An Intelligent Wired Capsule for the Treatment of Helicobacter pylori

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Featured Application: An intelligent active actuation system for intelligent treatment of Helicobacter pylori with light.

Abstract: An endoscopic capsule is a miniaturized ingestible video camera used to acquire images of the gastrointestinal tract wirelessly. Being morphologically equivalent to any ingestible pill, they can be simply swallowed. Endoscopic capsules therefore present an inviting alternative to the traditional endoscope for the examination of the gastrointestinal tract as well for therapeutic purposes. Endoscopic capsules are considered a disruptive technology, as they have revolutionized the examination of the gastrointestinal tract in a relatively short time. The implementation of an active locomotion system can improve the performance of a capsule and, in the solution proposed in this paper, allows providing the capsule the needed power for therapeutic purposes. Alternative therapeutic solutions, based on optical solutions and capsule endoscopy, can be applied to patients affected by Helicobacter pylori, a bacterium of the stomach that affects about half of the world population, mainly in developing countries. The infection can be asymptomatic or associated with slight symptomatology. In some cases, it can be taken to major pathologies or death. The literature reports results deriving from recent applications of photodynamic treatments to H. pylori. Specific wavelengths have been found to exhibit photo-killing capabilities toward the bacterium. Some solutions have been proposed based on the use of endoscopic devices and capsules capable of administering photodynamic therapy inside the stomach. The proposed treatments, however, are invasive and insufficient to achieve long-term eradication. In this work, the administration of photodynamic therapy is proposed, aimed at the eradication of H. pylori by means of an active endoscopic capsule with LED emission. The capsule design, in addition to the therapeutic module aimed at administering an appropriate light intensity at specific wavelengths already demonstrated in the literature, integrates an active locomotion system aimed at maximizing the efficiency of the treatment.

Keywords: capsule endoscopy; Helicobacter pylori; intelligent treatment method

1. Introduction

Helicobacter pylori is a Gram-negative microaerophilic bacterium [1,2]. It generally has a spiraling conformation, the typical shape, helical and elongated, is similar to that of a corkscrew or a curved shaft. The bacterium is characterized by the presence of filiform polar structures called flagella [3]. The flagella, in variable numbers between four and seven, are fixed to the basal body through an anchoring system, which constitutes one of the fundamental components of the flagellar structure. In fact, they are basically composed of the basal body, anchoring system and flagellar filaments. The basal body has various structural proteins and plays a crucial role in providing the bacterium with the energy necessary for motility. The flagellar filaments, on the other hand, are essentially made up of two proteins, called flagellins, FlaA and FlaB, respectively encoded from the flaA and flaB genes. The two genes, flaA and flaB, are considered, by preliminary studies, to be fundamental for the motility of H. pylori [3]. Flagella, in fact, provide the bacterium with the...
ability to selectively move within the stomach, allowing it to target the mucosa [4]. Under severe stress conditions, *H. pylori* may have a coccoid form. During the shape mutation, however, there is no variation in the protein content. Despite the conformational change, the bacterium remains genetically unchanged.

Studies with the electron microscope have actually revealed that *H. Pylori* can have three conformations: spiraling, coccoid and coccoid degenerate. The spiraling conformation is viable, cultivable, infectious, virulent and capable of inducing inflammation [5].

In this thesis work, the administration of photodynamic therapy is proposed, aimed at the eradication of *H. pylori* by means of a spun endoscopic capsule with LED emission.

The capsule designed, in addition to the therapeutic module aimed at administering an appropriate light intensity at specific wavelengths, integrates an active locomotion system aimed at maximizing the efficiency of the treatment.

The light source at the base of the therapeutic module consists of 56 LEDs with three different wavelengths driven by dedicated electronics aimed at making the treatment modular. In order to verify, through in vitro experimentation, the efficacy of the three selected wavelengths and the dose required for therapeutic eradication, a special experimental setup was developed, capable of providing reliable and repeatable results.

The active locomotion module maximizes the effectiveness of the treatment by identifying and focusing the treatment on the areas affected by the bacterium.

The basis of active locomotion is the design of a cable actuation system that does not require additional energy input. Various cable actuation mechanisms were designed and tested, through rapid prototyping, based on the use of a ball joint, a flexible multilumen cannula and appropriate structural changes to the casing. The introduction of a multilumen cannula justifies the use of an external power source, allowing the overcoming of the energy limitations related to battery power.

The area generally reserved for batteries is used for the integration of a commercial camera aimed at providing visual feedback on movement. The harmonic integration of the therapeutic module and the active locomotion module inside the capsule provides a highly performing device capable of operating on the entire surface of the stomach, identifying the areas to be treated and addressing the treatment in a targeted manner.

