Notice

DESCRIPTION CN102766267A

A method for preparing chitosan hydrogel containing magnetic nanoparticles

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一种含磁性纳米粒子的壳聚糖水凝胶的制备方法

[0001]

Technical Field

技术领域

[0002]

This invention relates to gel preparation techniques for chitosan and its derivatives, as well as techniques for preparing composite gels of chitosan and its derivatives containing magnetic nanoparticles.

本发明涉及壳聚糖及其衍生物的凝胶制备技术，以及含 磁性纳米粒子的壳聚糖及其衍生物的复合凝胶的制备技术。

[0003]

Background Technology

背景技术

[0004]

Chitosan is obtained from chitin, which is widely found in nature, through deacetylation. Its chemical name is polyglucosamine (1-4)-2-amino-β-D-glucose, and its molecular formula is as follows:

壳聚糖（chitosan）是由自然界广泛存在的几丁质 （chitin）经过脱乙酰作用得到的，化学名称为聚葡萄糖胺 (1-4)-2-氨基-B-D葡萄糖，分子式如下：

[0006]

It is tasteless, odorless, and non-toxic.

其无味、无臭、无毒性。

Chitosan macromolecules contain active hydroxyl and amino groups, which have strong chemical reactivity. Under specific conditions, chitosan can undergo chemical reactions such as hydrolysis, alkylation, acylation, carboxymethylation, sulfonation, nitration, halogenation, oxidation, reduction, condensation, and complexation, which can generate various chitosan derivatives with different properties and good water retention and chemical stability.

壳聚糖大分子中有活泼的羟基 和氨基，它们具有较强的化学反应能力，在特定的条件下， 壳聚糖能发生水解、烷基化、酰基化、羧甲基化、磺化、硝 化、卤化、氧化、还原、缩合和络合等化学反应，可生成各 种具有不同性能的壳聚糖衍生物，且具有良好的保水性和化 学稳定性。

By studying the antibacterial activity, antioxidant properties, and electrolyte adsorption capacity of chitosan and its derivatives, we can apply them to various fields such as daily life and medicine.

通过研究壳聚糖及其衍生物的抗菌活性，抗氧化 性，电解质吸附能力，应用于生活和医学等领域。

Especially in the medical field, chitosan and its derivatives have been widely used as microscopic medical materials, such as drug sustained-release matrix, hemostatic agents, and basic materials for artificial tissues and organs.

尤其在医 疗领域，壳聚糖及其衍生物已经作为微观医疗材料而被广泛 使用，如用作药物缓释基质，止血剂，人造组织和器官的基 础材料等等。

[0007]

Glutaraldehyde (GA), with the molecular formula , has two aldehyde groups on its monomer. It acts on the sulfhydryl, hydroxyl, carboxyl, and amino groups of bacterial proteins, causing them to alkylate, resulting in protein coagulation and bacterial death, thus killing microorganisms.

戊二醛（GA），分子式为 其单体上带有2 个醛基，作用于菌体蛋白的疏基、羟基、羧基和氨基，可使 之烷基化，引起蛋白质凝固造成细菌死亡起到对微生物的杀 灭作用。

Therefore, glutaraldehyde, as a highly efficient disinfectant, is widely used in sterilization and disinfection, and has the characteristics of broad spectrum, high efficiency and low toxicity.

因此，戊二醛作为高效消毒剂，被广泛应用于灭菌 和消毒，具有广谱、高效、低毒的特点。

Although it has some irritant effect on organisms, at the concentration used, the irritation is low, the corrosiveness is low, and it can be considered safe and low in toxicity.

虽然其对生物体有 一定的刺激性，但在使用浓度下，刺激性小、腐蚀性低、可 认为安全低毒。

It is also a good cross-linking agent for chemical cross-linking reactions. However, it has the characteristics of low corrosivity to metals, minimal impact from organic matter, and good stability.

也是化学交联反应的良好交联剂。 但、对金 属腐蚀性小、受有机物影响小、稳定性好等特点。

[0008]

Polyethylene glycol, also known as α-hydro-ω-hydroxy (oxy-1,2-ethylenedimethyl) polymer, is a type of polyethylene oxide (PEO-LS).

