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(71) Applicant: PROBIOMEDICA S.R.L. [IT/IT]; via di Santo Spirito 14, 50125 Firenze (IT).

(72) Inventor: TORTORA, Giuseppe Roberto; via G. Gambini, 56124 Pisa (IT).

(74) Agent: CELESTINO, Marco; ABM Agenzia Brevetti & Marchi, Viale Giovanni Pisano 31, 56123 Pisa (IT).

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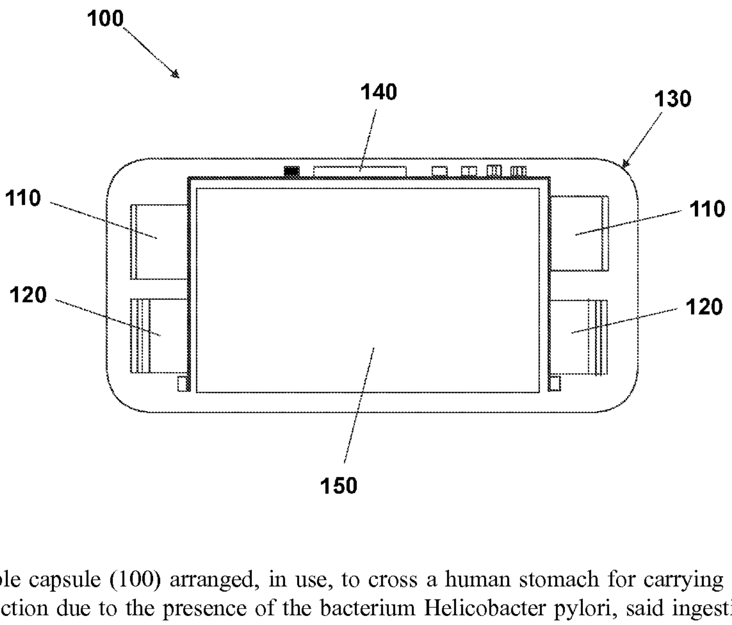
(54) Title: INGESTIBLE CAPSULE FOR THE PHOTOTHERAPEUTIC TREATMENT OF INFECTIONS

Fig. 1



(57) Abstract: An ingestible capsule (100) arranged, in use, to cross a human stomach for carrying out a phototherapic treatment arranged to combat an infection due to the presence of the bacterium Helicobacter pylori, said ingestible capsule (100) comprising at least one primary light source (110) arranged to emit an electromagnetic phototherapic wave having a wavelength λ_1, at least one auxiliary light source (120) arranged to emit an electromagnetic phototherapic wave having a wavelength λ_2, a wrapper (130) arranged to contain said or each primary light source (110) and said or each auxiliary light source (120), said wrapper (130) being at least partially transparent to said wavelengths λ_1 and λ_2, a control unit (140) arranged to selectively activate said or each primary light source (110) and/or said or each auxiliary light source (120), and at least one energy source (150)

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arranged to provide energy for feeding said control unit (140) and/or said light sources (110,120). In particular, $400nm < \lambda_1 < 525nm$ and $525nm < \lambda_2 < 650nm$. Furthermore, said control unit (140) is configured to receive an information of position reporting in real time an area of said stomach crossed by said ingestible capsule (100); to determine, known said information of position, a wavelength, a dosage and a duration of administration of said electromagnetic phototherapic waves for an optimal phototherapic treatment of said area of said stomach; to selectively activate said or each primary light source (110) and/or said or each auxiliary light source (120) to provide said optimal phototherapic treatment of said area of said stomach.

TITLE

Ingestible capsule for the phototherapeutic treatment of infections

DESCRIPTION

Field of the invention

The present invention relates to the field of treatment of intestinal infections.

In particular, the invention relates to an ingestible capsule for phototherapic treatment of Helicobacter pylori infections.

Description of the prior art

As well known, Helicobacter pylori (H. pylori) is a Gram-negative microaerophilous bacterium that colonizes the mucus layer of the stomach and duodenum. The prevalence of infection is higher than 50% of the world population, up to 90% in developing countries. H. pylori can cause various diseases such as chronic gastritis, gastric and duodenal ulcers, gastric lymphoma, adenocarcinoma, and extradigestive diseases. H. pylori is also considered a Class I carcinogen by the World Health Organization.

Currently, H. pylori infection is treated with a drug therapy that consists of a combination of a proton pump inhibitor with two or three antibiotics. Due to various side effects and antibiotic resistance, the efficacy of drug therapy is reduced to 70-85%.