2. Materials and Methods

The PDT photodynamic therapy is a non-invasive treatment based on the effects resulting from the combination of individually inert agents. The conversion of molecular oxygen into reactive oxygen species, ROS, which can damage the cytoplasmic organelles or the cell membrane of the treated cells, originates from the stimulation of a light-sensitive substance through appropriate wavelengths [6]. Spectroscopic characterization and fluorescence imaging of *Helicobacter pylori* endogenous porphyrins as been also performed in literature [7].

The effect generated on many bacteria, both Gram-negative and Gram-positive, led to the evaluation of PDT in the eradication of *H. pylori*, with a view to determine an effective treatment that overcomes the problem of antibiotic resistance [8–11].

In reality, the action of the PDT against *H. pylori* was tested by Bedwell as early as 1990 [12]. Further experiments, aimed at detecting the action of different PS, reported interesting results following the application of Protoporphyrin IX in the treatment of *H. pylori* [13]. The determination of the ability, by various strains of *H. pylori*, to spontaneously synthesize porphyrins was the real step forward in considering PDT as an alternative treatment to the antibiotic. The bacterium, cultured in an aqueous medium, has, in fact, shown the ability to synthesize a quantity of protoporphyrins IX and coproporphyrins sufficient to kill even the most virulent and antibiotic resistant species, simply by using visual light. All strains involved in the experiment showed 99.9% eradication following irradiation at 20 J/cm² with a wavelength of 405 nm [14]. The absorption spectrum of the bacterium’s endogenous porphyrins varies in relation to the relative concentration between PPIX (protoporphyrin IX), and CP (coproporphyrin I). However, this spectrum is characterized by
a maximum absorption peak around 400 nm followed by a second peak, approximately 10 times lower in intensity, located between 500 nm and 650 nm. Porphyrin extracted from various strains of *H. pylori* shows, in fact, the same fluorescence spectrum as commercial porphyrin [6].

Ganz and co. developed the first clinical trial aimed at verifying the eradication of *H. pylori* by blue light. The treatment focuses on the gastric antrum, which was uniformly exposed to the wavelength of 450 nm for 4.5 min, using a laser diode endoscope, also used to identify the areas to be treated and to take samples, both before and after treatment. The comparison between the samples taken before and after the treatment shows that *H. pylori* can be eradicated in a single therapeutic session. At the relatively low levels of energy and power used, there is no appreciable overheating of the stomach wall or tissue damage [15]. However, it is necessary to verify the ability of the wavelength used to hit the *H. pylori* undermined within the mucosa. Previous studies, aimed at determining the depth of penetration of visible light into the tissues, found that light at 400 nm penetrates only 2 mm into bovine muscles [16].

Lembo and co. created a device capable of supplying 12 W to the entire surface of the stomach with a wavelength of 408 nm. The comparison between the samples taken before and after the treatment shows a significantly different bacterial load in the antrum and in the body, but not in the fundus of the stomach. The long-term results of the urea breath test show no changes following treatment, indicating the failure of the proposed therapy. One result could be derived from the presence of bacterial colonies undermined in depth in the wrinkles or in the crypts of the mucosa, difficult to reach by the wavelength used, regardless of the duration of irradiation. The result also indicates that a small residual bacterial fraction is enough to re-establish the colonization of *H. pylori*.

2.1. Importance of Actuation

The pre-industrial prototype created due to dimensional and, consequently, energy limitations, manages to integrate only 8 LEDs at 625 nm, ending up delivering an average dose of 12 J/cm² compared to the 16 J/cm² necessary for eradication of the bacterium with red light [11]. The device is shown in Figure 1. In order to deliver the minimum dose necessary for eradication, it is therefore necessary to ingest two capsules in the case of a collapsed stomach and 11 capsules in the case of a distended stomach. The LEDs at 405 nm, on the other hand, although we have shown their efficiency to be similar to red LEDs, they were integrated only into an experimental prototype powered by batteries not certified for clinical use. Theoretical calculations indicate that three capsules are needed in the case of a collapsed stomach and ten with a distended stomach (capsules of 8 LEDs at 405 nm to reach a total of 9 J/cm² necessary for the eradication of the bacterium with blue light) [17].

Figure 1. Current prototype of capsule for *Helicobacter pylori* eradication.
Given the limitation of the current device, the aim of this paper is the introduction of an actuation mechanism for improving the overall performance of the device. The realization of the implementation of a capsule can follow two approaches defined, respectively, as internal locomotion and external locomotion. In internal locomotion systems, an attempt is made to integrate a miniaturized locomotion system inside the capsule, while external locomotion is generally entrusted to sources of magnetic fields. There are several approaches to building an internal locomotion system [18]. Tortora and co. developed an interesting actuation system based on the integration of four miniaturized propellers, placed on the back of the capsule, independently actuated by means of DC brushed motors [19]. The performance in the capsule was improved with the work by De Falco and co. [20], which, by integrating a vision system and a wireless transmission system, created an advanced version of the same capsule. The simultaneous powering of the motors and the vision system, however, provides the capsule with only 13 min of autonomy. Several endoscopic capsules integrate bio-inspired locomotion systems. The locomotion system devised by Kim and co., for example, is inspired by the movement of the earthworm [21]. The implementation of the capsule derives from the compression and elongation cycles of an SMA spring in combination with an anchoring system with directional micro needles. However, the power required by the system is too high to be delivered by means of batteries that can be dimensionally integrated inside the capsule [22]. Not even the development of a special piezoelectric spring actuator, in a second version of the capsule, solved the problem related to the power supply [22].

