqueous solution of the active substance may have a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 mg/ml, or any other value falling within this range and a pH value of 6.0, 6.2, 6.4, 6.6, 6.8, 7.0, 7.2, 7.4, 7.6, 7.8, 8.0, or any other value falling within this range.

[0061] In the step S22, the aforementioned aqueous solutions of the negatively charged polymer, sodium tripolyphosphate, and active substance are reacted for a period of time. Then the step S23 proceeds. Preferably, the reaction time is 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25 minutes, or any other value falling within this range. Preferably, the reaction temperature is 5℃, 6℃, 7℃, 8℃, 9℃, 10℃, 11℃, 12℃, 13℃, 14℃, 15℃, 16℃, 17℃, 18℃, 19℃, 20℃, 21℃, 22℃, 23℃, 24℃, 25℃, or any other value falling within this range.

[0062] In the step S23, the aqueous solution of chitosan having 830 to 2500 parts by weight and a pH value from 3 to 5 is added to form an active mixture. Then the step S24 proceeds. The active mixture is reacted for 5 to 60 minutes so that the negatively charged polymer, sodium tripolyphosphate, active substance, and chitosan self-assemble to form the drug carrier containing the active substance. In other words, when the aqueous solution of the negatively charged polymer has 100 parts by weight, the aqueous solution of chitosan may have 830, 850, 900, 950, 1000, 1050, 1100, 1150, 1200, 1250, 1300, 1350, 1400, 1450, 1500, 1550, 1600, 1650, 1700, 1750, 1800, 1850, 1900, 1950, 2000, 2050, 2100, 2150, 2200, 2250, 2300, 2350, 2400, 2450, 2500 parts by weight, or any other value falling within this range, a concentration of 0.1, 0.2, 0.3, 0.4, 0.5, 0.6, 0.7, 0.8, 0.9, 1.0, 1.1, 1.2, 1.3, 1.4, 1.5, 1.6, 1.7, 1.8, 1.9, 2.0 mg/ml, or any other value falling within this range and a pH value of 3.0, 3.2, 3.4, 3.6, 3.8, 4.0, 4.2, 4.4, 4.6, 4.8, 5.0, or any other value falling within this range.

[0063] Preferably, the reaction time after adding the chitosan is 5, 6, 7, 8, 9, 10, 11, 12, 13, 14, 15, 16, 17, 18, 19, 20, 21, 22, 23, 24, 25, 26, 27, 28, 29, 30 minutes, or any other value falling within this range. Preferably, the reaction temperature is 4℃, 5℃, 6℃, 7℃, 8℃, 9℃, 10℃, 11℃, 12℃, 13℃, 14℃, 15℃, 16℃, 17℃, 18℃, 19℃, 20℃, 21℃, 22℃, 23℃, 24℃, 25℃, 26℃, 27℃, 28℃, 29℃, 30℃, or any other value falling within this range.

[0064] Similarly, carrier structure manufactured according to the aforementioned method can maintain a stable charged state and a stable structure during storage. The aforementioned method does not include the steps related to the uniformity of the particle size and the minimization of carrier structure in order to manufacture the carrier structure with the required particle size. To maintain an appropriate charged state in each ingredient of the carrier structure and maintain the carrier structure, the carrier structure is preferably maintained and/or used in a solution state. Preferably, the pH value of the solution is preferably adjusted during the storage and/or use to maintain the charge state of each ingredient more stably. For example, the appropriate pH value is 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, or any value falling within this range.

[0065] In the carrier structure of this embodiment, chitosan, negatively charged polymer, and sodium tripolyphosphate are combined with each other through the electrostatic attraction to self-assemble into particles of a specific size, thus having a fine biocompatibility. Preferably, the particle size of the assembled carrier structure is in a nanoscale such as 100 nm, 105 nm, 110 nm, 115 nm, 120 nm, 125 nm, 130 nm, 135 nm, 140 nm, 145 nm, 150 nm, 155 nm, 160 nm, 165 nm, 170 nm, or any other value falling within this range. The aforementioned nanoparticle is beneficial to the absorption efficiency of a drug in a living organism to enhance the function and use of the drug carried by the carrier structure.

[0066] In addition, the surface potential at the surface of the assembled carrier structure is a positive value. Preferably, the surface potential is 15 mV, 16 mV, 17 mV, 18 mV, 19 mV, 20

mV, 21 mV, 22 mV, 23 mV, 24 mV, 25 mV, or any other value falling within this range. The structure with the aforementioned surface charge is beneficial to the residence time of the carrier structure in stomach.