To overcome these limitations, we use an approach based on a photodynamic therapy of the bacterium (PDT). PDT was introduced at the beginning of the last century and was originally used for the treatment of tumors. In traditional PDT, a non-toxic dye, called an external photosensitizer, is injected or applied by topical administration to the patient, being selectively accumulated in the target (i.e., a malignant tissue or bacterium). After about 48-72 hours, the lens is exposed to visible light. The interaction between the photosensitizer and the light, in the presence of oxygen, causes reactive oxygen species to be produced, inducing cell death. Applications of PDT to kill pathogenic microorganisms have met the increasing attention of clinicians, and this system has been proposed as a therapy for a wide variety of localized infections.

The recent return of interest to PDT has been largely driven by unstoppable growth in drug resistance, including many classes of pathogens. H. pylori, for example, is known to be photo-labile without the exogenous intake of photosensitizers. H. pylori, in fact, naturally possesses photoactive porphyrins, coproporphyrin and protoporphyrin IX, which are natural photosensitizers. For this reason, H. pylori can be killed by exposing it to light with appropriate wavelengths.

WO2011055395 describes an ingestible capsule for the specific phototherapy of H. pylori infections, in which the presence of at least a semiriflexing mirror is provided for increasing the illumination provided by the therapeutic light source.

However, this solution is not very efficient, since it is not adaptable to the different areas of the stomach, and therefore to the different stages of the infection caused by the H. pylori bacterium. Therefore, using this device, the patient should take more than one capsule, each suitable for a different area of the stomach, increasing the costs of therapy and making it more complex to implement for an untrained user.

WO2012123939A1 describes an ingestible capsule for the phototherapy of the gastrointestinal tract of a patient, in which the presence of one or more phototherapeutic light sources and a control unit suitable for activating the light sources is provided in order to administer a specific dose of therapeutic illumination in the gastrointestinal tract. The described capsule therefore allows a more adaptable administration to different areas of the gastrointestinal tract.

However this solution, not having as target specific the infection from H. pylori, is not much effective in the support to this particular therapy for which are necessary wavelength and methods of administration not provided by WO2012123939A1.

In particular, although the efficacy of some wavelengths for killing the bacterium *in vitro* has been demonstrated (*M. R. Hamblin, J. Viveiros, C. Yang, A. Ahmadi, R. A. Ganz, and M. J., Tolkoff "Helicobacter pylori accumulates photoactive porphyrins and is killed by visible light," Antimicrobial Acting Chemother., vol. 49, no. 7, pp. 2822–2827, Jul. 2005*) it should be considered that *in vivo* the bacterium is distributed differently and generally in a more complex way. It must therefore be considered that the bacterium must be treated in vivo within a human stomach, in which other factors are fundamental, among which for example the depth of penetration of light at different wavelengths. The gastric wall in fact, consisting of macroscopic structures (folds) and microscopic structures (pits), is a completely different situation respect to that one in which the bacterium is illuminated on a Petri dish under in vitro conditions. Folds and pits are characterized by lateral dimensions of the order respectively 2-4 mm and 100-200 μm, in which the bacterium can nestle and hide. In general, bactericidal efficiency in a real stomach is a multiparametric problem, whose parameters are represented both by the optical properties of the endogenous photosensitizer and by the photophysical properties of the stomach (absorption spectrum and ROS production efficiency) and by the optical properties of the tissue, which can strongly influence the spectrum of effective wavelengths for killing the bacterium. Considering the optical parameters of each layer of the gastric mucosa, it follows that the filtering action woven on certain wavelengths must be taken into account to optimize the effectiveness of photo-killing.

In order to optimize the efficacy of phototherapy by a small, ingestible device, the choice of the best emission wavelengths for the endoscopic capsule is essential to have a good eradication of the bacterium. The choice of the best spectral irradiation band is essential to obtain an effective photo-killing action and optimized energy management, without spending it in photons at different wavelengths from the most efficient one, also allowing to reduce the number of therapeutic sessions which, in this case, are translated with the effective reduction of the number of capsules necessary for the treatment. The use of specific and non-random wavelengths, allows to increase more than 50% the therapeutic efficacy of the single device without wasting energy in photons that are not useful for phototherapy of the specific bacterium.

Moreover, considering that the distribution of the bacterium inside the stomach is certainly dynamic and subject to variability in relation to the state of the infection, a dynamic selection of the wavelengths to be used is fundamental. It is known, for example, that H. pylori, although having adaptation systems that allow it to survive the acidic environment of the stomach, prefers an environment where the pH is higher. So it is possible to state that in an acute colonization phase the H. pylori is found exclusively in the antrum. As the infection continues, however, and you get to the chronic phase of gastritis or for the use of antacids eg, the bacterium tends to position itself in the highest parts of the stomach up to the body. In the most long-infected areas (antrum) the bacterium is located more deeply in depth, while in the areas of the body and the bottom the bacterium is more localized on the surface.

Not considering the aspects described above, both documents cited are not very effective in the treatment of H. pylori.