The capsule made by Li and co. inspired by the movement of the cilia of the gastric mucosa. The device consists of six cilia-like units, each of which is connected to two SMA actuators to ensure bi-directional movement. The capsule does not integrate an on-board power system. It is powered by cable [23].

Park and co. proposed a solution inspired by the movement of canoes [24]. The capsule is equipped with six legs activated simultaneously by a single step motor associated with a screw, in order to guarantee linearity of the movement. Glass and co. created a three-legged capsule inspired by the locomotion of geckos and cockroaches [25]. The system is able to withstand peristaltic loads, allowing the capsule to remain anchored to the intestinal wall. The system based on three SMA legs with strain gage was proposed by Tognarelli and co. for anchoring the capsule in the esophageal tract [26].

At the biorobotics institute of the Sant’Anna School, several capsules with legs were developed [18]. However, both the capsule with four superelastic legs connected to a single DC motor and the one with eight legs, organized in two groups of four implemented separately, need to be powered by cable [27,28].

Valdastri and co. created a prototype with 12 legs capable of improving the distension of the lumen and, probably, anchoring in the event of reflux. In the experimental phase, the capsule was fed by wire [29].

Another example of internal locomotion is presented by a progression of the capsule obtained by means of a series of vibrations [30]. The system is very simple but does not allow directional changes, capsule anchoring or active orientation control.

2.2. Overall Characteristics of the Device

The work is aimed at the design and construction of a device capable of providing an attractive, alternative and universally applicable approach for the eradication of H. pylori.

It was established that an acceptable therapeutic solution must exhibit an eradication rate of no less than 90%. Some pharmacological therapies traditionally used against H. pylori infection show a failure rate of 32% and the ineffectiveness is clearly increasing due to the progressive increase in antibiotic resistance. The latest therapies based on bismuth and non-bismuth-based quadruple therapy administered for 14 days have > 90% eradication rate. However, they are still based on a pure drug approach.

The recent literature shows preliminary experimental tests that show the good photo-killing capacity of H. pylori by specific wavelengths in the visible range. The bacterium, in
fact, has endogenous porphyrins that allow the administration of photodynamic therapy without the need to introduce exogenous photosensitizers. The application of PDT to \textit{H. pylori}, therefore, simply translates into the illumination of the bacterium with appropriate wavelengths.

The thesis developed a hypothetical approach for photodynamic therapy against \textit{H. pylori} administered via a spun capsule.

The device has the objective of carrying out an effective and targeted therapeutic treatment. In fact, the aim is to focus the administration only in the areas affected by the bacterium in order to maximize therapeutic efficiency, reducing unnecessary energy dissipation and minimizing the overheating of healthy tissues. The device, therefore, consists of the integration of two distinct but complementary modules that work synergistically to achieve the set goal.

The therapeutic module, as the name itself suggests, is aimed at administering the actual therapeutic treatment. It is therefore based on the release of light energy at appropriate wavelengths, considered optimal for the eradication of the bacterium. Given the typical dimensional constraints associated with the creation of a capsule for the gastrointestinal tract, only LED energy sources were considered and integrated. In fact, thanks also to the developments in microelectronics, the market offers small-sized LEDs capable of delivering high power, which are ideal for the application in question. The module can be powered by batteries approved for clinical use that can be integrated inside the capsule. It was, in fact, conceived and designed as a energetically and functionally autonomous system, which can be integrated and used without the need for additional components. It could, in fact, be considered the realization of a therapeutic capsule constituted solely by the therapeutic module in question. This capsule would still be able to administer PDT against \textit{H. pylori} but would be characterized by a low energy content and passive locomotion by peristalsis. Basically, you would have a capsule with little energy randomly released inside the stomach. The device, therefore, would be inefficient and, with great probability, ineffective.

The active locomotion module has the objective of focusing the treatment in the area of interest, maximizing its efficiency. It is based on the combined action of vision and actuation, which guarantees movement toward the target area after having visually identified it.

The implementation allows the active movement of the capsule, allowing it to move in a targeted manner. Considering the various problems related to the different implementation proposals for capsules and the limitations presented by the therapeutic module, deriving from battery power, a cable actuation mechanism is proposed that does not require additional energy requirements. The mechanism introduces a minimal invasiveness in the treatment, which is amply compensated by the increase in efficiency.

