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(54) **COMPOSITION FOR CONTROLLED RELEASE AND METHOD FOR MANUFACTURING THE SAME**

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(57) **ABSTRACT**

A method for manufacturing a composition for controlled release including multiple steps is provided. Firstly, an inclusion and a polymer aqueous solution are provided. The polymer aqueous solution has weight percentage ranging from 0.4% to 2%. Then, the inclusion is mixed with the polymer aqueous solution well so as to form a mixture; a molding process is performed on the mixture to form a plurality of colloids. Next, a cross-linking process is performed to conduct a reaction between the colloids and an aqueous solution having divalent metal ion so as to form a plurality of reticular structures. Finally, a drying process is performed on the reticular structures. A composition for controlled release is also provided.

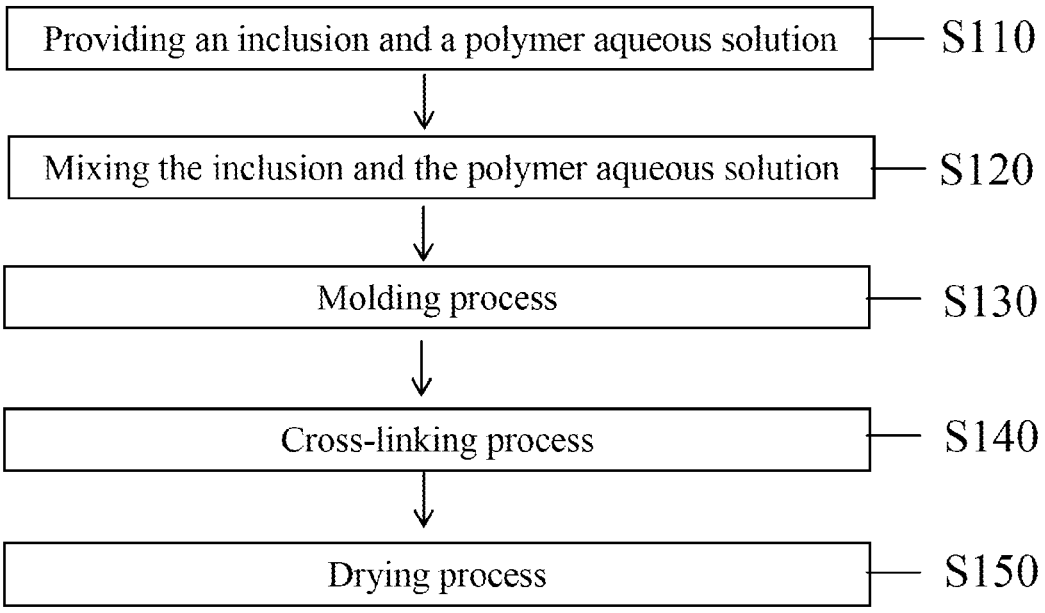
Providing an inclusion and a polymer aqueous solution
S110
Mixing the inclusion and the polymer aqueous solution
S120
Molding process
S130
Cross-linking process
S140
Drying process
S150