聚乙二醇又名α-氢-ω-羟基(氧-1,2-乙二基)的聚合物、聚氧 化乙烯(PEO-LS)。

It is a general term for ethylene glycol polymers with an average molecular weight of about 200 to at least 6000. The properties also differ depending on the average molecular weight. Colorless and odorless viscous liquid to waxy solid. It is soluble in water, ethanol, and many other organic solvents. Low vapor pressure. It is thermally stable. It does not react with many chemicals, does not hydrolyze, and does not deteriorate. It is non-toxic and causes no significant irritation to the eyes and skin.

是平均分子量在约200到至少6000的乙二 醇高聚物的总称。 随着平均分子量的不同，性质也有差异。 无色无臭粘稠液体至蜡状固体。 溶于水、乙醇和许多其他有 机溶剂。 蒸汽压低。 对热稳定。 与许多化学品不起作用，不 水解，不变质。 无毒，对眼睛和皮肤无明显刺激。

[0009]

Formaldehyde is a colorless gas with a strong, pungent odor.

甲醛是一种无色，有强烈刺激型气味的气体。

It is readily soluble in water, alcohol, and ether. Formaldehyde is gaseous at room temperature and usually appears in the form of an aqueous solution. Formaldehyde is readily soluble in water and ethanol; a 35-40% aqueous solution of formaldehyde is called formalin. Formaldehyde is an important organic raw material, mainly used in the plastics industry, synthetic fiber industry, leather industry, pharmaceuticals, dyes, etc.

易溶于水、 醇和醚。 甲醛在常温下是气态，通常以水溶液形式出现。 易 溶于水和乙醇，35～40%的甲醛水溶液叫做福尔马林。 甲醛 是一种重要的有机原料，主要用于塑料工业、合成纤维、皮 革工业、医药、染料等。

[0010]

Magnetic nanoparticles are groups of atoms or molecules composed of a small number of atoms or molecules, with particle sizes ranging from 1 to 100 nm. The distinguishing feature of

nanoparticles from bulk structures is their shell structure. Since the surface layer constitutes a large proportion of the particle, and the surface atoms are non-crystalline layers lacking both long-range and short-range order, the actual state of the particle surface layer can be considered closer to a gaseous state. At the core of the particle, there are well-crystallized, periodically arranged atoms, although their structure differs slightly from that of bulk samples. This special structural type of nanoparticle results in four effects: surface effect, volume effect, quantum size effect, and macroscopic quantum tunneling effect, leading to many unique properties: exotic mechanics, electrical, magnetic, thermal, optical, and chemical activity.

磁性纳米粒子是纳米粒子是由数目很少的原子或分子 组成的原子群或分子群,其颗粒的大小在1-100nm之间， 纳米粒子区别于本体结构的特点为:纳米粒子具有壳层结 构，由于粒子的表面层占很大比例,而表面原子是既无长程 序,又无短程序的非结晶层,可以认为粒子表面层的实际状 态更接近气态,而在粒子的心部,存在结晶完好周期排布的 原子,不过其结构与本体样品略有不同,纳米粒子的这种特殊类型的结构导致了它具有四方面的效应:表面效应、体积 效应、量子尺寸效应和宏观量子隧道效应,并由此产生出许 多特殊性质:奇异力学、电学、磁学、热学、光学和化学活 性等。

Due to their unique paramagnetic properties, magnetic nanoparticles have broad application prospects in giant magnetoresistance, magnetic liquids and magnetic recording, soft

magnets, permanent magnets, magnetocooling, giant magnetoresistance materials, magneto-optical devices, and magnetic detectors.

由于磁性纳米粒子具有其特殊的顺磁特性,因而在巨 磁电阻、磁性液体和磁记录、软磁、永磁、磁致冷、巨磁阻 抗材料以及磁光器件、磁探测器等方面具有广阔的应用前 景。

[0011]

Hydrogels are high-molecular cross-linked network structures containing hydrophilic and hydrophobic groups, with water as the dispersion medium.

水凝胶是以水为分散介质，含亲水基团和疏水集团的高 分子交联网络结构。

As a highly absorbent and water-retaining material, hydrogels are widely used in various fields, including cosmetics (face masks, fever-reducing patches, analgesic patches), food (preservatives, thickeners), and medical (drug carriers).

作为一种高吸水高保水材料，水凝胶被 广泛用于多种领域化妆品中的面膜、退热贴、镇痛贴，以及食品工业中的保鲜剂、增稠剂，医疗中的药物载体等等。

[0012]

In burn treatment, the patient's plastic surgery and postoperative rehabilitation are key aspects of the treatment process.