Summary of the invention

It is therefore a feature of the present invention to provide an ingestible capsule for the phototherapic treatment of Helicobacter pylori infections that allows a targeted and effective therapy, so as to reduce the number of capsules to be taken.

It is also a feature of the present invention to provide an ingestible capsule for the phototherapic treatment of Helicobacter pylori infections which allows to adapt in real time to the different areas of the stomach to be treated and to the different conditions to which the bacterium may be located.

It is still a feature of the present invention to provide an ingestible capsule for the phototherapic treatment of Helicobacter pylori infections which allows an optimized energy consumption with respect to the prior art capsules, so as to extend the therapeutic effect of each capsule.

These and other objects are achieved by an ingestible capsule arranged, in use, to cross a human stomach for carrying out a phototherapic treatment arranged to combat an infection due to the presence of the bacterium Helicobacter pylori, said ingestible capsule comprising:

- at least one primary light source arranged to emit an electromagnetic phototherapic wave having a wavelength λ_1;
- at least one auxiliary light source arranged to emit an electromagnetic phototherapic wave having a wavelength λ_2;
- a wrapper arranged to contain said or each primary light source and said or each auxiliary light source, said wrapper being at least partially transparent to said wavelengths λ_1 and λ_2;
- a control unit arranged to selectively activate said or each primary light source and/or said or

each auxiliary light source;

- at least one energy source arranged to provide energy for feeding said control unit and/or said light sources;

said wavelength λ_1 and λ_2 being such that $400nm < \lambda_1 < 525nm$ and $525nm < \lambda_2 < 650nm$;

whose main feature is that said control unit is also arranged to:

- receive an information of position reporting in real time an area of said stomach crossed by said ingestible capsule;
- determine, known said information of position, a wavelength, a dosage and a duration of administration said electromagnetic phototherapic waves for an optimal phototherapic treatment of said area of said stomach;
- selectively activate said or each primary light source and/or said or each auxiliary light source to provide said optimal phototherapic treatment of said area of said stomach.

The advantage with respect to the prior art is that it is possible to activate more phototherapeutic frequencies and manage their administration more effectively, maximizing the number of released photons (J/cm^2), without the need to insert more capsules into the stomach.

Advantageously, $\lambda_2 \cong 625nm$ and $\lambda_1 \cong 500nm$.

More specifically, in a first step, in the body-bottom area of the stomach, it is possible to activate the light sources in such a way that the radiation emitted is for 20% composed of $\lambda_1 \cong 500nm$ and for 80% composed of $\lambda_2 \cong 625nm$, in order to obtain a more effective and less penetrating radiation (around the blue/green) to treat the bacteria arranged on the surface.

In a second phase, while the capsule arrives in the antral area in the stomach, the proportion can instead gradually be varied, until it is inverted, arriving at a radiation composed for 80% of $\lambda_1 \cong 500nm$ and for 20% of $\lambda_2 \cong 625nm$, so you can penetrate more into the mucus or between the folds of the stomach.

Advantageously, said control unit is also arranged to receive an information concerning the temperature of said light sources, said information concerning the temperature allowing to determine the duration of administration of said electromagnetic phototherapic waves to allow a lower consumption of the energy supplied by said energy source.

In particular, knowing the temperature of the light sources, the control unit can activate and deactivate the sources in order to optimize the ratio between emitted radiation and dispersed energy. It is in fact known that the working temperature influences the luminous efficiency of the

LEDs (relative luminous efficiency of 100% at 20°C, of 80% at 40°C, of 60% at 60°C for some types of LEDs, and this varies in function of the wavelength and the type of source used).

If, for example, the working temperature rises too much, the luminous efficiency may be negatively affected, and therefore it may be more convenient to switch the sources on and off, rather than keeping them on permanently. In this way the average luminous efficiency (the photons irradiated in the time unit) would become almost constant and in any case greater than in a situation in the absence of control. In this way, there would be a further improvement in the performance in terms of therapeutic efficacy of the single device, considering that the dynamic selection of wavelengths, driven by the operating temperature of the device and its position, allows an improvement in therapeutic efficacy of individual light sources. Always to reduce the temperature of the light sources, and increase the energy efficiency, the control unit, depending on the temperature sensor, may decide to turn off some LEDs unused at that time.

Advantageously, a detector of pH is also provided configured to measure the level of pH in the environment surrounding said ingestible capsule to provide said information of position to said control unit.

In particular, a more acidic environment will suggest that the capsule is in the antrum, while a less acidic environment will suggest that the capsule in the cecum.

Some reference values of the pH are the following:

- esophagus $pH = 5 - 6$
- fundus $pH = 4 - 5$
- body of stomach $pH = 3 - 4$
- antrum $pH = 1 - 2$
- duodenum $pH = 7 - 8$

In particular, an inertial sensor is also provided arranged to determine linear and angular speed and acceleration of said ingestible capsule to provide said information of position to said control unit.