The introduction of a cannula, functional to the actuation mechanism, justifies the integration of a commercial video camera with wire. The camera, being fully integrated into the active locomotion system, does not increase the invasiveness of the device but certainly increases its efficiency, allowing the identification of the target area.

The components aimed at carrying out the implementation and the camera are harmoniously integrated within the dimensions, 11 mm in diameter by 26 mm in length, of the capsule.

However, it must be emphasized that the active locomotion system, like the therapeutic module, is capable of operating autonomously. It could, in fact, be implemented separately within a device that performs screening or diagnostic tests.

The two modules used separately would, however, give rise to inefficient devices and, probably, poor functionality. Only the combined action of the two allows for good performance and a targeted treatment of desirable effectiveness.

2.2.1. Therapeutic Module

The therapeutic module is presented as the main component of the capsule to eradicate the bacterium. As the name itself suggests, in fact, it is the functional module for
administering the treatment of PDT. To ensure effective photodynamic therapy, careful selection of the wavelengths that are optimal for photo-killing is essential.

The most effective wavelengths, at least intuitively, should be those at which the endogenous porphyrins of *H. pylori* show increased sensitivity.

The number of ROS generated, in fact, can be considered, as a first approximation, directly proportional to the quantity of photons absorbed by the PS.

By analyzing the absorption spectrum of the endogenous porphyrins of *H. pylori*, there is an important peak around 400–410 nm. The spectrum reveals, in reality, other peaks in the visible range, which, however, are clearly lower than the main one and less and less important proceeding in the direction of the infrared. For this reason, it would seem that the most effective wavelength for photo-killing is in the violet range. However, the first therapeutic solutions based on the use of this wavelength have found a high rate of long-term reinfection. Although, in fact, the eradication rate manifested immediately after the administration of the treatment was 99%, the results of the breath test revealed the reappearance of the infection already after 5 days [11]. Additionally, taking into account the 99.9% eradication detected by in vitro experimentation, it is assumed that the reappearance of the infection is due to the rapid proliferation of bacterial colonies nested in the innermost layers of the gastric mucosa that cannot be reached by photons at 400 nm.

In fact, if the penetration depth of visible light inside the gastric mucosa is also taken into consideration, the graph on the right in Figure 2, it can be seen that wavelengths around 400 nm have low penetrating power. Penetration is optimal in the red range. A small peak of penetrating power is also recorded near 500 nm.

![Figure 2. Left: absorption spectrum of the endogenous porphyrins of *H. pylori*. Right: depth of penetration of visible light inside the gastric mucosa.](image)

Comparing the two graphs in Figure 2, it is clear that photons at 400 nm are ideal for the excitation of PS but not very suitable for penetrating into tissues. On the other hand, in the red range, characterized by maximum penetrating power within visible light, the absorption spectrum of the porphyrins endogenous to *H. pylori* has a small spike close to 630 nm. It could, therefore, be assumed that the wavelength of 630 nm, combining the high penetration into the mucosa with the discrete ability to be absorbed by the PS, could somehow compensate for the inefficient penetrating capacity of blue, optimizing the outcome of the therapy.

In the same vein, the wavelength of 500 nm attracted attention. At 500 nm, in fact, there is an average penetrating power inside the mucosa and a medium absorption capacity by porphyrins. The combination of the two actions of medium intensity could have an even better effect than that of red and blue, which tend to excel in one aspect but are mediocre in the other.

By virtue of the provisions and also taking into account the results obtained in the simulation of Romano et al. on the effectiveness of photo-killing, it was decided to integrate three wavelengths into the therapeutic module: 405 nm, 630 nm and 500 nm.
Having to administer a therapeutic treatment in addition to selecting the wavelengths, it is also essential to consider the emission of the light source. The energy released by the therapeutic module per unit of surface in the unit of time, otherwise identified as a dose, must be suitable for the eradication of the bacterium. It would be preferable to be able to carry out the treatment in the shortest possible time in order to provide an efficient therapy without reducing effectiveness.

The purposes of the therapeutic module in fact require great attention in the selection of an appropriate light source. To verify the photo-killing capacity of the selected wavelengths and determine the amount of dose necessary to obtain a possible therapeutic eradication rate, a special experimental setup was developed.

2.2.2. Experimental Setup for Preliminary Evaluation of the Effectiveness of the Chosen Wavelengths on the Eradication of \( H. pylori \)

The design of the experimental setup is aimed at determining the effectiveness of the chosen wavelengths on the eradication of \( H. pylori \). It basically looks like a device that allows the lighting of the bacterium and is capable of varying the light energy emitted by variations in the duration and/or intensity of the emission.

We tried to create a solid and reliable tool that guarantees high reproducibility of the tests in order to obtain results that are valid not only for the work in question, but for the scientific community in general.