在烧伤治疗中，病人的整形和术后的康复问题是治疗过 程中的关键。

In the process of rehabilitation and scar treatment, elastic fabrics and plastic masks are widely used for compression therapy. Because human faces are complex and vary in height, even compression therapy cannot achieve ideal results.

在康复和瘢痕治疗的过程中，广泛使用弹力织 物和塑料面具，以压迫疗法进行治疗。 由于人脸形貌复杂， 高低不一，即使采取压迫疗法也不能取得理想的结果。

[0013]

Summary of the Invention

发明内容

[0014]

In order to overcome the shortcomings of the prior art, the purpose of this invention is to provide a chitosan derivative hydrogel containing magnetic nanoparticles.

为了克服现有技术的不足，本发明的目的在于提供一种 含磁性纳米粒子的壳聚糖衍生物水凝胶。

[0015]

Another objective of this invention is to provide a method for preparing chitosan derivative hydrogels containing magnetic nanoparticles.

本发明的另一个目的在于提供一种含磁性纳米粒子的 壳聚糖衍生物水凝胶的制备方法。

[0016]

To achieve the above objectives, the technical solution provided by the present invention is as follows:

为了实现上述目的，本发明提供的技术方案如下：

[0017]

A method for preparing chitosan hydrogel containing magnetic nanoparticles includes the following steps:

一种含磁性纳米粒子的壳聚糖水凝胶的制备方法，包括 以下步骤：

[0018]

(1) Dissolve chitosan powder in 0.5%-5% acetic acid solution, stir mechanically until clear, and prepare a chitosan solution of 0.002%-1% (i.e., 0.002-1g chitosan dissolved in 100ml acetic acid solution) for later use.

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(1)、将壳聚糖粉末溶于0.5%-5%的乙酸溶液中，机械搅 拌直至澄清，配制成0.002%-1%（即0.002-1g壳聚糖溶于 100m l醋酸溶液形成的壳聚糖溶液）的壳聚糖溶液，备用。

[0019]

(2) Take 5-10 mL of the mixture from step (1) and add 200 μL-1500 μL of magnetic nanoparticle dispersion with an iron content of 1.2 g/ml-1.4 g/ml;

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(2)、取步骤(1)的混合液5-10mL，添加铁含量为 1.2g/ml-1.4g/ml磁性纳米粒子分散液200μL-1500μL；

[0020]

(3) Add 200uL-1000uL of crosslinking agent and react at room temperature for 2h-36h to produce a Schiff reaction and generate chitosan hydrogel containing magnetic nanoparticles.

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(3)、添加交联剂200uL-1000uL，室温下反应2h-36h， 发生席夫反应，生成含磁性纳米粒子的壳聚糖水凝胶；

[0021]

The magnetic nanoparticles are polyacrylic acid-coated iron oxide nanoparticles with an average particle size of 10nm-20nm.

所述的磁性纳米粒子是聚丙烯酸包覆的四氧化三铁纳米 粒子，平均粒径为10nm-20nm；

[0022]

The crosslinking agent is a mixture of 1wt%-25wt% glutaraldehyde or 0.05g-0.6g polyethylene glycol and formaldehyde (36wt%-40wt% stock solution).

所述的交联剂为1wt%-25wt%的戊二醛或者聚乙二醇 0.05g-0.6g和甲醛（36wt%-40wt%原液）的混合液。

The molecular weights (Mw) of polyethylene glycol are 10K and 20K, respectively.

聚乙二 醇分子量Mw分别为10K与20K。

[0023]

Principle Explanation: Chitosan's molecular chain contains positively charged amino groups, while the surface of polyacrylic acid-coated iron oxide nanoparticles contains a large number of negatively charged carboxyl groups. The two undergo electrostatic adsorption. Then,

glutaraldehyde, a crosslinking agent, is added to react with chitosan through a Schiff reaction, directly obtaining a hydrogel containing nanoparticles. Alternatively, formaldehyde is first added to react with chitosan through a Schiff reaction, forming C=N double bonds. Then, polyethylene glycol is added to react with the resulting Schiff base through an addition reaction, obtaining a chitosan hydrogel containing nanoparticles. This hydrogel is brown, transparent, and has no obvious internal precipitation or aggregation.