The dynamic selection of wavelengths and their optimized management of ignition by the control unit could also be based on the positioning of the capsule or on its speed. Likewise, in some cases, it may select some wavelengths and some LEDs with lower intensity (for example in the final stages of therapy, when the capsule is about to cross the stomach and therefore is certainly in antral position where the lumen is restricted and there is no need to dose the light).

On the basis of the information coming from the inertial sensors, moreover, which show the path made by the capsule and its spatial orientation, it will also be possible to select the number and type of sources to be activated and the relative administration doses (which may be reduced in the case of stationing of the capsule at one point). In this way, it is possible to know both the path made by the capsule and its spatial orientation. From the position the control unit can determine the doses of administration, while depending on the orientation can select which sources to activate.

In particular, at least one magnetic sensor is also provided configured to measure a magnetic signal out of said stomach to provide said information of position to said control unit. In this way, by placing magnets/electromagnets in predetermined positions outside the user's body, the magnetic sensor allows to establish the position of the capsule on the basis of the intensity and direction of the magnetic signal.

Advantageously, at least one proximity sensor is also provided configured to measure the proximity of a wall of said stomach from said ingestible capsule. This way, if the capsule is attached to the wall, the control unit can turn off the light sources opposite to it.

By combining the localization information coming from the magnetic sensor and the orientation information coming from the proximity sensor, it is therefore possible to establish whether it is convenient to switch the LEDs on or off in a particular area of the capsule with respect to others.

Advantageously, said or each primary light source and said or each auxiliary light source are put in said transparent wrapper.

In particular, said or each primary light source and said or each auxiliary light source comprise organic and flexible diodes.

Advantageously, within said transparent wrapper a diffusive fluid is provided arranged to increase the diffusion of said light sources. In this way, the maximum angular coverage of the light radiation around the capsule is possible.

Furthermore, said transparent wrapper can comprise light guides arranged to convey said electromagnetic phototherapic waves along predetermined trajectories.

Advantageously, a ferromagnetic and/or magnetic element is also provided for allowing a guide of said ingestible capsule in said stomach by means of a magnet or an electromagnet external to said stomach. The ferromagnetic element may also be the battery itself, if there is one inside the capsule.

In particular, a device for receiving energy by wireless transmission is provided. It can be, for example, a winding used also as an electromagnet for remote driving by means of a magnet.

In particular, the primary energy source for the capsule can be a battery located inside the capsule itself.

To this a winding system can be added or replaced with the aim of supplying energy to the capsule remotely. One possibility could be to guide the capsule, through a magnetic system or with an external electromagnet, at a specific point to maximize the transfer of energy in a continuous or not, to allow the same capsule to continue to carry out therapy for a long time higher than the average time spent in the stomach.

In this way, thanks to the present invention, a single device is able to irradiate when necessary and in a variable manner with respect to the wavelengths selected and identified by the control unit, as is the case with the active ingredient management in drugs. The device makes it possible to irradiate the same point of the stomach with light of different colours specially selected overcoming the problem of random movements of the stomach that would otherwise not allow proper lighting of some gastric areas, reducing the effectiveness of the treatment.

In particular, a therapy combined with selected wavelengths allows:

- immediate action concerning the reduction of the number of capsules that the patient must take, then a reduction of the risks associated with each capsule;

- the possibility of composing in a controlled manner the advantages of all the wavelengths used, making it possible to achieve the best possible compromise in the future with regard to photodynamic therapy through a capsule.

In addition, given the presence of a control unit, the capsule is able to release a "variable dose combination" in relation to a multiparametric analysis with respect to the elapsed time, to the variation of pH, to the presence of external magnetic fields, based on proximity sensors, and accelerometers, for optimal management of the energy source.

Brief description of the drawings

Further characteristic and/or advantages of the present invention are more bright with the following description of an exemplary embodiment thereof, exemplifying but not limitative, with reference to the attached drawings in which:

- Fig. 1 shows a first exemplary embodiment of the ingestible capsule, according to the present invention, wherein 4 light sources are provided;
- Fig. 2 shows a second exemplary embodiment of the ingestible capsule, according to the present invention, wherein a plurality of light sources is

provided;

- Figs. 3A, 3B, 3C and 3D show other exemplary embodiments of the ingestible capsule having different forms and dispositions of the components.

Description of a preferred exemplary embodiment

With reference to Fig. 1, in a first exemplary embodiment, the ingestible capsule 100, according to the present invention, comprises two primary light sources 110 arranged to emit an electromagnetic phototherapic wave having a wavelength λ_1 and two auxiliary light sources 120 arranged to emit an electromagnetic phototherapic wave having a wavelength λ_2. The ingestible capsule 100 then comprises a wrapper 130 at least partially transparent to the wavelengths λ_1 and λ_2 and arranged to contain the light sources 110 and 120. They are also present a control unit 140, arranged to selectively activate the light sources 110 and 120, and an energy source 150 arranged to provide energy for feeding the control unit 140 and the light sources 110 and 120.

