Title: HEMOSTATIC AGENT INTERNALLY APPLIED THROUGH ENDOSCOPE AND APPLICATION METHOD THEREOF

Abstract: Provided is a hemostatic agent for internal body use, which can be applied onto a bleeding lesion of the gastrointestinal tract by an endoscopic hemostatic method, and a method of applying the hemostatic agent onto the bleeding lesion. The coating agent is a polymer solution prepared by dissolving a cationic or an anionic reaction product into a polysaccharide solution. The coating agent hemostatic agent for stopping bleeding from a lesion of a mucous membrane by being applied onto the lesion of the mucous membrane through an endoscope, comprising a coating agent as a polymer solution prepared by dissolving a cationic or an anionic reaction product into a polysaccharide solution, wherein the coating agent has adherence high enough to flow through an endoscope catheter, biocompatibility, and bioadherence induced by the interaction with mucous membrane due to hydrogen bonds, ion bonds or hydrophobic bonds. According to the hemostatic agent and method thereof, since the hemostatic agent is applied onto an ulcer through an endoscope, the ulcer can be completely covered with the hemostatic agent. As a result, bleeding from the ulcer can be totally stopped and there is no major probability of rebleeding. Further, since the hemostatic agent contains the supplement, the ulcer can be cured by the medical effect and growth factor of the supplement.
[DESCRIPTION]
Invention Title
HEMOSTATIC AGENT INTERNALLY APPLIED THROUGH ENDOSCOPE AND APPLICATION
METHOD THEREOF
Technical Field
The present invention relates to a hemostatic agent for internal body use and a method of applying the same inside the human body using an endoscope apparatus. More particularly, the present invention relates to a hemostatic agent for internal body use and a method of applying the same onto a hemorrhagic lesion of the gastrointestinal tract in the human body in an endoscopic stanching manner.
Background Art
Gastrointestinal bleeding is a fairly common medical problem. It has been reported that generally about one hundred people from one hundred thousand people are treated in the hospital for gastrointestinal bleeding every year, and the mortality rate from gastrointestinal bleeding is about 8 to 10%. In about 80% of the cases gastrointestinal bleeding mostly occurs in the upper-gastrointestinal tract. In upper-gastrointestinal bleeding, the bleeding originates in the first part of the gastrointestinal tract, i.e., the esophagus, stomach, or duodenum, and results in haematemesis and melaena. A bleeding site in upper-gastrointestinal bleeding can be easily identified by an endoscopic method. The identification rate in this case is about 90%.
Polytectomy, endoscopic mucosal resection, and endoscopic treatment are common treatments to treat stomach cancer or colon cancer. However, during or after such treatments, sometimes bleeding from the stomach or colon occurs, which can require emergency surgical interventions or even lead to the death of the patient.
Gastrointestinal bleeding has been treated mainly by surgical interventions. However, recently, endoscopic hemostatic methods have become the standard treatment for gastrointestinal bleeding.
In the endoscopic hemostatic method, a hypertonic solution.
epinephrine, or alcohol is directly injected into an ulcer, and then a coagulation therapy using electric heat or laser, or a physical hemostatic method using a clip is used.

However, the conventional bleeding control methods aim at reducing the amount of bleeding by pressing or ligating a vascular tract by injecting a liquid agent into a vascular vessel around an ulcer. Accordingly, the ulcer remains as its mucous membrane is exfoliated. As a result, even after the treatment, the bleeding often continues. According to many research studies, the conventional endoscopic hemostatic treatment is successful in only 70 to 80% of the cases. Further, bleeding reoccurs in 20 to 25% of the cases, 3 to 4 days after the endoscopic hemostatic treatment.

Rebleeding refers to bleeding from a vascular vessel, and occurs before the ulcer is completely cured by the regeneration of tissue around the ulcer. Thus, it is difficult to be treated by the conventional endoscopic hemostatic method that stops bleeding when the mucous membrane of the ulcer is exfoliated.