Conventional microbiology bags placed inside an incubator at 37 \(^\circ\)C were used to carry out the tests. Being that \( H. pylori \) is a microaerophilic bacterium, it is necessary that the tests are carried out in a controlled environment. To recreate optimal experimental conditions, the typical bags for microbiological experimentation are used, placed inside an incubator at 37 \(^\circ\)C.

Therefore, it is also necessary that the resulting device, the illuminator for bacterial culture, is entirely contained within the 33 cm length and 15 cm width of the bag used. It is essential to introduce a battery power supply, as it does not have the ability to introduce cables inside the bag. The energy supplied by the battery must be released in a relatively short time. The time of experimental interest is set at 1 h and represents the maximum established duration of the experiment, that is, of the lighting. This is quite a short time, compared to the 3.5 h it takes for the bacterium to replicate. It is important that the emitted power remains constant throughout the duration of the experiment and that it is almost entirely transferred to the bacterium.

To allow the setup to work optimally, the components it consists of must be carefully selected. The experimental setup, having to test the photo-killing effect of the various wavelengths, must be adequate to ensure homogeneous and uniform illumination of the Petri dish, avoiding the interaction of the light emission with other components before reaching the bacteria. To achieve the purpose, it is therefore essential to use a photo-absorbent material to create the support in order to avoid scattering, reflection of light or other phenomena that could generate indirect illumination of \( H. pylori \). To achieve the purpose, the device was built according to a modular architecture, shown in Figure 3.

The fundamental component is certainly the electronic board. The electronic board is in fact the component that provides the lighting, adapting it to the experimental needs. It is good to carefully consider the electronic components used in order to reuse the therapeutic module of the capsule in the electronics.
2.2.3. Manufacturing of the Illuminator Boards

The configurations used for the last three types of LEDs described above can be superimposed both with respect to the position and the very similar size of the LEDs.

It is, therefore, possible to create all the electronic boards you need by standardizing them to only two schematic types, called Type A and Type B, shown in the following figure.

To allow adequate light output, in addition to the careful selection and reasoned positioning of the LEDs, the use of electronic components capable of programming and modulating the operation of the LEDs and ensuring the stability of the power supply during the experiments is essential. While the upper board is dedicated to the location of the light source, the lower board houses the electronic components aimed at ensuring reliable and repeatable delivery. The lower board, in fact, can be considered, at least structurally, identical for all LED types. All the boards all shown in Figure 4.

2.2.4. Outcomes from Preliminary Testing of the Illumination Module

The illumination module was extensively tested in previous articles [7–9]. The effectiveness of the illumination module was already demonstrated and reported here for the sake of clarity. However, basing on the scientific outcomes, it was calculated the number of capsules a patient should swallow for achieving complete eradication.

If a capsule with the calculated light output was static, the time required for the delivery of a therapeutic dose could be determined by carrying out a simple modeling of the regions most affected by H. pylori within the stomach. This was calculated with the aim of a simplified model of the stomach, approximated by means of a series of equivalent cylinders (Figure 5).
An attempt is made to evenly distribute the selected types of LEDs along the perimeter of the capsule. Considering that the volume of the slightly distended stomach is around 0.5 L and that, from the literature, it is indicated that the volumes occupied by the antrum and the body are, respectively, 20% and 65% of the total, it can be considered a volume of the cave equal to $100 \text{ cm}^3$ and that of the body equal to $325 \text{ cm}^3$. The antrum generally has a diameter of 1–2 cm, while the diameter of the body, in conditions of slight expansion, can reach 6 cm. Taking as a reference a diameter of 2 cm for the cave and 6 cm for the body, a surface to be treated of $100 \text{ cm}^2$ and $325 \text{ cm}^2$, respectively, are obtained. The average power density transmitted by the capsule is therefore equal to $3.15 \text{ mW/cm}^2$ in the cave and $1.49 \text{ mW/cm}^2$ in the body. As no experimental data are available on the effective dose at 500 nm and with different wavelengths in the capsule, we are in an intermediate situation between the efficacy of red and that of blue, considering as a reference a therapeutic dose of $18 \text{ J/cm}^2$. The eradication, according to the theoretical calculations, would be obtained in 1.5 h in the cavern and in 3.3 h in the body, a value not compatible with the power in one single swallowable capsule.

The capsule conceived, however, having an edge with an active locomotion system, aims to focus the treatment exclusively on the areas affected by the bacterium. It therefore offers the great advantage of considerably increasing the local power times by greatly reducing treatment. Treatment times could be reduced by creating a future version of the therapy module which, by presenting the cable power, integrates equally small but more powerful LEDs. The use of an active intelligent locomotion module will allow to reduce the invasiveness of the approach. Although the single capsule can be still considered not invasive, ingesting more than one capsule can result in additional risks and an impact on the environment. In fact, although a recovery of the capsule was foreseen, the fact that the patient recovers the capsule after expulsion cannot be guaranteed.