In Fig. 2 a second exemplary embodiment is shown in which there is a plurality of light sources 110 and 120 alternate to each other along all the perimeter of the capsule. This way, it is very increased the probability that the capsule 100, independently of its position and its orientation inside the stomach, can emit effective light waves, i.e. that reach the desired target for therapy.

In the figures 3A, 3B, 3C and 3D some exemplary embodiments of the capsule are shown that have different forms of the wrapper 130 and, therefore, different dispositions of the inner components.

The foregoing description some exemplary specific embodiments will so fully reveal the invention according to the conceptual point of view, so that others, by applying current knowledge, will be able to modify and/or adapt in various applications the specific exemplary embodiments without further research and without parting from the invention, and, accordingly, it is meant that such adaptations and modifications will have to be considered as equivalent to the specific embodiments. The means and the materials to realise the different functions described herein could have a different nature without, for this reason, departing from the field of the invention. it is to be understood that the phraseology or terminology that is employed herein is for the purpose of description and not of limitation.

CLAIMS

1. An ingestible capsule (100) arranged, in use, to cross a human stomach for carrying out a phototherapic treatment arranged to combat an infection due to the presence of the bacterium Helicobacter pylori, said ingestible capsule (100) comprising:

- at least one primary light source (110) arranged to emit an electromagnetic phototherapic wave having a wavelength λ_1;
- at least one auxiliary light source (120) arranged to emit an electromagnetic phototherapic wave having a wavelength λ_2;
- a wrapper (130) arranged to contain said or each primary light source (110) and said or each auxiliary light source (120), said wrapper (130) being at least partially transparent to said wavelengths λ_1 and λ_2;
- a control unit (140) arranged to selectively activate said or each primary light source (110) and/or said or each auxiliary light source (120);
- at least one energy source (150) arranged to provide energy for feeding said control unit (140) and/or said light sources (110,120);

said wavelength λ_1 and λ_2 being such that $400nm < \lambda_1 < 525nm$ and $525nm < \lambda_2 < 650nm$;

said ingestible capsule (100) **characterized in that** said control unit (140) is also arranged to:

- receive an information of position reporting in real time an area of said stomach crossed by said ingestible capsule (100);
- determine, known said information of position, a wavelength, a dosage and a duration of administration said electromagnetic phototherapic waves for an optimal phototherapic treatment of said area of said stomach;
- selectively activate said or each primary light source (110) and/or said or each auxiliary light source (120) to provide said optimal phototherapic treatment of said area of said stomach.

2. The ingestible capsule (100), according to claim 1, wherein $\lambda_2 \cong 625nm$ and $\lambda_1 \cong 500nm$.

3. The ingestible capsule (100), according to claim 1, wherein said control unit (140) is also arranged to receive an information concerning the temperature of said light sources (110,120), said information concerning the temperature allowing to determine the duration of administration of said electromagnetic phototherapic waves to allow a lower consumption of the energy supplied by said energy source (150).

4. The ingestible capsule (100), according to claim 1, wherein a detector of pH is also provided configured to measure the level of pH in the environment surrounding said ingestible capsule (100) to provide said information of position to said control unit (140).

5. The ingestible capsule (100), according to claim 1, wherein an inertial sensor is also provided arranged to determine linear and angular speed and acceleration of said ingestible capsule (100) to provide said information of position to said control unit (140).

6. The ingestible capsule (100), according to claim 1, wherein at least one proximity sensor is also provided configured to measure the proximity of a wall of said stomach from said ingestible capsule (100).

7. The ingestible capsule (100), according to claim 1, wherein within said transparent wrapper (130) a diffusive fluid is provided arranged to increase the diffusion of said light sources (110,120).

8. The ingestible capsule (100), according to claim 1, wherein said transparent wrapper (130) comprises light guides arranged to convey said electromagnetic phototherapic waves along predetermined trajectories.