[0067] It is noteworthy that the sequence of mixing the three ingredients, namely the aqueous solutions of the negatively charged polymer, chitosan, and sodium tripolyphosphate in the manufacturing method of the carrier structure and drug carrier in accordance with the present invention can be changed. Preferably, the aqueous solutions of the negatively charged polymer, chitosan, and sodium tripolyphosphate are mixed directly in the manufacturing method of the carrier structure, and the aqueous solutions of the negatively charged polymer and sodium tripolyphosphate are mixed first and then the mixed aqueous solution is mixed with the aqueous solution of the active substance in the manufacturing method of the drug carrier in order to improve the encapsulation rate.

[0068] In this embodiment, the drug carrier encapsulating the active substance has an encapsulation rate of 55%, 56%, 57%, 58%, 59%, 60%, 61%, 62%, 63%, 64%, 65%, 66%, 67%, 68%, 69%, 70%, 71%, 72%, 73%, 74%, 75%, or any other value falling within this range. The active ingredient has a weight approximately equal to 30%, 31%, 32%, 33%, 34%, 35%, 36%, 37%, 38%, 39%, 40% of the weight of the drug carrier or any other value falling within this range.

[0069] In addition, the present invention further provides a use of a drug carrier for the manufacture of a medicament for treatment of a gastrointestinal disease. In the use according to an embodiment, the use includes: manufacturing a drug carrier according to the aforementioned manufacturing method, and applying an effective dose of the drug carrier to the helicobacter pylori in a body of a host or the group thereof. In addition, the use further includes other steps that are not intended for the inhabitation of the helicobacter pylori, such as reducing the number of times of taking the drug, soothing the side effects caused by the drug, assisting the individual to be treated to rest.

[0070] In this embodiment, the effective dose is the dose of the drug carrier capable of inhibiting helicobacter pylori effectively without causing physical discomfort to the host or producing side effects. Preferably, the effective dose is 0.1, 0.5, 1.0, 1.5, 2.0, 2.5, 3.0, 3.5, 4.0, 4.5, 5.0, 5.5, 6.0, 6.5, 7.0, 7.5, 8.0, 8.5, 9.0, 9.5, 10 mg/kg/day, or any other value falling within this range. In addition, the daily effective dose may be divided and applied for several times or applied once every several days. Preferably, the effective dose is once a day, twice a day, three times a day, once every two days, once every three days, or any arrangement falling within this range.

[0071] The carrier structure and drug carrier in accordance with an embodiment of the present invention are described below, and the physical and chemical properties are analyzed and measured.

[0072] In the carrier structure in accordance with an embodiment of the present invention, a chitosan solution having a concentration of 0.5 mg/ml and pH=4.0 is prepared and then dissolved in 0.01M acetic acid; an alginic acid salt solution or a polyacrylic acid solution having a concentration of 0.05 mg/ml and a pH=7.4 is prepared and then dissolved in 0.01 N NaOH; a sodium tripolyphosphate solution having a concentration of 0.5 mg/ml and a pH=7.4 is prepared and then mixed in 0.01 N NaOH; and an amoxicillin solution having a concentration of 1.5 mg/ml and a pH=7.4 is prepared and then mixed into 0.01 N NaOH. In the steps S11 to S13, samples prepared according to the proportion listed in Tables 1 and 2 are selected, the particle size and surface potential of the obtained samples 1 to 7 are analyzed, and the results are given in Table 3.

[0073] Table 1:

Sample	Chitosan:	Alginic acid salt:	Sodium tripolyphosphate
1	25	1	10
2	16.7	1	6.7

3	12.5	1	5
4	8.3	1	3.3

[0074] Table 2:

Sample	Chitosan:	Polyacrylic acid:	Sodium tripolyphosphate
5	25	1	10
6	16.7	1	6.7
7	12.5	1	5

[0075] Table 3:

Sample	Average particle size (nm)	PDI	Surface potential (mV)
1	111.7±6.65	0.364	25.9±1.12
2	118.1±2.49	0.402	25.9±0.37
3	127.6±5.27	0.363	25.2±0.55
4	147.2±8.80	0.406	22.2±0.24
5	97.0±1.56	0.378	24.3±0.45
6	112.1±2.37	0.299	23.1±0.55
7	129.9±3.41	0.296	21.3±0.80

[0076] In a drug carrier according to an embodiment of the present invention, the settings of the chitosan solution, alginic acid salt solution, and sodium tripolyphosphate solution are the same as those for the aforementioned carrier structure. In the steps S21 to S24, samples prepared according to the proportion listed in Tables 4 and 5 are selected, and the particle size,

the surface potential, and the encapsulation rate of the active substance of the obtained samples A to G are analyzed, and the results are given in Table 6.