FIG. 1

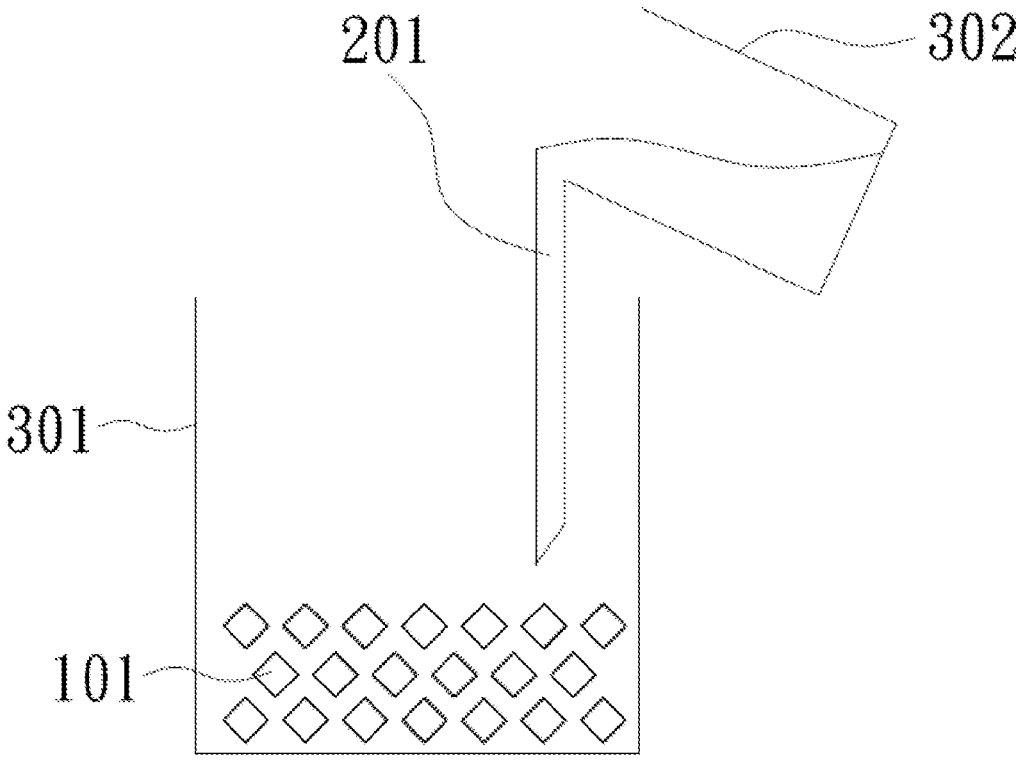

FIG. 2A

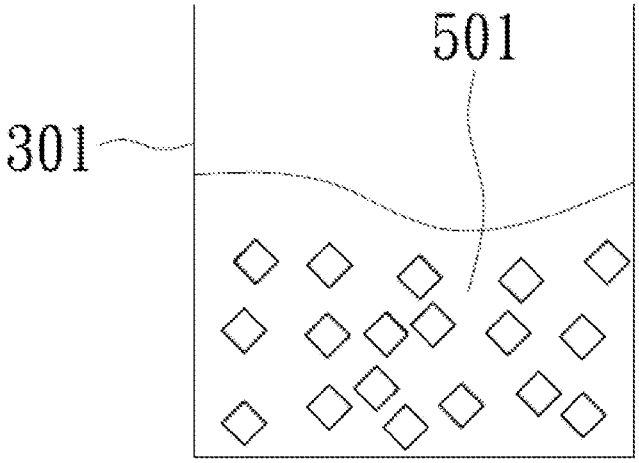

FIG. 2B

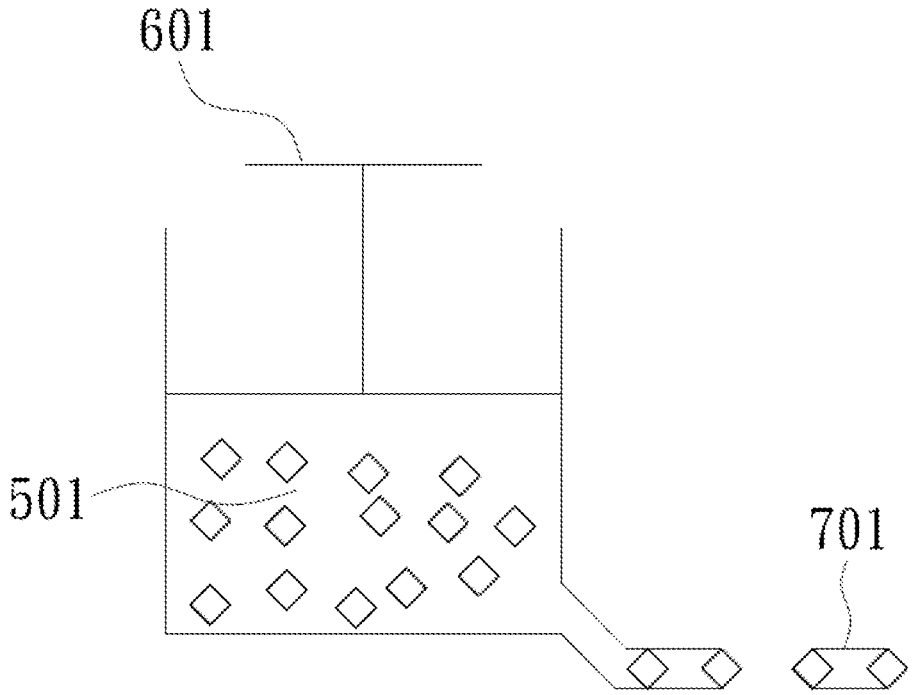

FIG. 2C

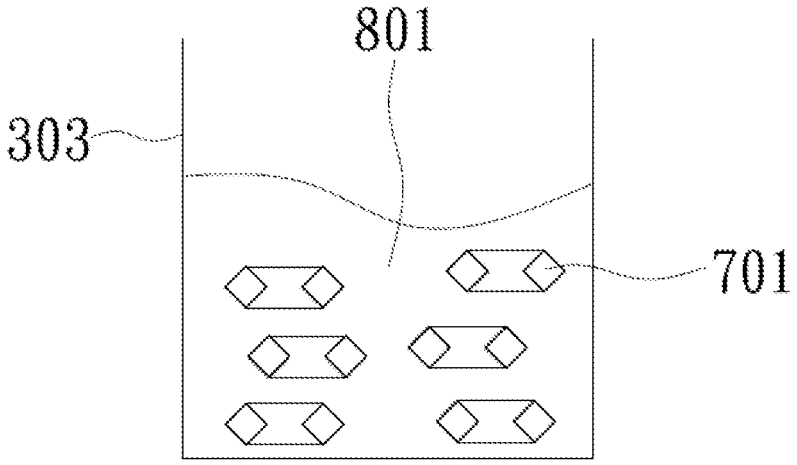

FIG. 2D

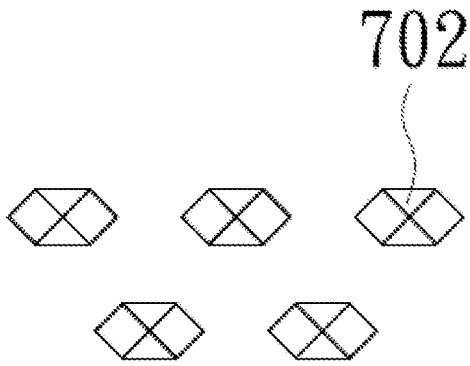

FIG. 2E

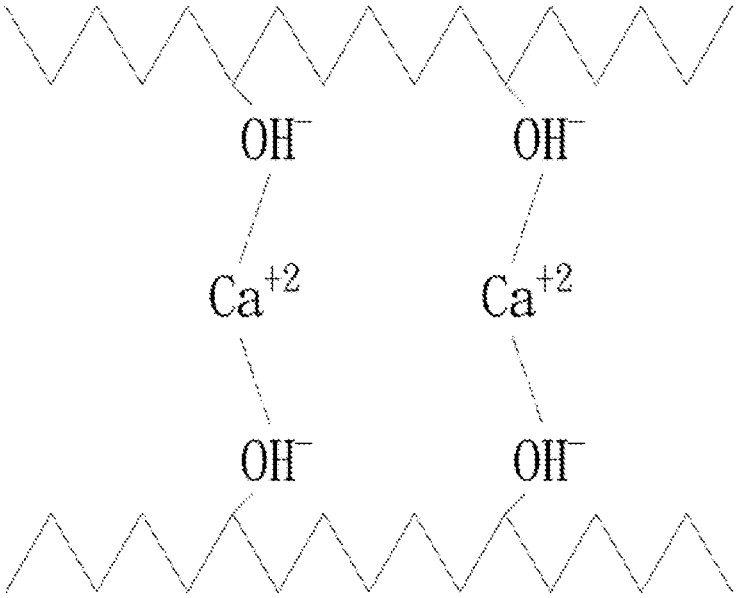

FIG. 3

COMPOSITION FOR CONTROLLED RELEASE AND METHOD FOR MANUFACTURING THE SAME

CROSS-REFERENCE TO RELATED APPLICATION

[0001] This application claims the benefit of U.S. Provisional Application No. 61/933,675, filed on Jan. 30, 2014 in the United State Patent and Trademark Office, the disclosure of which is incorporated herein by reference.

BACKGROUND OF THE INVENTION

[0002] 1. Field of the Invention

[0003] The present invention generally relates to composition for controlled release and method for manufacturing the same.