Fig. 1

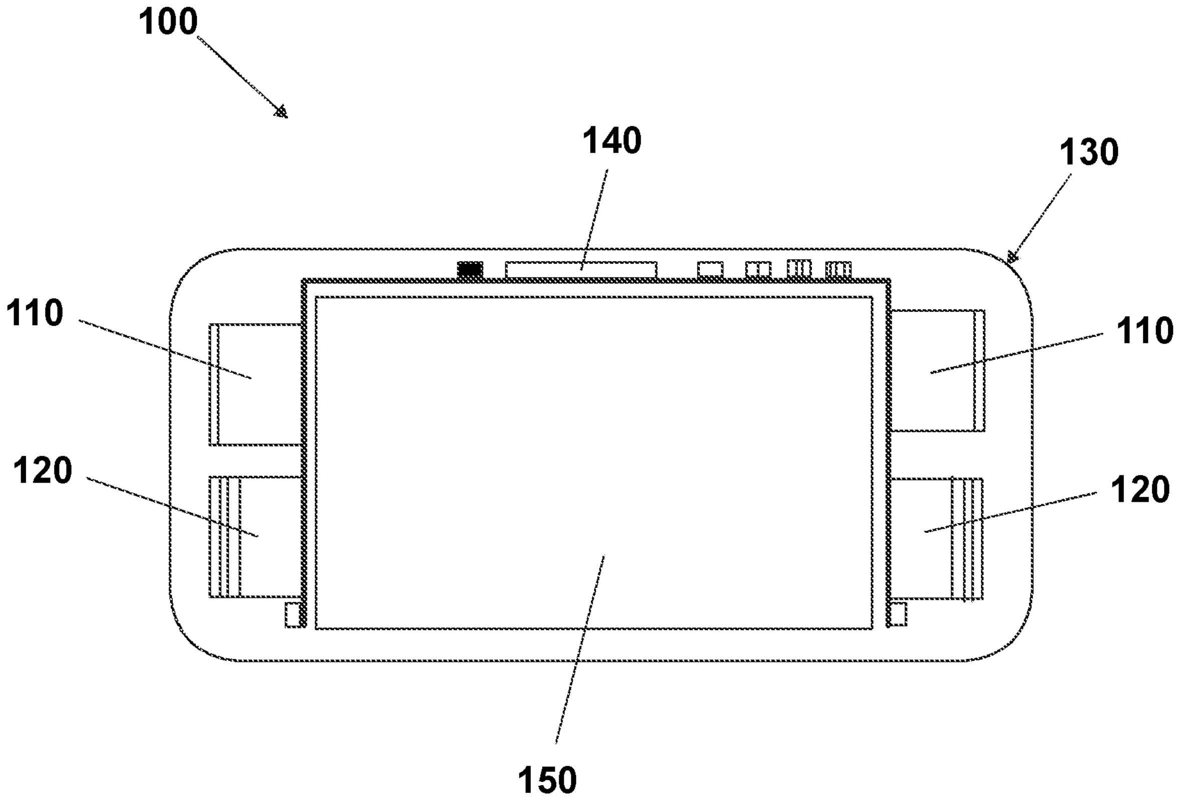
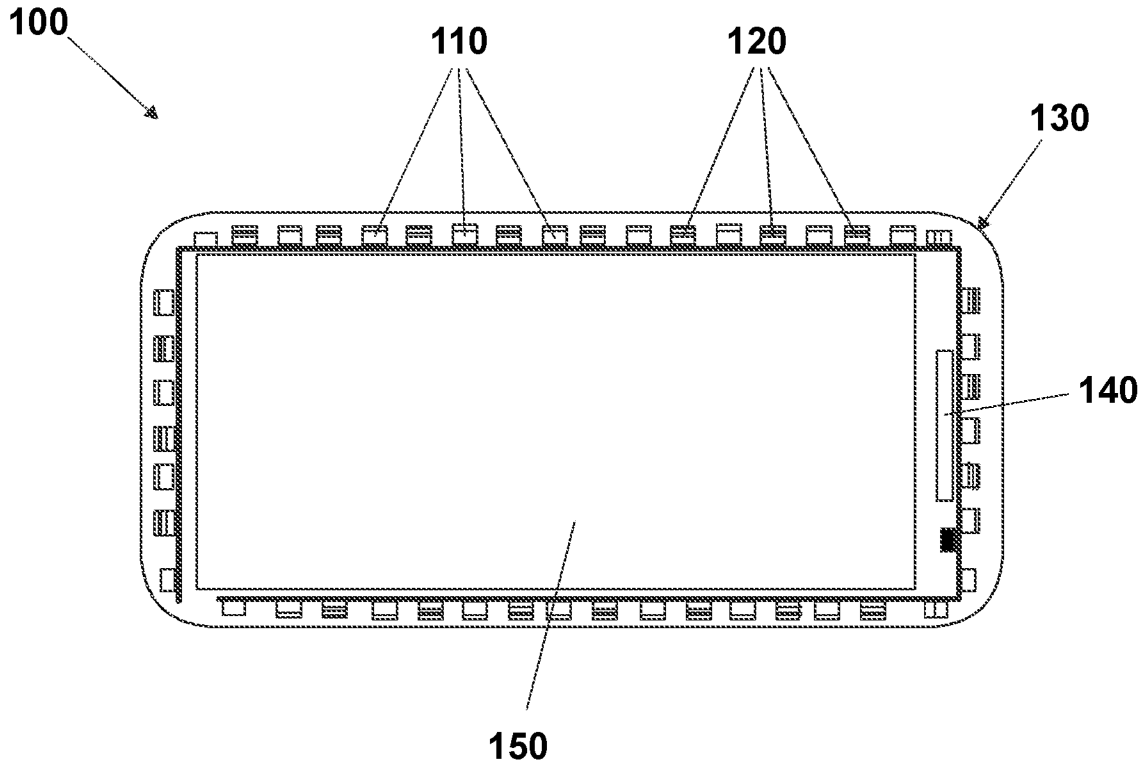