Also, the conventional endoscopic treatment aims at stopping bleeding, not curing the ulcer. Accordingly, after performing the conventional endoscopic treatment, cure of the ulcer or the lesion is too slow and rebleeding might occur frequently.

[Disclosure]

[Technical Problem]

To solve the above problems, it is an objective of the present invention to provide a hemostatic agent for internal body use and a method of applying the hemostatic agent onto an ulcer inside the human body, in which a coating agent serving as the hemostatic agent is dispersed and coated onto the ulcer in an endoscopic manner to totally stop bleeding from the ulcer and prevent completely rebleeding of the ulcer.

It is another object of the present invention to provide a hemostatic agent that can be endoscopically applied inside the human body, can stop bleeding of an ulcer, and promote cure of the ulcer, and a method of applying
the same inside the human body.

[Technical Solution]

To accomplish the above object of the present invention, there is provided a hemostatic agent for internal body use, which can be endoscopically applied onto a mucous membrane lesion in the human body in order to stop bleeding from the mucous membrane lesion. The hemostatic agent comprises a coating agent as a polymer solution prepared by dissolving a cationic or an anionic reaction product into a polysaccharide solution, wherein the coating agent has adherence high enough to flow through an endoscope catheter, biocompatibility, and bioadherence induced by the interaction with mucous membrane due to hydrogen bonds, ion bonds or hydrophobic bonds.

According to another aspect of the present invention, there is provided a method of applying a hemostatic agent inside the human body using an endoscope catheter, the method including (a) inserting an endoscope catheter in the human body and placing a front end of the catheter near a lesion of a mucous membrane; and (b) injecting the hemostatic agent through the endoscope catheter to apply the hemostatic agent onto the lesion of the mucous membrane, wherein the hemostatic agent is a polymer solution prepared by dissolving a cationic or an anionic reaction product into a polysaccharide solution, wherein the coating agent has adherence high enough to flow through an endoscope catheter, biocompatibility, and bioadherence induced by the interaction with mucous membrane due to hydrogen bonds, ion bonds or hydrophobic bonds.
[Description of Drawings]

FIG. 1 is a photograph showing an ulcer before treatment with a hemostatic agent for internal body use, according to an embodiment of the present invention:

FIG. 2 is a photograph showing the ulcer after applying the hemostatic agent thereonto; and

FIG. 3 is a photograph showing the ulcer 72 hours after the application of the hemostatic agent.

[Best Mode]

As repeated of experiments, the present inventors have found the following materials could be adopted as coating agents for internal body use according to an embodiment of the present invention.

A coating agent having a cationic reaction product in an aqueous solution or a polysaccharide solution includes at least one selected from the group consisting of chitosan, polycrin, polyhistidine, polydiethylaminomethyl, methacrylate, and a combination thereof.

A coating agent having an anionic reaction product in an aqueous solution or a polysaccharide solution includes at least one selected from the group consisting of alginate, carrginnan, hyaluronic acid, chondroitin sulfate, or a combination thereof.

A coating agent having a nonionic reaction product in an aqueous solution or a polysaccharide solution includes at least one selected from the group consisting of cellulose, caccia gum, ploexamer, polyglycol/polyactic acid (PLLA) copolymer, polyactic acid-polyglycolic acid, and a combination thereof.

According to another aspect of the present invention, a first coating agent made of a polymer solution containing a cationic reaction product is used together with a second coating agent made of a polymer solution containing an anionic reaction product. In this case, the first coating agent may be applied onto a lesion site of a mucous membrane in the human body using an endoscope, and then the second coating agent is applied onto the
surface of the first coating agent using the endoscope.

By the double-coating, cationic ions of the first coating agent and anionic ions of the second coating agent are bonded by interaction, and a bonded portion becomes hydrophobic. Accordingly, each coating agent applied to the ulcer in a stomach or an intestine maintains the adherence with its mucous membrane while having hydrophobic outer surface that is exposed to water or gastric juice. Accordingly, the composition of the coating agent can have a relatively long durability.