原理说明：壳聚糖的分子链上含有带正电的氨基，而聚 丙烯酸包覆的四氧化三铁纳米粒子表面含有大量带负电的 羧基，两者发生静电吸附，然后加入交联剂戊二醛与壳聚糖 与发生席夫反应，交联直接获得含纳米粒子的水凝胶；或者 先加入甲醛与壳聚糖发生席夫反应，形成C=N的双键，然后 再加入聚乙二醇与所得席夫碱发生加成反应，获得含纳米粒 子的壳聚糖水凝胶，呈棕色，透明，内部无明显沉淀和团聚。

[0024]

Chitosan can be directly reacted with crosslinking agents glutaraldehyde or a mixture of formaldehyde and polyethylene glycol to prepare hydrogels. However, due to the use of

acetic acid as a solvent, the product has a certain yellow color and properties similar to silica gel. It has a high degree of crosslinking and a high shear modulus, but it is brittle.

壳聚糖可直接与交联剂戊二醛或甲醛与聚乙二醇的混合 液反应制得水凝胶，但由于采用乙酸做溶剂，产物带有一定 的黄色，性质与硅胶相似，交联度较大，其剪切模量越高， 但易碎。

[0025]

Attached Figure Description

附图说明

[0026]

Figure 1. Electron micrograph of the chitosan hydrogel containing magnetic nanoparticles obtained in Example 1.

图1实施例1获得的含磁性纳米粒子的壳聚糖水凝胶的 电镜图。

The freeze-dried chitosan gel is porous.

冻干后的壳聚糖凝胶呈多孔状。

[0027]

Figure 2. Electron micrograph of the chitosan hydrogel containing magnetic nanoparticles obtained in Example 3.

图2实施例3获得的含磁性纳米粒子的壳聚糖水凝胶的 电镜图。

Similarly, when observed under a 100 μm scale, compared with Example 1, as the amount of glutaraldehyde used increased, the degree of cross-linking increased, and the porosity of the lyophilized chitosan gel increased.

同样在100μm的标尺下观察，与实施例1相比较， 随着戊二醛使用量的增加，交联度增大，壳聚糖凝胶的冻干 结构孔隙率增大。

[0028]

Detailed Implementation

具体实施方式

[0029]

Polyacrylic acid-coated iron oxide nanoparticles were purchased from Beijing Deco Island Gold Technology Co., Ltd. (average particle size 10nm-20nm); chitosan was purchased from Sinopharm Group (1. degree of deacetylation 80%-95%, molecular weight 590K-600K; 2. degree of deacetylation >95%, molecular weight 280K-310K).

聚丙烯酸包覆的四氧化三铁纳米粒子购自于北京德科 岛金科技有限公司（平均粒径为10nm-20nm）；壳聚糖购自 国药集团（1、脱乙酰度为80%-95%，分子量590K-600K；2、 脱乙酰度>95%,分子量280K-310K）。

[0030]

Example 1

实施例1

[0031]

A method for preparing chitosan hydrogel containing magnetic nanoparticles:

一种含磁性纳米粒子的壳聚糖水凝胶的制备方法：

[0032]

(1) Dissolve 0.29g of chitosan powder in 30mL of 1% acetic acid solution, stir mechanically for 3h until clear, and then let stand for 3h to remove bubbles.

（1）、将0.29g壳聚糖粉末溶于30mL 1%的乙酸溶液中， 机械搅拌3h之后至澄清，之后静置3h除去气泡。

And filter;

并过滤；

[0033]

(2) Add 500 µL of dispersion containing Fe₃O₄ nanoparticles (average particle size of 10nm-14nm) (iron content of 1.285mg/mL) to the mixture obtained in step (1), and shake for 1 hour.

（2）、向步骤（1）所得到的混合液中加入500µL含Fe₃O₄ 纳米粒子的分散液(平均粒径为10nm-14nm)（铁含量为 1.285mg/mL），再震荡1h；

[0034]

(3) Place the mixture obtained in step (2) in a 40°C water bath, add 500 μL of 1% glutaraldehyde solution dropwise, and mechanically stir or shake for 3 hours to obtain a brown transparent hydrogel.

（3）、将步骤（2）所得到的混合液置于40°C水浴，向其 中逐滴滴加1%的戊二醛溶液共500μL，并施以机械搅拌或震 荡3h，即可获得棕色的透明水凝胶。

[0035]

Example 2

实施例2

[0036]

The difference from Example 1 is that the degree of deacetylation of the chitosan powder used in step one is >95%.