Fig. 2



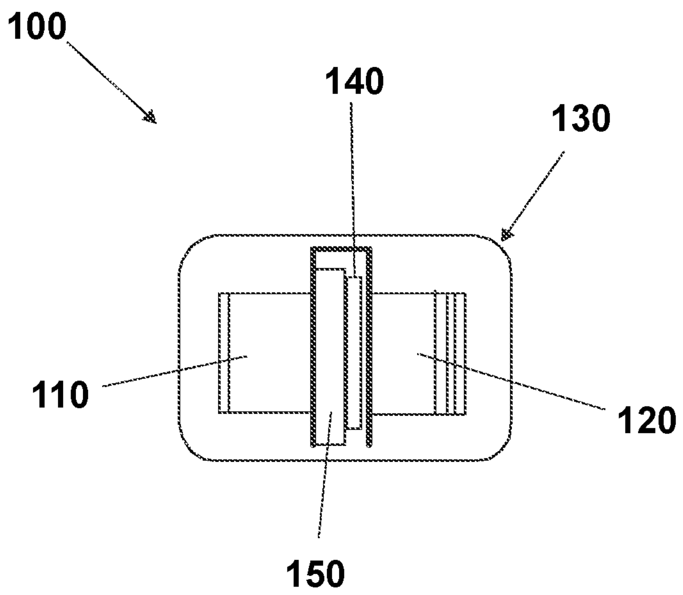


Fig. 3A

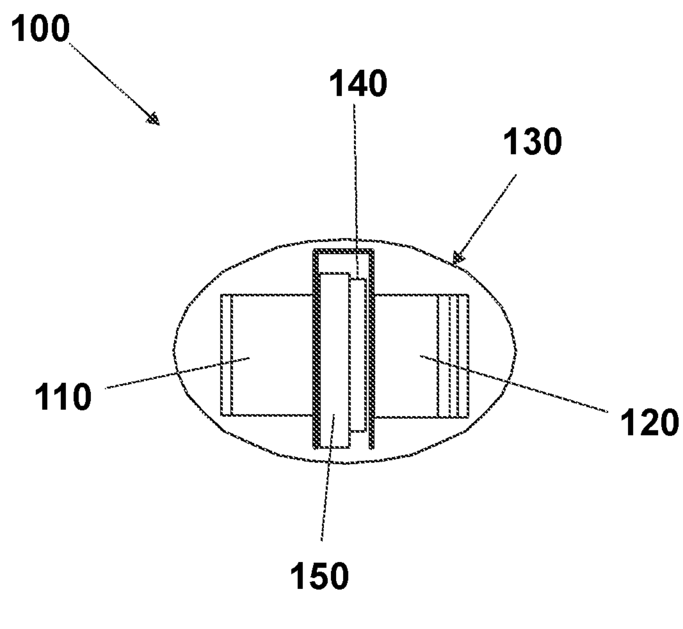


Fig. 3B

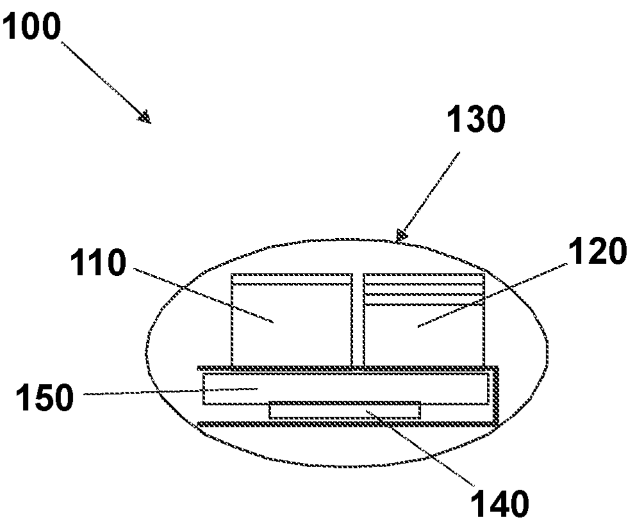


Fig. 3C

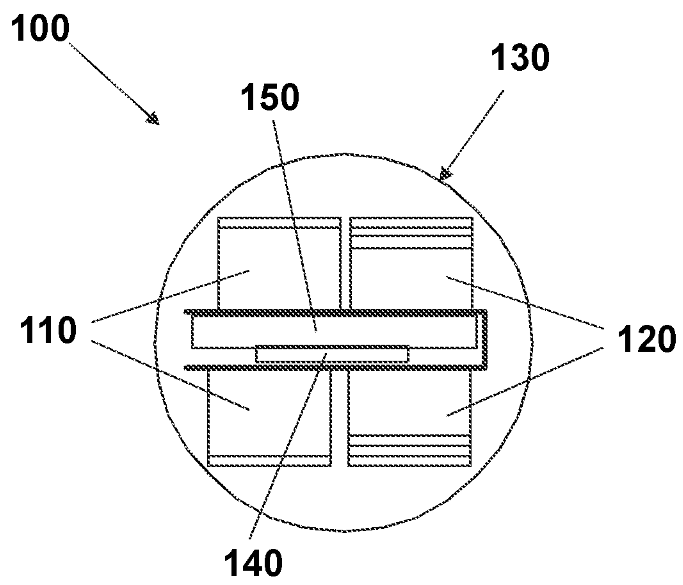


Fig. 3D

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/058227

A. CLASSIFICATION OF SUBJECT MATTER
INV. A61N5/06 A61B5/06 A61B5/07 A61B5/145 A61B5/00
ADD.

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)
A61N A61B

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

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

EPO-Internal, WPI Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 2012/123939 A1 (PHOTOPILL MEDICAL LTD [IL]; BEN-YEHUDA SHARON [IL]; BEN-YEHUDA RAM [IL) 20 September 2012 (2012-09-20) the whole document -----	1-8
A	WO 2011/055395 A1 (UNIV FIRENZE [IT]; SURRENTI CALOGERO [IT]; FUSI FRANCO [IT]; SURRENTI) 12 May 2011 (2011-05-12) claim 5 -----	1-8
A	US 2013/053928 A1 (GAT DANIEL [IL] ET AL) 28 February 2013 (2013-02-28) paragraph [0015] paragraph [0013] paragraph [0016] paragraph [0049] paragraph [0067] -----	1-8

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[X] Further documents are listed in the continuation of Box C.

[X] See patent family annex.

* Special categories of cited documents :

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Date of the actual completion of the international search	Date of mailing of the international search report
22 March 2018	03/04/2018