The coating agents according to the present invention can stop bleeding when they are applied onto an ulcer, and prevent the ulcer from being exposed to gastric juice, thereby protecting the ulcer from secondary infection.

In the above embodiment, the first coating agent is a polymer solution containing a cationic reaction product and the second coating agent is a polymer solution containing an anionic reaction product. In the another embodiment of the present invention, however, the first coating agent directly applied to the interior of a human body can be a polymer solution containing an anionic reaction product and the second coating agent applied onto the surface of the first coating agent can be a polymer solution containing a cationic reaction product. However, taking into account that skin of the interior of the human body is charged with negative ions, the first coating agent may be preferably a polymer solution containing a cationic reaction product.

The coating agent serving as the hemostatic agent according to the embodiment of the present invention may further contain a supplement which will be described in more detail below. The supplement includes a \( \text{H}_2 \) receptor antagonist, antacid, a hydrogen ion pump inhibitor, a jump defense agonist, and so on.

The \( \text{H}_2 \) receptor antagonist is an acid secretion inhibitor, and examples thereof include cimetidine, ranitidine, famotidine, nizatidine, roxatidine,
and a combination thereof. Examples of the antacid include calcium carbonate, aluminum hydroxide, magnesium hydroxide, a combination thereof. Examples of the hydrogen ion pump inhibitor (PPI) include omeprazole, rabeprazole, pantoprazole, and a combination thereof. The jump defense agonist includes rebaipide.

Since the coating agent according to an embodiment of the present invention contains the supplements stated above, the coating agent can promote curing of the ulcer by medical effects of the supplements and growth factor and can also stop bleeding from the ulcer.

Hereinafter, a method of applying the hemostatic agent inside the human body through an endoscope will be described.

The method according to an embodiment of the present invention includes (a) introducing a catheter into the human body so that a front tip of the catheter reaches a lesion of a mucous membrane, and (b) injecting the hemostatic agent into the human body through an endoscope catheter to apply the hemostatic agent to the lesion of the mucous membrane.

In the case in which the double-coating method is used, the step (b) includes (b-1) applying a first coating agent made of a polymer solution containing a cationic reaction product to the lesion of the mucous membrane, and (b-2) coating a second coating agent of a polymer solution containing an anionic reaction product on the surface of the first coating agent.

The composition of the hemostatic agent used in the above method is the same as that of the homeostatic agent described above. Accordingly, the detailed description of the hemostatic agent will be omitted.

Hereinafter, results from testing the hemostatic agent according to the embodiment of the present invention and the method of applying the hemostatic agent will be described below.

For the test, 1 to 5 g of chitosan containing a cationic reaction product is introduced into acetic acid (pH 3.0 to 5.5), and then mixed together to be dissolved, thereby preparing a first coating solution. Next, 1 to 10 g of alginate containing an anionic reaction product is introduced into
distilled water and mixed together to be dissolved, thereby preparing a second coating solution. The concentration of the coating solutions is determined so that the solutions can flow through an endoscope.

After introducing the endoscope catheter into the human body and placing the front end of the catheter at an ulcer, the first coating solution is injected through the catheter so that the first coating solution is sprayed onto the ulcer. Next, the second coating solution is injected through the catheter so that the second coating solution is sprayed onto the surface of the first coating solution.

FIG. 1 is a photograph showing an ulcer before treatment with a hemostatic agent for internal body use, according to an embodiment of the present invention. FIG. 2 is a photograph showing the ulcer after applying the hemostatic agent thereto, and FIG. 3 is a photograph showing the ulcer 72 hours after the application of the hemostatic agent.

As apparent from the test results, the coating agent remains on the ulcer even after 72 or more hours after it was applied onto the ulcer, and also the ulcer is almost cured.

[Industrial Applicability]

According to the present invention, the hemostatic agent and the method of applying the same inside the human body using an endoscope have the following advantages.