2.3. Design of the Therapeutic Module of the Intelligent Capsule

We set ourselves the goal of creating a capsule capable of releasing the illumination uniformly in order to maintain a constant amount of light energy delivered to the unit of surface in the unit of time. In fact, an attempt is made to design a device with reliable behavior that does not add to the subjectivity variability of each individual uncertainty linked to variations in the performance or operation of the device.

The uniformity of the lighting is obtained by distributing the chosen LEDs as evenly as possible and by adjusting the lighting parameters using appropriate electronic components. An attempt is made to evenly distribute the selected types of LEDs along the perimeter of the capsule. Stringent dimensional constraints, linked above all to the size of the battery...
power supply and the characteristics of the casing, require that the surface of the capsule is not entirely covered with LEDs.

The design of the electronic card, shown in Figure 4, is articulated on two identical round cards from which four arms branch off. The distribution of the LEDs in the various areas tries to recreate an equal light intensity of the three integrated wavelengths. The two round boards, in fact, are less tied to dimensional constraints, and each have ten LEDs, of which three are Bivar, SM0603UV-40555, three are Everlight, EL-19-21UBGC/TR856 and four are Panasonic, LNJ247W82RA57. In the side arms, on the other hand, due to the limited space available, it is possible to place only the Panasonic, LNJ247W82RA57, having a size equal to $1 \times 0.5 \times 0.2$ mm. The other two types of LEDs, having similar overall dimensions, precisely equal to $1.6 \times 0.8 \times 0.6$ mm for the Bivars, SM0603UV-40555, and $1.6 \times 0.8 \times 0.8$ mm for the Everlight, EL-19-21UBGC/TR856, have submillimetric heights, which are, in any case, too high to be integrated into the lateral areas of the capsule. Even by decentralizing the electronics with respect to the external casing and halving the number of side arms, it is possible to insert only the Panasonic, LNJ247W82RA57, laterally without increasing the 11 mm diameter and 26 mm capsule height.

Nine Panasonic, LNJ247W82RA57, are inserted into each side arm. By adding the LEDs inserted in the six parts into which the board is divided, a total of 56 LEDs on board the capsule are obtained of which, however, 44 emit a wavelength of 630 nm. It is clearly evident that Panasonic’s number, LNJ247W82RA57, is decidedly greater than that of the other two types. This imbalance between the types of LEDs on board the capsule is not simply linked to reasons of space. Wanting to create a module capable of operating autonomously, the electronics are enabled for housing the battery power supply by inserting the appropriate contacts. Given the size and the desire to have the greatest possible amount of energy on board the capsule, the series of four Renata batteries, 380 SR936W, is considered a hypothetical power supply for the therapeutic module. The capsule electronic board design is shown in Figure 6 while the complete electronics embedded with batteries is shown in Figure 7.

![Figure 6. Capsule electronic board design.](image-url)
2.4. Active Locomotion of the Intelligent Capsule

Active locomotion is aimed at focusing the treatment on the regions affected by the bacterium, avoiding the transfer of light energy to healthy tissues. Although the wavelengths used do not induce the onset of tissue damage, it is still desirable not to carry out unjustified administration of doses to avoid energy waste and, potentially, tissue overheating.

The focus of the treatment on the areas affected by the infection requires the identification of the same areas and the possibility of placing oneself in the vicinity of the areas to be treated. The integration of an active locomotion system based on the interaction between vision and implementation is, therefore, essential. In fact, vision allows to identify the target areas, while locomotion offers the possibility of optimizing the position of the capsule for the administration of the treatment.

Actuation System

Based on the energy limitations that characterize the capsules implemented and taking into account the limits related to the battery power supply of the therapeutic module, the best solution for the implementation of the capsule seems to be the one with cables.

The cable actuation system designed is energetically very convenient, as it does not require the use of active power sources. The position and orientation of the capsule, in fact, are varied through the application of external forces by the user.

The realization of an actuation system for endoscopic capsules without energy limitations is very advantageous since the main limitation in the realization of implemented capsules is precisely the insufficient energy made available by the use of batteries that can be integrated inside the capsule.

The realization of the cable implementation, however, involves the generation of a spun device from which a slight invasiveness is derived. The introduction of minimal invasiveness is the main flaw of the proposed implementation system. However, it is necessary to underline that the level of invasiveness linked to the implemented actuation system is far lower than that deriving from traditional endoscopy practices of usual clinical use. The introduction of the system inside therapeutic capsules made to carry out treatments normally performed using an endoscope would, however, generate less invasive treatment alternatives than those in use.

In fact, it should be emphasized that the implementation system, as well as the therapeutic module, was conceived and implemented as an independent component. As such, it can be integrated and used in any other device compatible with cable actuation mechanisms.
The actuation system is based on a very simple design and operating mechanism. At the base of the whole, there is an appropriate modification of the casing, aimed at enabling the passage of the actuation cables. The cables through the gastrointestinal tract connecting the capsule to the user using a multilumen cannula, shown on the left in Figure 8, with an external diameter of 2.2 mm from the Microspec Corporation. The cannula has a main central hole inside it, with a diameter of 0.9 mm, around which eight smaller through holes with a diameter of 0.4 mm extend radially.