[0004] 2. Description of the Related Art

[0005] Recently, it is found that controlled release system or sustained release system is better than dump system in pharmaceuticals, cosmetics and personal skincare, food sciences, and agriculture. There are six categories about controlled release systems: Diffusion-Control System, Matrix Diffusion System, Swelling-Controlled System, Erosion-Controlled System, Chemically-Controlled System, and Osmotic Pumps System.

[0006] However, the above-mentioned conventional technology cannot achieve long-term releasing of inclusions stably like the present invention. In addition, the thickness of capsule shell is difficult to composite during manufacturing. In other words, this invention is to manufacture a composition for achieve releasing inclusions stably and conserving activity of the inclusions.

[0007] The above information disclosed in this Background section is only for enhancement of understanding of the background of the described technology and therefore it may contain information that does not form the prior art that is already known to a person of ordinary skill in the art.

SUMMARY OF THE INVENTION

[0008] The primary objective of the present invention is to provide a method for manufacturing a composition for controlled release including multiple steps is provided.

[0009] Therefore, to achieve the foregoing objective, the present invention provides a method for manufacturing a composition for controlled release, comprising the following steps: (a) utilizing an inclusion and a polymer aqueous solution, wherein the weight percentage ranging from 0.4% to 2%; (b) mixing the inclusion and the polymer aqueous solution to form a mixture; (c) molding the mixture to form a plurality of colloids; (d) cross-linking by adding an aqueous solution of divalent metal ions to colloids to form reticular structures, and (e) drying of the reticular structures.

[0010] The following description of the drawing and examples are presented in order to allow for a more thorough understanding of the subject matter and experimental procedure of the present invention. The drawing and examples are meant to illustrate the embodiments of the present invention, and are not to be construed as limiting the scope of the invention.

BRIEF DESCRIPTION OF THE DRAWINGS

[0011] The detailed structure, operating principle and effects of the present invention will now be described in more details hereinafter with reference to the accompanying drawings that show various embodiments of the invention as follows.

[0012] FIG. **1** is a flow diagram of manufacturing a composition for controlled release;

[0013] FIG. **2**A illustrates an inclusion and a polymer aqueous solution in different containers.

[0014] FIG. **2**B illustrates the mixing process of manufacturing a composition for controlled release.

[0015] FIG. **2**C illustrates the molding process to manufacture the composition for controlled release.

[0016] FIG. **2**D illustrates the addition of aqueous solution of divalent metal ions to the composition for controlled release.

[0017] FIG. **2**E illustrates the drying process to manufacture the composition for controlled release.

[0018] FIG. **3** illustrates the partial microscopic schematic diagram for cross-linking in the composition for controlled release

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

[0019] Details of the objects, technical configuration, and effects of the present invention will be described more fully hereinafter with reference to the accompanying drawings, in which exemplary embodiments of the invention are shown. The like reference numerals indicate the like configuration throughout the specification, and in the drawings, the length and thickness of layers and regions may be exaggerated for clarity. The technical content of the present invention will become apparent by the detailed description of the following embodiments and the illustration of related drawings as follows. As used herein, the term "and/or" includes any and all combinations of one or more of the associated listed items.

[0020] Various embodiments will now be described more fully with reference to the accompanying drawings, in which illustrative embodiments are shown. The inventive concept, however, may be embodied in various different forms, and should not be construed as being limited only to the illustrated embodiments. Rather, these embodiments are provided as examples, to convey the inventive concept to one skilled in the art. Accordingly, known processes, elements, and techniques are not described with respect to some of the embodiments.

[0021] The invention is described more fully hereinafter with reference to the accompanying drawings, in which embodiments of the invention are shown. This invention may, however, be embodied in many different forms and should not be construed as limited to the embodiments set forth herein. Rather, these embodiments are provided so that this disclosure is thorough, and will fully convey the scope of the invention to those skilled in the art.

[0022] One of object of the present invention is to provide a method for manufacturing a composition for controlled release. The process is described thereafter.

[0023] With reference to FIG. **1**, a flow diagram of manufacturing a composition for controlled release is illustrated. A method for manufacturing a composition for controlled release comprises the following steps: (S**110**) utilizing an inclusion and a polymer aqueous solution, wherein the weight percentage ranging from 0.4% to 2%; (S**120**) mixing the inclusion and the polymer aqueous solution to form a mixture; (S**130**) molding the mixture to form a plurality of colloids; (S**140**) cross-linking by the addition of an aqueous

solution of divalent metal ions to the colloids to form reticular structures, and (S**150**) drying of the reticular structures.