Name and mailing address of the ISA/	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Fax: (+31-70) 340-3016	Rodríguez Cosío, J

INTERNATIONAL SEARCH REPORT

International application No
PCT/IB2017/058227

C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indioation, where appropriate, of the relevant passages	Relevant to olaim No.
A	CN 203 935 519 U (LIFOTRONIC TECHNOLOGY CO LTD) 12 November 2014 (2014-11-12) abstract -----	1-8
A	US 2008/161748 A1 (TOLKOFF MARC JOSHUA [US] ET AL) 3 July 2008 (2008-07-03) paragraph [0047] paragraph [0099] paragraph [0106] paragraph [0120] paragraph [0141] -----	1-8

INTERNATIONAL SEARCH REPORT

Information on patent family members

International application No

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专利名称(译)	用于感染的光疗治疗的可摄取胶囊		
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[标]发明人	TORTORA GIUSEPPE ROBERTO		
发明人	TORTORA, GIUSEPPE ROBERTO		
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外部链接	Espacenet		

摘要(译)

一种可摄入的胶囊（100），其在使用中布置成穿过人胃以进行光疗治疗，所述光疗法被设置为抵抗由于幽门螺杆菌的存在而引起的感染，所述可摄取的胶囊（100）包括至少一个主光源。（110）布置成发射具有波长λ1的电磁光疗波，至少一个辅助光源（120）布置成发射具有波长λ2的电磁光疗波，包装物（130）布置成包含所述或每个主光源（110）所述或每个辅助光源（120），所述包装物（130）对所述波长λ1和λ2至少部分透明，控制单元（140）设置成选择性地激活所述或每个主光源（110）和/或所述或每个辅助光源（120）和至少一个能量源（150），其布置成为馈送所述控制单元（140）和/或所述光源（110,120）提供能量。特别地，400nm <λ1<525nm和525nm <λ2<650nm。此外，所述控制单元（140）被配置为接收实时报告由所述可摄入胶囊（100）穿过的所述胃的区域的位置信息;确定，已知所述位置信息，所述电磁光疗波的波长，剂量和给药持续时间，以对所述胃的所述区域进行最佳的光疗治疗;选择性地激活所述或每个主光源（110）和/或所述或每个辅助光源（120）以提供所述区域的所述最佳光疗治疗胃。