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A swallowable smart pill for drug delivery into the gastrointestinal tract

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Chapter 1

Introduction

Gastrointestinal system diseases are the most common cause of mortality and hospitalization (21.7 million 2010 in USA (2010)) in developed countries and, due to demographic changes, are still on the rise [1]. Statistics for United States estimate 60 to 70 million people affected by digestive diseases in 2010 [2], with 21.7 million hospitalizations in 2010 [3] and about 250000 yearly deaths[4].

Different pathologies are specific for every tract of the gastrointestinal system, from the esophagus to the bowel. In particular, chronic inflammatory diseases are widespread and require long lasting therapies. In Europe about 2.5 – 3 million people are affected by IBD, with a direct healthcare cost of 4.6-5.6 bn Euros/year [5]. A new frontier in treatment of chronic diseases is represented by localized therapies that can bring benefits in terms of quantity of medication delivered and costs of the treatment.

In recent years technologies in medical robotics and micromechatronics are steadily growing and are capable of producing safe enough solutions to be applied in medicine. In fact, it is possible to find robots that help in several subdomains such as surgery, diagnosis and therapy.

In addition, the development of Micro-Electro-Mechanical Systems (MEMS) technology permits the miniaturization of robots to use them in a less invasive way.

In particular, untethered endoscopic tools have been developed and commercialized in order to reduce discomfort to the patients.

To date, it has been shown that endoscopic capsules can provide more cost effective solutions than wired endoscopes for the same performance [6]. As an example, capsule endoscopes overcome problems of insertion and intubation. Furthermore, capsules can navigate deeply into the small intestine, that usually is a dead zone for wired endoscopes.

Despite capsule endoscopes are widespread, new tools are to be developed for drug delivery and biopsy in order to implement therapeutic and intervention properties on the capsule.

Focusing on therapeutic properties, capsules for drug delivery provide the possibility to improve the treatment of chronic gastrointestinal diseases.

Major advantages that the use of capsule for drug delivery can bring are i) localized therapy, with a consequent reduction of drug doses and reduced side effects compared to systemic administration, ii) costs reduction, thanks to significantly reduced drug doses and iii) shortened hospitalization periods for patients.

These advantages confer to capsules for therapeutic action a dominant role in new medical treatments, in particular for local drug delivery.

Thesis overview

The aim of this thesis is to investigate how to develop an autonomous micromechatronic system and how therapeutic functionalities can be embedded on a swallowable capsule.

To this aim the following main topics have been addressed:

1. Design and fabrication of an autonomous smart pill, considering environmental requirements and biocompatibility.
2. Integration of micro-electronics on-board for autonomous navigation and sensors to monitor physiological conditions of the gastrointestinal tract and trigger the activation of the drug delivery system.
3. Development of an active drug delivery system to be integrated on a swallowable capsule.

To these purposes special attention has been given to:

- the environment requirements in term of size, materials biocompatibility and power supply.

- The development of a sensing system capable of triggering the activation of the drug delivery system.

- The development of an effective drug delivery system capable of delivering a controlled desired amount of drug thanks to a custom made drug delivery pump sensorized with a novel strain sensor.

The thesis is organized as follows:

Micromechatronics design principles and their specific application to medicine are detailed in Chapter 2 while features of smart pills are highlighted in Chapter 3. Analyzing the state of the art, requirements and open challenges in the field of smart pills are pointed out, so chapter 4 is focused on the architecture of the system developed and the design of the capsule is described considering biocompatibility and size issues (topic 1). Chapter 5 is devoted to the description of the sensing system (topic 2). The impedance sensor developed is described. The use of impedance measurement in medical practice and the advantages of using impedance as a medical index for pathological alterations of gastrointestinal tissue properties are explored. The developed sensor is then tested and results are presented.
Chapter 6 is dedicated to the development of the drug delivery system (topic 3). The design and fabrication of the custom made drug delivery system are presented together with its performances. The pump for drug release is sensorized with a novel strain sensor and different solutions for the sensorization are presented and discussed. The sensorization of the membrane is functional to the control of the volume of drug released. One major advantage of the use of a strain sensor is the resulting versatility of the system: the smart pill can be used to deliver different types of drugs, not being influenced by the viscosity of the medication, neither by external conditions (e.g. gastric fluids pressure). Finally, Chapter 7 is devoted to conclusions.

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Chapter 2

Micromechatronics

2.1 Micromechatronics systems design

Mechatronics has been a natural stage in the evolutionary process of modern engineering design [1].