与实施例1不同之处在于步骤一中使用的壳聚糖粉末的 脱乙酰度>95%。

[0037]

Example 3

实施例3

[0038]

The difference from Example 1 is that in step 3, 200 μL of 25% glutaraldehyde solution is added dropwise and mechanically shaken for 10 min to obtain a brownish-black transparent hydrogel.

与实施例1不同之处在于步骤3滴加25%的戊二醛溶液共 200μL，并施以机械震荡10min，即可获得棕黑色的透明水 凝胶。

[0039]

The chitosan hydrogel prepared in Example 3 of this invention is used as an auxiliary pressure material in the burn treatment mask. According to the requirements of rehabilitation treatment, the scar area generally needs to maintain a compressive stress of at least 18 mmHg, i.e. 2400 Pa. The glutaraldehyde cross-linked chitosan gel obtained in Example 3 can withstand a pressure of more than 2500 Pa as a stress-providing material. If the degree of cross-linking is further increased, the load can continue to increase.

采用本发明实施例3制备的壳聚糖水凝胶作为烧伤治 疗面具中的辅助压力材料，根据康复治疗的要求，一般对 瘢痕处至少需保持18mm汞柱，即2400Pa的压应力，实施 例3获得戊二醛交联的壳聚糖凝胶作为应力提供材料，能 负荷2500Pa以上的压力，如果进一步提高交联度，载荷仍 可继续上升。

This allows the mask to fit the face better, further enhancing the effect of pressure therapy.

能使面具更能贴合人脸，起到进一步加强压 力治疗的效果。

The addition of magnetic nanoparticles can not only enhance the mechanical properties of the gel, but also cause local segregation under the influence of an external magnetic field, resulting in a controllable local enhancement effect.

磁性纳米粒子的加入，既能起到强化凝胶 力学性能的作用，同时也能在外磁场的引发下，发生局部的偏聚，起到可控的局部增强的效果。

Finally, the compressive deformation state of the hydrogel is fed back into the manufacturing of the facial mold.

最后，根据水凝胶 的受压形变状态，反馈于面部模具的制造。

[0040]

Example 4

实施例4

[0041]

The difference from Example 1 is that in step 2, 1000 μL of Fe₃O<sub>4<

/sub>magnetic nanoparticles are added; a brownish-black transparent hydrogel is obtained.

与实施例1不同之处在于步骤2加入1000μL含Fe₃O₄磁 性纳米粒子；获得棕黑色的透明水凝胶。

[0042]

Example 5

实施例5

[0043]

The difference from Example 1 is that in step 2, 1500L of an aqueous solution containing Fe₃O₄ magnetic nanoparticles is added to obtain a brownish-black

transparent hydrogel. At this point, the brown color is darker than that in Example 3, but there is no aggregation or precipitation.

与实施例1不同之处在于步骤2加入1500L加入含Fe₃O₄ 磁性纳米粒子的水溶液，获得棕黑色的透明水凝胶，此时相 比与实施例3，棕色更深，但无团聚或沉淀。

[0044]

Example 6

实施例6

[0045]

The difference from Example 4 is that in step 3, 0.2g of polyethylene glycol (PEG) with an average molecular weight of 10k is added, mechanically shaken for more than 1 hour until no precipitation occurs, and then 0.3mL of formaldehyde standard solution (36wt%-40wt%) is added to obtain a brown, transparent chitosan composite hydrogel.

与实施例4不同之处在于，在步骤3中加入平均分子量 为10k的聚乙二醇（PEG）0.2g，机械震荡1h以上至无沉淀， 再加入0.3mL的甲醛标准液（36wt%-40wt%），即可获得棕色、 透明的壳聚糖复合水凝胶。

[0046]

Example 7

实施例7

[0047]

The difference from Example 6 is that in step 3, 0.4g of polyethylene glycol M_n=20K was added to obtain a brownish-black transparent hydrogel.

与实施例6不同之处在于步骤3中，加入0.4g的聚乙二 醇M_n=20K，获得棕黑色的透明水凝胶。

[0048]

The materials used in Examples 8-10 are shown in Table 1:

实施例8-10所采用材料如表1所示：

[0049]

Table 1

表1