[0024] With reference to FIG. **1** and FIG. **2**A, the manufacturing of a composition of controlled release are illustrated. In this invention, STEP S**110** provides an inclusion **101** and a polymer aqueous solution **201**. The inclusion **101** can be plant extracts, probiotics, such as lactobacillus, yeasts, polysaccharides, fat, proteins, saponins, medicines, organic compounds, bio-extracts or combinations thereof. The size of the inclusion **101** can be on the order of micrometer to nanometer. The inclusion **101** can be in liquid or in solid form. The polymer aqueous solution **201** can be prepared from plant-extract polymers such as an alginate extract aqueous solution or chemical-synthesized polymers. The inclusion **101** and the polymer aqueous solution **201** can be placed in containers **301** and **302** such as beakers or graduates.

[0025] With reference to FIG. **1** and FIG. **2**B, the manufacturing of a composition of controlled release are illustrated. In this invention, STEP S**120** mixes an inclusion **101** and a polymer aqueous solution **201** to form a mixture **501** in a container **301**. The mixing process can be manually stirred by a stirring stick or automatically stirred by a homogenizer, an ultrasonic oscillator or a cell disruptor. The volume ratio of the inclusion **101** and the polymer aqueous solution **201** ranges from ⅛-4, preferably ¼-2. It should be noted that, if weight percentage of the polymer aqueous solution above 4%, the polymer aqueous solution would be too dense to stir. Thus, the inclusion **101** cannot be evenly dispersed in the polymer aqueous solution **201**.

[0026] In this preferred embodiment, pH value of the polymer aqueous solution **201** may be ranging from 4 to 10. Furthermore, different inclusions have its optimal pH environment. For instance, yeast extract prefers pH 5.5.

[0027] With reference to FIG. **1** and FIG. **2**C, the manufacturing of the composition of controlled release are illustrated. In this invention, STEP S**130** is molding a mixture **501** and forms a plurality of colloids **701**. Referring to FIG. **2**C, the mixture **501** is transferred from a container **301** and compressed by a compressor **601**. The mixture **501** forms the plurality of colloids **701** through an exit of the compressor **601**. In the preferred embodiment, the compressor **601** can be automated machine or a manual operated tool such as an extruder, a syringe, a titration tube, a pipette, or cake-decorating tool. If users need large size of the colloids **701**, the size of the colloids **701** can be adjusted through this molding process by the compressor **601**. For instance, the compressor **601** has a large opening to exit.

[0028] With reference to FIG. **1** and FIG. **2**D, the manufacturing of the composition of controlled release are illustrated. In this invention, STEP S**140** is cross-linking by adding an aqueous solution of divalent metal ions **801** to colloids **701** to form reticular structures by cross-linking reaction. Referring to FIG. **2**D, the aqueous solution having divalent metal ion **801** is placed in a container **303** and place the colloids **701** into the aqueous solution **801**. Or the colloids **701** are placed in a container and the aqueous solution having divalent metal ion **801** is poured into the container (not shown). Furthermore, spray of the aqueous solution having divalent metal ion **801** to the surface of the colloids **701** can also result in the cross-linking reaction (not shown). The cross-linking mainly occurs on the surface of the colloids **701** not inside of the colloids **701** by spraying of the aqueous solution **801**. Thus, this leads to fast release of a composition for controlled release.

[0029] In the preferred embodiment, the divalent metal ions in the aqueous metal solution **801** is Be^{2+}, Ma^{2+}, Ca CS^{2+}, Ba^{2+} or combinations thereof. The equivalent concentration of the aqueous solution having divalent metal ion **801** is from 0.05-5N.

[0030] When the colloids **701** contact with the aqueous solution with divalent metal ion **801**, the cross-linking reaction occurs shown in FIG. **3**. The colloids **701** having a polymer aqueous solution **201** such as alginate extract have hydroxyl groups. This hydroxyl group and divalent metal ion such as calcium ion form an ionic bond and the colloids **701** become a reticular structure **702** shown in FIG. **2**E. The inclusion **101** is encapsulated inside the reticular structure **702** or on the reticular structure **702**. In addition, the degree of cross-linking can be adjusted by different divalent metal ion. Ba^{2+} has higher degree of cross-linking than Ca^{2+} and Cs^{2+}.