The original definition of mechatronics by Yasakawa Electric Company states that [2][3]:"the world mechatronic is compound of "mecha" for mechanism and "tronics" for electronics. In other words, technologies and developed products will be incorporating electronics more and more into mechanisms, intimately and organically, and making it impossible to tell where one ends and the other begins."

Harashima, Tomizuka and Fukuda in 1996 enlarged the original definition, describing mechatronics as a synergistic combination of a number of engineering spheres (mechanical engineering, electronic control and systems) [4].

The synergy of those elements results in a complete integration of all of them and not just an union of different components, providing the possibility of improving and creating new functions.

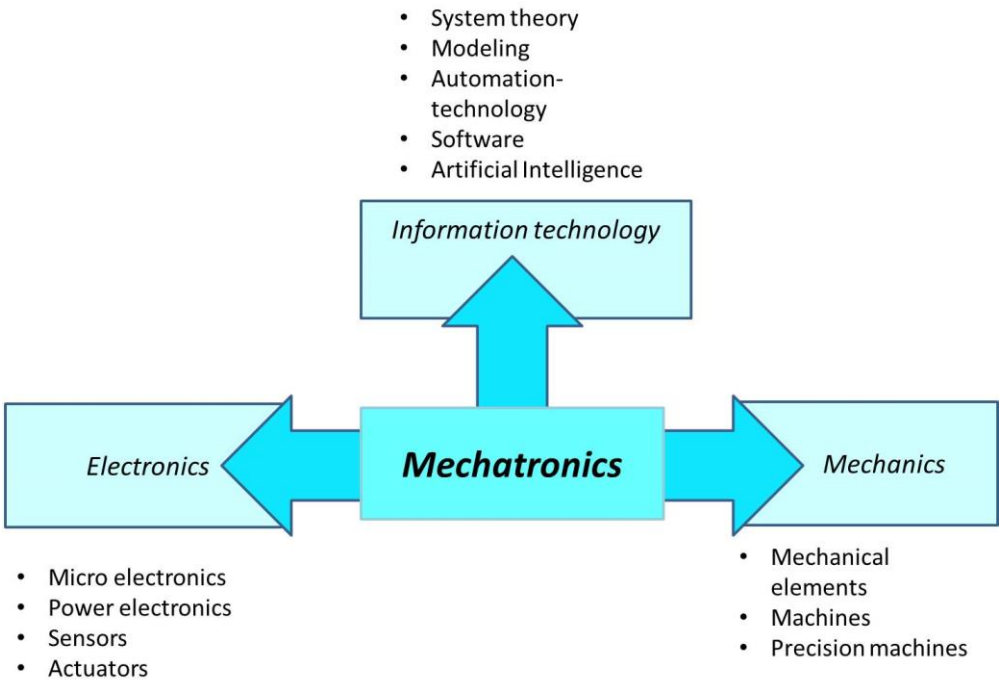

Figure 1 *Mechatronics synergetic integration of different disciplines [5]*

Mechatronic systems can then be sub divided into [5]:

- Mechatronic systems
- Mechatronic machines
- Mechatronic vehicles
- Precision mechatronics
- Micro mechatronics

The concept of micro mechatronics has evolved from that of mechatronics starting from the miniaturization of mechanisms, sensors, actuators, and embedded electronics and their integration into smaller systems.

One of the principal components of micro mechatronic systems is a microelectromechanical system that can convert physical stimuli into electrical or mechanical signals and vice versa, and perform actuation and sensing [6, 24].

The design procedure of a micromechatronic systems includes the following steps:

- Define application and environment requirements
- define performance specifications
- devise microelectromechanical motion devices

- define technologies, techniques, processes and materials to fabricate the device
- design ICs control
- develop mathematical model
- design a control law
- verify and modify the design in order to optimize the performance.

Micro mechatronics is expected to be applied in many different application fields such as medical, bio-engineering, industrial, and service fields.

Some examples can be given about the field of application and they are reported by Fukuda in [7].

Field	Application	Examples
Medical Field	Microsurgery Inspection Drug delivery Healthcare Artificial Organ	Micro pumps Micro catheter
Bio-Engineering field	Gene Operation Cell Fusion Application Agricultural Products Observation Marine resource	Micro manipulator
Industrial Field	Optical Industry Information electronics Technology Micro Functional Material Micro Functional Material	Micro sensors Micro scanners
Service	Home Automation Amusement Social Welfare Device Transportation	Piezoelectric elements

Table1 *Fields of application of the micromechatronic design.*

2.2 Micromechatronics in medicine

The application of micromechatronics in biomedical field has spread together with the request of minimally invasive techniques.