![Figure 8. Left: multilumen cannula, Microspec Corporation. Right: right spherical made.](image)

To enable angular movements, a suitable ball joint was designed and built in rapid prototyping, shown on the right in Figure 8. The joint was created ad hoc to optimize the interaction with the multilumen cannula used. The goal was to obtain, following the assembly of the two parts, a joint–cannula system that operates as a single part, optimizing the displacements resulting from the application of forces.

The joint is hollow, and the architecture of the lower surface exactly reproduces the morphology of the multilumen cannula. On the lower cap of the joint, in fact, a central hole with a diameter of 1.2 mm was designed, surrounded by eight equally spaced holes, with a diameter of 0.4 mm, arranged circularly.

The housing, with a depth of 0.8 mm, for the cannula was prepared in the upper part of the joint. The cannula is inserted by exploiting the compliance of the material it is made of in order to avoid future detachments after assembly.

A special hemispherical housing was obtained on the casing to contain the joint, guaranteeing complete rotational freedom. While the bidirectional translation in height and the bidirectional axial rotation on 360° of the capsule were trivially obtained by translating and rotating, respectively, the multilumen cannula, to enable angular rotations with respect to the central axis, it is necessary to have a joint that disrupts the movement.

Through the holes of the joint–cannula coupling, the implementation wires on which the user has to operate are brought to the outside to generate the angular movement of the capsule with respect to the central axis. The need for a sturdy, thin and low-friction cable led to the use of the 0.18 mm diameter Fladen, Vantage.

The actuation wires are appropriately associated with the casing in order to create a mechanism based on the generation of angular moments.

The first version of the devised mechanism is based on the generation of very small slots inside the thickness of the casing. The slots are positioned, as in Figure 9, so as to ensure the sliding of a single thread, for each direction, along the perimeter of the capsule. The mechanism therefore provides for a thread that crosses the capsule from right to left and another that crosses it from front to back. Both ends are available for each thread. To tilt the capsule in one of the two directions, it is necessary to hold one end of the wire still and pull the other.
The mechanism was implemented in two configurations. The configuration visible on the left in Figure 9 is more congenial to integration with the therapeutic module, as it takes full advantage of the free spaces between one radial arm and the other of the electronic board. It involves the creation of a special housing in which to insert the joint. Given the limited space available for the creation of the housing, the joint cannot have a radius greater than 3 mm. The position of the cannula in this configuration seems rather inconvenient, even for the ingestion of the capsule.

The other configuration of the mechanism appears much less invasive, on the left in Figure 9. The housing of the joint can exploit the material already present at the end of the capsule. Thus, there is the opportunity to create a joint with a radius of 4 mm.

Starting from the limitations encountered in the first version, the second version of the mechanism was designed. We tried not to completely eliminate the system based on the sliding of a single wire along the same perimeter direction. This system is aimed at the distribution of stresses avoiding the formation of points of application of the forces that could cause cracks or breaks in the millimeter thickness of the casing.

The slots are replaced by more bulky housings that extend from the inner surface of the shell toward the inside of the capsule. The housings, on the right in 8, have a hole for sliding the wire. In reality, the morphology of the housing allows for the implementation of two different implementation mechanisms on the same design. The version is implemented using two configurations, shown as the graph on the left and in the center in 9, following the architectural line already used in the first version of the implementation. Therefore, four different configurations are obtained, the operating mechanism of which is illustrated in 9. The first two boxes implement a mechanism that is completely similar to that used in the first version. They have two wires which, passing through the housings, run along the perimeter of the capsule.

The other actuation mechanism, visible in the two boxes, requires the use of four separate wires, one for each side. Each wire is tied to only one housing. The inclination on each side can be impressed by pulling the corresponding wire.

2.5. Vision

The integration of a cable implementation introduced the presence of a multilumen conduit that allows taking advantage of the performance of spun components. Of the nine through holes present in the joint–cannula complex, only four necessarily are reserved for
the implementation system. There are, therefore, four free holes available, which can, for example, be used for the use of spun elements.

The main hole in the center of the joint–cannula is reserved for the passage of the camera wires. In fact, having a duct available that offers the possibility of introducing spun systems inside the capsule, it would make no sense not to take advantage of the advantages of a spun video camera.

In view of the two different configurations in which the implementation appears, two different commercial cameras were selected, one for each configuration, both of which can be integrated into the capsule.

3. Results and Discussion

The integration of both modules inside the capsule leads to the creation of a yarn device. The cannula, essential for creating an actuation system that does not require active energy, has nine through holes in an overall diameter of 2.2 mm. The actuation mechanism, however, does not need more than four wires, so it does not occupy more than four holes. The central hole of the cannula is reserved for the passage of the wire connected to the camera. Using the cannula to organize the entire active locomotion module, four through holes remain available. It is, therefore, obvious to think of using two of these to introduce an external power supply to the therapeutic module.