[0077] Table 4:

Sample	Chitosan:	Alginic acid salt:	Sodium tripolyphosphate:	Amoxicillin
A	25	1	10	30
B	16.7	1	6.7	20
C	12.5	1	5	15
D	8.3	1	3.3	10

[0078] Table 5:

Sample	Chitosan:	Alginic acid salt:	Sodium tripolyphosphate:	Amoxicillin
E	25	1	10	30
F	16.7	1	6.7	20
G	12.5	1	5	15

[0079] Table 6:

Sample	Average Particle size (nm)	PDI	Surface Charge (mV)	Encapsulation Rate (%)
A	111.7±3.01	0.373	24.4±0.73	71.6±11.1
B	119.2±0.75	0.390	23.7±0.50	74.5±3.39
C	124.7±1.85	0.340	23.3±0.64	73.7±2.96
D	153.2±4.10	0.382	21.1±0.93	75.4±0.51
E	110.3±4.26	0.381	23.4±0.98	59.1±0.56
F	118.5±6.11	0.342	21.7±0.48	59.1±0.10

G	139.6±1.91	0.261	21.1±0.41	58.9±1.17

[0080] According to the data listed in Tables 3 Table 6, the carrier structure and drug carrier prepared according to the aforementioned embodiments are nanoscale, and thus they are expected to have excellent absorption efficiency in a living organism. In addition, the carrier structure and drug carrier of the present invention are not shell-core structures, so that the method of the present invention uses a solution type manufacturing method instead of a water-in-oil emulsification method. In other words, the solution of each ingredient is mixed uniformly, and the carrier structure and drug carrier of the present invention is manufactured with the help of the mutual electrostatic attraction produced by their charge property. The solution type manufacturing method not only has the advantage of simple operation, but also provides a good homogeneity (since the PDI data shows that both of the manufactured drug carrier and the manufactured drug structure have a small particle size).

[0081] To simulate the situation of the carrier structure and the drug carrier of the present invention in the environment of gastric acid, Samples A and E are placed in an environment with pH value equal to 2.5, 4.0, 5.0, 6.0, and 7.4 to represent different gastric acid environments and different depths of the mucosal layer of the gastric wall and the cell layer of the gastric wall. Then a nanoparticle size and potential analyzer (Zetasizer NANO-ZS90) and a transmission electron microscope TEM are used for analysis, and the change of the structure characteristics is observed.

[0082] With reference to FIGS. 3 to 6 for the analysis results, FIGS. 3 and 4 show the results of the sample A, and FIGS. 5 and 6 show the results of the sample E. In a gastric acid environment similar to that having a pH=2.5, the nanostructure of the drug carrier of either sample A or sample E will not be eroded or damaged by the gastric acid, and the surface thereof still carries a positive charge from 39 to 40 mV. Since the chitosan, alginic acid salt,

and polyacrylic acid contained in the drug carrier of the present invention have the property of adhering to mucosal tissues, the drug carrier will not tend to adhere with a mucosal layer of the gastric wall. The mucosal layer of the gastric wall has a pH value of about 4.0, 5.0 and 6.0 depending on its depth. Both the sample A and the sample E obviously show that the particle size of the nanostructure of the drug carrier is stable in the environment with a pH=4.0 and 5.0, and the surface potential is still maintained at a level from 20 to 30 mV. On the other hand, when the drug carrier is situated at a simulated environment with a deeper layer of the gastric mucosa with a pH=6.0 or a simulated environment of a cell layer of the gastric wall with a pH=7.4, the chitosan is changed to a non-charged state, the surface potential tends to be 0 mV, and the nanostructure of the drug carrier becomes loosened due to the pH value tending to be neural. In addition to the observation from Tables, the change of the nanostructure may also be observed from the TEM photos. An obvious aggregation shows in the environment with a pH=6.0, making it difficult to see the nanoparticle structure.

[0083] FIGS. 7 and 8 show the in vitro result of the drug carrier of the present invention applied to a living body. In an in vitro experiment of a living body, a suspension of helicobacter pylori (having a maximum inhibitory concentration of about 0.5 μg/ml) is obtained first, and then amoxicillin is added separately into the sample 1, sample 5, sample A, and sample E (the drug concentration of amoxicillin is fixed to 0.5 μg/ml). After the aforementioned suspension of the helicobacter pylori is cultivated continuously for 48 hours, OD_{450} is measured to determine the effect of the inhabitation of the helicobacter pylori. The experimental results are shown in FIG. 7. The active substance contained in the samples A and E of the present invention is amoxicillin, so either adding the samples A and E or adding amoxicillin basically has the same inhabitation effect. The experimental results have shown that even though no active substance is contained, the carrier structure of the sample 5 of the present invention has a capability of slightly inhibiting the helicobacter pylori. Through these experiments, it is obvious to see that both the carrier structure and the drug carrier of the

present invention have the capability of inhibiting helicobacter pylori, and the effect is more obvious when they are used together with a drug carrier having an appropriate active substance.