[0031] With reference to FIG. **1** and FIG. **2**E, the manufacturing of the composition of controlled release are illustrated. In this invention, STEP S**150** dries the reticular structure **702** and forms the composition for controlled release. The drying process can be air-drying or freeze-drying of the reticular structure **702**. If users need to shorten the drying process, then forced air current generated from a fan or heat from a heater may be applied (not shown). If a heater is used for drying the reticular structure **702**, the heating temperature should not be higher than 120° C. High temperature environment may reduce the activity of the inclusion **101**, such as probiotics. In addition, high temperature environment may only dry the surface of the reticular structure **702** but not the inside of the reticular structure **702**. This results in the reticular structure **702** becoming fragile.

[0032] In this preferred embodiment of the present invention, the drying process step S**150** may increase the storage period of the composition for controlled release.

[0033] In addition, the degree of cross-linking of a reticular structure **702** can be determined by Step S**140** where cross-linking between colloids **701** and aqueous divalent metal ion solution **801** occurs. For example, the following two scenarios have the same concentration of the polymer aqueous solution **201** to form the colloid **701**. If time for cross-linking is shorter within 5 min, the reticular structure **702** of the composition for controlled release will be thinner. On the contrary, if time for cross-linking is longer, such as 5 min-20 min, the condensed reticular structure **702** of the composition for controlled release will be formed. The former with thinner reticular structure **702** releases the inclusions **101** sooner; the later with condensed reticular structure **702** releases the inclusions **101** slower. In addition, the degree of cross-linking of the reticular structure **702** can be determined by the concentration of the polymer aqueous solution **201**. For examples, if the colloid **701** is formed from high concentration of the polymer aqueous solution **201**, time for cross-linking between the colloid **701** and the aqueous solution having divalent ions **801** can be shorten to form the reticular structure **702**. On the contrary, if the colloid **701** is formed from low concentration of the polymer aqueous solution **201**, time for cross-linking needs to increase to form the reticular structure **702**.

[0034] The present invention further provides another method for manufacturing a composition for controlled release. The major difference for manufacturing the composition for controlled release is addition of a surfactant (not shown). For examples, the surfactant can be added into a polymer aqueous solution **201** or an inclusion **101** before the

mixing step S**120**. The surfactant can also be added into a mixture **501** before the molding step S**130**. Preferably, the surfactant is a non-ionic surfactant or an anionic surfactant. In the preferred embodiment, the anionic surfactant is a phospholipid such as phosphatidyl choline, phosphatidyl ethanolamine or phosphatidyl inositol. Furthermore, an alginate extract aqueous solution is hydrophilic. If the inclusion **101** is hydrophobic, the surfactant can used to increase the stability between the alginate extract aqueous solution and the inclusion **101**.

[0035] In agriculture, ampullariidae, or common name the apple snail, becomes a serious threat to rice production because rice seedling is an attractive food source for the snails. Tea tree powder having saponins can damage mucus secretion system of the apple snail and could be used as an organic pesticide in rice farms. However, the tea tree powder would often be prematurely removed by water irrigation or rain in the rice farm after farmers had sprayed the tea tree powder. Consequently, farmers would need to continuously spray tea tree powder in order to prevent the apple snails from eating rice seedlings. Therefore, if the tea tree powder could be released in a controlled fashion in a long-term period, a significant reduction in labor to consistently spray tea tree powder to prevent the growth of apple snails could be achieved.

[0036] In the preferred embodiment of the present invention, compositions of tea tree powder for controlled release comprises following steps: (S**110**) utilizing tea tree powder as an inclusion and an alginate extract polymer aqueous solution, wherein the weight percentage ranging from 0.6% to 1.5%, preferably 0.65%; (S**120**) mixing the tea tree powder and the polymer aqueous solution to form a mixture; (S**130**) molding the mixture to form a plurality of colloids; (S**140**) cross-linking by adding an aqueous solution of divalent metal ions to the colloids to form reticular structures, wherein time for cross-linking is 1 minute, and (S**150**) drying of the reticular structures. Two experiments: experimental group (2 kg composition of tea tree powder for controlled release) and control group (5 kg tea tree powder) were conducted in two different rice farms with the same size (0.1 Hectare). In order to study release of the tea tree power, chemical oxygen demand (COD) was measured from the experimental group and the control group on Day 14, Day 21 and Day 27.