The capsule designed, however, having an active locomotion system on board, aims to focus the treatment exclusively on the areas affected by the bacterium. Therefore, it offers the great advantage of significantly increasing the local power density, greatly reducing treatment times.

The treatment times could be further reduced by creating a future version of the therapeutic module, which, having a cable power supply, integrates equally small but more powerful LEDs.

The assembly based on the sliding of two perimeter wires was found to be inefficient. The absence of concentric forces, in fact, means that there is no well-defined fulcrum with respect to which the angular movement occurs.

The use of four distinct wires, on the other hand, shows much better results. However, in configuration A, it is possible to obtain a rather discreet inclination with respect to the central axis, as shown in Figure 10, even in the second type of assembly. As expected, the movement in both directions is strongly asymmetrical. While, in fact, the right–left inclination, shown in Figure 10, manages to cover an angle of 20°, in the other direction, the very small arm of the force determines an almost imperceptible inclination.

By the inclination of the capsule, however, no translation of the capsule structure is obtained.

The behavior of the other configuration is much better. Configuration B, in both types of assembly, provides uniform inclination on both sides of both directions.

From the two-wire mechanism, shown on the left in Figure 11, we obtain a maximum inclination angle of 45° from which an axial translation of 1.8 cm is derived. It is therefore possible to bring the therapeutic module closer to the gastric mucosa by improving irradiation. The maximum efficiency is expected in fasting conditions, when the diameter of the stomach is comparable to that of the intestine.

The best results are presented by the implementation of the four-wire mechanism in configuration B. The capsule, as shown on the right in Figure 11, is able to reach an inclination of 135°. Taking advantage of the considerable inclination obtainable in the four directions and combining the application of forces on the wires, we have the opportunity to cover almost entirely the surface of the stomach, managing to also treat the fundus, which is generally less affected by *H. pylori* infection.

The translation of the capsule by means of four-wire actuation in configuration B also manages to enable an optimal translation of the therapeutic module. The greatest translation is obtained by inclination, with respect to the central axis of 90°. In a condition of inclination of 90°, a translation of the therapeutic module of about 4.5 cm is generated,
which is able to optimize the administration of the treatment, even in the presence of medium expansion of the walls.

Figure 10. Left maximum inclination of configuration A.

Figure 11. Configuration B: 2-wire mechanism (left); 4-wire mechanism (right).

In order to test the contribution of the flexible cannula in the results achieved, it was replaced, in the four-wire mechanism, with a multilumen cannula from Microspec Corporation with high rigidity, having an external diameter and internal structure equivalent to those of the flexible cannula.

The tests revealed decidedly lower angles of inclination, comparable to those obtained with configuration A. The stiffness of the cannula used probably affects the applied force; the inclination that is obtained derives from the action of the joint alone. As expected, the marked inclination reached in configuration B derives from the combination of the action of the joint and the flexibility of the cannula.
On the basis of the results achieved, the one in Figure 11 was defined as the optimal design of the capsule. The device in Figure 12 integrates both the therapeutic module and the active locomotion mechanism, which proved to be better performing.

Figure 12. Complete intelligent capsule design.

The construction of the envelope will be carried out by molding and entrusted to companies experienced in the production of biomedical components.

4. Conclusions

The integration of a therapeutic and a wired locomotion modules within the capsule leads to the creation of a device capable of delivering photodynamic therapy within the entire surface of the stomach. Active locomotion guarantees full mastery of the gastric environment, allowing complete vertical translation, horizontal translation of 4.5 cm, in both directions, with respect to the axis of the stomach, rotation on 360° both sides along its axis and inclination of 135° with respect to the main axis in all directions. Therefore, we have the opportunity to visually investigate and specifically treat the entire surface of the stomach. The possibility of untreated bacterial colonies is minimized and, with it, the re-onset of the infection in the short term.

The efficiency of the device, which already appears very promising, can be further improved through the use of high-power LEDs, partly already identified, which would help reduce the duration of the treatment.

We could also think of an extension of the visual field through the creation of a dedicated vision system which, by exploiting the unused through holes of the multilumen cannula, presents a rotation capacity relative to the axis of the casing, further optimizing the inspection of the mucosa. However, before focusing attention on further technical improvements, it is good to start the experimental phase of the device aimed at effectively and quantitatively testing its effectiveness, theoretically supposed in this work. PDT for H. pylori is still not addressed extensively in clinical practice. However, H. pylori is similar to other bacteria for which PDT is very common, such as the bacteria that cause acne. Having the possibility to rely on an intelligent system, future PDT of H. pylori could be possible, helping to save huge indirect costs of health system due to antibiotic resistance matters.

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