First, since the hemostatic agent is applied onto an ulcer through an endoscope, the ulcer can be completely covered with the hemostatic agent. As a result, bleeding from the ulcer can be totally stopped and there is no major probability of rebleeding.

Second, since the hemostatic agent contains the supplement, the ulcer can be cured by the medical effect and growth factor of the supplement.
[CLAIMS]

[Claim 1]

A hemostatic agent for stopping bleeding from a lesion of a mucous membrane by being applied onto the lesion of the mucous membrane through an endoscope, comprising:

- a coating agent as a polymer solution prepared by dissolving a cationic or an anionic reaction product into a polysaccharide solution, wherein the coating agent has adherence high enough to flow through an endoscope catheter, biocompatibility, and bioadherence induced by the interaction with mucous membrane due to hydrogen bonds, ion bonds or hydrophobic bonds.

[Claim 2]

The hemostatic agent according to claim 1, wherein the coating agent comprises one or more chemicals selected from the cationic polymer group consisting of chitosan, polyricin, polyhistidine, polydiethylaminoethyl, and methacrylate, the anionic polymer group consisting of alginate, carrginnan, hyaluronic acid, and chondroitin sulfate, or the nonionic polymer group consisting of cellulose, caccia gum, ploaxamer, polyglycol/polyalactic acid (PLLA) copolymer, and polylactic acid/polyglycolic acid.

[Claim 3]

The hemostatic agent according to claim 1, comprising a first coating agent which is directly applied onto the lesion of the mucous membrane and made of a polymer solution containing a cationic reaction product, and a second coating agent which is applied onto the outer surface of the first coating agent and made of a polymer solution containing an anionic reaction product.

[Claim 4]

The hemostatic agent according to claim 1, wherein the coating agent further comprises one or more supplements selected from the group consisting of a H₂ receptor antagonist, an antacid, a hydrogen ion pump inhibitor, and a jump defense agonist:
wherein the H₂ receptor antagonist is selected from the group consisting of cimetidine, ranitidine, famotidine, nizatidine, and roxatidine;

wherein the antacid is selected from the group consisting of calcium carbonate, aluminum hydroxide, and magnesium hydroxide;

wherein the hydrogen ion pump inhibitor (PPI) is selected from the group consisting of omeprazole, rabeprazole, and pantoprazole; and

wherein the jump defense agonist comprises rebiapide.

[Claim 5]

A method of applying a hemostatic agent inside the human body using an endoscope catheter, comprising:

(a) inserting an endoscope catheter in the human body and placing a front end of the catheter near a lesion of a mucous membrane; and

(b) injecting the hemostatic agent through the endoscope catheter to apply the hemostatic agent onto the lesion of the mucous membrane,

wherein the hemostatic agent is a polymer solution prepared by dissolving a cationic or an anionic reaction product into a polysaccharide solution, wherein the coating agent has adherence high enough to flow through an endoscope catheter, biocompatibility, and bioadherence induced by the interaction with mucous membrane due to hydrogen bonds, ion bonds or hydrophobic bonds.

[Claim 6]

The method according to claim 5, wherein the step (b) comprises:

(b-1) applying a first coating agent made of a polymer solution containing a cationic reaction product onto the lesion of the mucous membrane; and

(b-2) applying a second coating agent made of a polymer solution containing an anionic reaction product on the surface of the first coating agent.
A. CLASSIFICATION OF SUBJECT MATTER

A61K 31/74(2006.01)i

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC: A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Korean patents and applications for inventions since 1975

Electronic database consulted during the international search (name of database and, where practicable, search terms used)

Medline, CAPLUS(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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☐ Further documents are listed in the continuation of Box C.  ☐ See patent family annex.

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Name and mailing address of the ISA/KR
Korean Intellectual Property Office
920 Dunsan-dong, Seo-gu, Daejeon 302-701, Republic of Korea
Facsimile No. 82-42-472-7140

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