[0037] Please refer to the following table 1:

TABLE 1

No.	Sampling	Group	COD (mg/L)	Loss (%)
1	Day 14	Experimental	55.4	0
		Control	13.8	0
2	Day 21	Experimental	51.7	6.68%
		Control	19.6	−42.03%
3	Day 27	Experimental	38.3	25.92%
		Control	7.2	63.27%

[0038] With reference of Table 1, CODs from experimental group were higher than CODs from control group. CODs from the experimental group were gradually decreased, compared to the control group. This suggests that the compositions of tea tree powder for controlled release can slowly release the tea tree powder in rice farms.

[0039] Furthermore, to enable any person skilled in the art to understand the characteristics the composition for controlled release, the embodiments and the technical principles used are described above. However, these uses are merely exemplary, but not restricted. All variations and modifications of the present invention and the uses thereof are included in the scope of the present invention if they do not depart from the spirit of the disclosure of this specification and drawings. Any limitations for the scope of the present invention should be defined by the appended claims and their equivalents.

What is claimed is:

1. A method for manufacturing a composition for controlled release, comprising the following steps:

(a) utilizing an inclusion and a polymer aqueous solution, wherein weight percentage ranging from 0.4% to 2%;

(b) mixing the inclusion and the polymer aqueous solution to form a mixture;

(c) molding the mixture to form a plurality of colloids;

(d) cross-linking by adding an aqueous solution of divalent metal ions to the colloids to form reticular structures, and

(e) drying of the reticular structures.

2. The method of claim **1**, wherein the volume ratio of the inclusion and the polymer aqueous solution is between ⅛-4.

3. The method of claim **1**, wherein the polymer aqueous solution is an alginate extract aqueous solution.

4. The method of claim **1**, wherein the pH value of the polymer aqueous solution is ranging from 4-10.

5. The method of claim **1**, wherein the divalent metal ion is Be^{2+}, Mg^{2+}, Ca^{2+}, Cs^{2+}, Ba^{2+} or combination thereof.

6. The method of claim **5**, wherein equivalent concentration of the aqueous solution having divalent metal ion is ranging from 0.05-5N.

7. The method of claim **1**, wherein the cross-linking is spraying aqueous solution having divalent metal ion on the surface of the colloids.

8. The method of claim **1**, wherein the cross-linking is immersing the colloids into aqueous solution having divalent metal ion.

9. The method of claim **1**, wherein the drying processing is using freeze-drying to dry the reticular structures.

10. The method of claim **1**, wherein the drying processing is using heater with heating temperature below 120° C. to dry the reticular structures.

11. The method of claim **1**, wherein the drying processing is using air-drying to dry the reticular structures.

12. The method of claim **1**, wherein a surfactant is added before molding.

13. The method of claim **1**, wherein the inclusion is plant extracts, probiotics, yeasts, polysaccharides, fat, proteins, saponins, medicines, organic compounds, bio-extracts or combinations thereof.

14. Compositions of controlled release comprise an inclusion, a polymer aqueous solution and divalent metal ion, wherein the inclusion is encapsulated inside of the reticular structure or on the reticular structure.

15. The method of claim **14**, wherein the inclusion is plant extracts, probiotics, yeasts, polysaccharides, fat, proteins, saponins, medicines, organic compounds, bio-extracts or combinations thereof.

16. The method of claim **14**, wherein the polymer aqueous solution is an alginate extract aqueous solution.

17. The method of claim **14**, wherein the polymer aqueous solution is a chemical-synthesized polymer solution.

18. The method of claim **14**, wherein the divalent metal ion is Be^{2+}, Mg^{2+}, Ca^{2+}, Cs^{2+}, Ba^{2+} or combination thereof.

19. The method of claim **14**, wherein a surfactant is added.

20. The method of claim **14**, wherein the surfactant is phosphatidyl choline, phosphatidyl ethanolamine or phosphatidyl inositol.

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