[0084] In summary, when the drug structure of the present invention is adhered to mucosal tissues and disposed near a neutral environment of the cell layer of the gastric wall, the change of charge property of the chitosan and the alginic acid salt or polyacrylic acid breaks down the nanostructure of the drug carrier gradually, so that the active ingredient in the drug carrier will be released. Such release property allows the drug to be released at a position where pathogens are gathered, and helps improve the treatment effect of the active ingredient.

[0085] While the present invention has been described by means of specific embodiments, numerous modifications and variations could be made thereto by those skilled in the art without departing from the scope and spirit of the present invention set forth in the claims.

WHAT IS CLAIMED IS:

1. A manufacturing method of a carrier structure, comprising the following steps:

   providing an aqueous solution of a negatively charged polymer having 100 parts by weight and a pH value from 6 to 8;

   providing an aqueous solution of sodium tripolyphosphate having 330 to 1000 parts by weight and a pH value from 6 to 8;

   providing an aqueous solution of chitosan having 830 to 2500 parts by weight and a pH value from 3 to 5;

   mixing the aqueous solution of the negatively charged polymer, the aqueous solution of sodium tripolyphosphate, and the aqueous solution of chitosan to form a starting mixture; and

   making the starting mixture react from 5 to 60 minutes to allow the negatively charged polymer, the sodium tripolyphosphate, and the chitosan to self-assemble to form the carrier structure.

2. The manufacturing method according to claim 1, wherein the carrier structure has a particle size from 90nm to 150nm.
3. The manufacturing method according to claim 1, wherein the carrier structure in the aqueous solution has a surface potential from 15mV to 30mV.
4. The manufacturing method according to claim 1, wherein the negatively charged polymer comprises an alginic acid salt, heparin, polyacrylic acid, polystyrene sulfonate, polymalic acid, hyaluronic acid, or any combination thereof.
5. A carrier structure, manufactured according to the manufacturing method of claim 1.
6. A manufacturing method of a drug carrier, comprising the following steps:

   providing an aqueous solution of a negatively charged polymer having 100 parts by weight and a pH value from 6 to 8;

providing an aqueous solution of sodium tripolyphosphate having 330 to 1000 parts by weight and a pH value from 6 to 8;

providing an aqueous solution of an active substance having 2000 to 3000 parts by weight and a pH value from 6 to 8;

mixing the aqueous solution of the negatively charged polymer, the aqueous solution of sodium tripolyphosphate, and the aqueous solution of the active substance;

adding an aqueous solution of chitosan having 830 to 2500 parts by weight and a pH value from 3 to 5 to form an active mixture; and

making the active mixture react from 5 to 60 minutes to allow the negatively charged polymer, the sodium tripolyphosphate, the active substance, and the chitosan to self-assemble to form the drug carrier.

7. The manufacturing method according to claim 6, wherein the drug carrier structure has a particle size from 110nm to 160nm.
8. The manufacturing method according to claim 6, wherein the drug carrier structure in the aqueous solution has a surface potential from 15mV to 25mV.
9. The manufacturing method of claim 6, wherein the active substance comprises amoxicillin, clarithromycin, omeprazole, penicillin, or any combination thereof.
10. The manufacturing method of claim 6, wherein the negatively charged polymer comprises alginic acid salt, heparin, polyacrylic acid, polystyrene sulfonate, polymalic acid, hyaluronic acid, or any combination thereof.
11. The manufacturing method of claim 6, wherein the drug carrier encapsulating the active substance has an encapsulation rate from 55% to 75%.
12. The manufacturing method of claim 6, wherein the active substance in the drug carrier has a weight equal to 32% to 38% of the weight of the drug carrier.
13. A drug carrier, manufactured according to the manufacturing method of claim 7.
14. Use of a drug carrier according to claim 13 in the manufacture of a medicament for

treatment of a gastrointestinal disease wherein an effective dose of the drug carrier is to be applied to helicobacter pylori in a body of a host.

15. The use according to claim 14, wherein the effective dose falls within a range from 1 mg/kg of body weight daily to 10 mg/kg of body weight daily.
16. The use according to claim 14, wherein the host is a human body.
17. The use according to claim 14, wherein the gastrointestinal disease is a disease caused by helicobacter pylori.
18. The use according to claim 17, wherein the gastrointestinal disease comprises chronic gastritis, duodenal ulcer, gastric ulcer, gastric lymphoma, gastric cancer, gastric mucosal atrophy, gastric intestinal metaplasia, or any combination thereof.