The introduction of micro systems in the medical field is justified by the increasing demand for high quality medical care intended as prevention, rather than intervention, accuracy, repeatability, low invasiveness, and high cost-efficacy. In fact, micromechatronics can provide technical solutions for such medical needs developing miniaturized devices with better performance, lower costs and high reliability.

Biomicromechatronics addresses the need to develop novel technologies for the integration of biological and artificial elements.

Biomicromechatronic systems provide solutions to the problem of accessing a living organism by measurement instrumentation and surgical tools. So many aspects are involved such as material compatibility, sizing, heat dissipation, power supply, etc. [8].

Solutions lie in the range of a few microns to a few centimeters. The small dimensions and the compatibility with IC technologies, allow the batch production of Micro-Electro-Mechanical–Systems (MEMS), that convert physical stimuli to electrical and mechanical signals, acquire data and process signals, control processes and perform diagnosis [5].

The development of micromechatronics implies not only the investigation of typical engineering issues (e.i. electronics and mechanical design) but also the need for investigation of biological topics concerning the interaction with the environment. Moreover, issues peculiar of the down scaled sizes are to be considered since the devices assume completely different features than the medical instrumentation for macro operations.

Micromechatronics has led to significant advances in different areas of medicine and biology (fig. 2) such as diagnostics, therapeutics, tissue engineering, minimally invasive surgery.

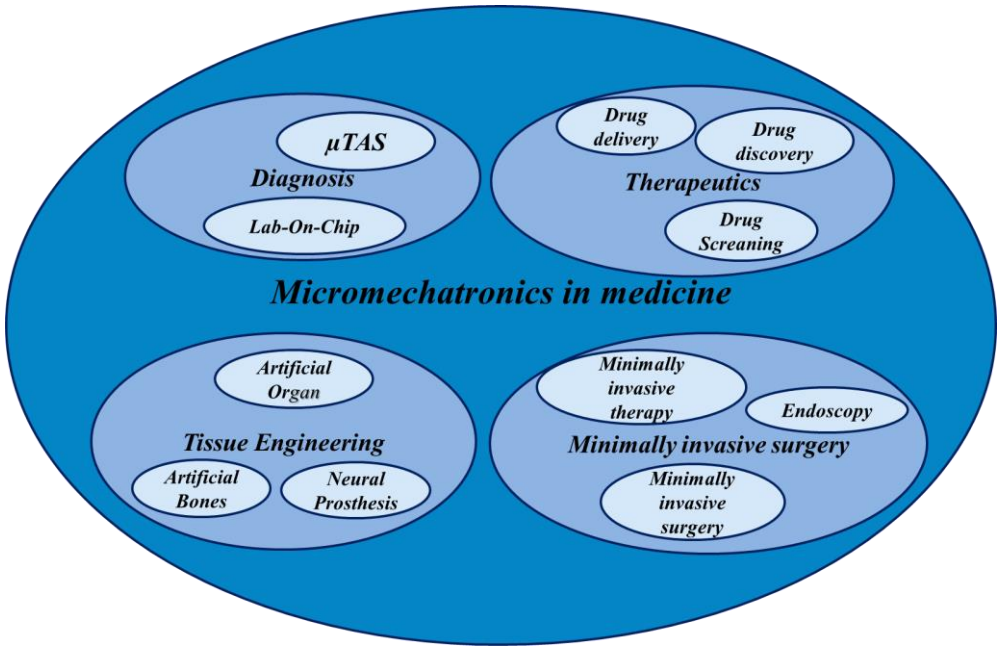

Figure 2 *Micromechatronics in medicine*

Down scaling of diagnostic tools has been made possible by advances in material science and fabrication technologies [9]. MEMS are used to develop diagnostic equipment for laboratory analyses that need to be carried out in miniaturized scale. As an example, µTAS (Micro Total Analysis Systems) or Lab-on-a-Chip devices can perform purification, isolation and samples characterization putting all the above mentioned operations on a single chip.

Therapeutics includes the use of microdevices for drug discovery, drug screening, and drug delivery.

Drug discovery involves the possibility to identify drug targets and to study the molecular interaction in order to achieve therapeutic results.

Drug delivery includes devices designed and fabricated to release drugs in a controlled manner, such as different dosages in different delivery patterns. These include transdermal patches, implants, microparticles, microencapsulation and ingestible capsules. Transdermal delivery systems are driven by passive diffusion through the skin. In the US they constitute the 10% of the whole market of drug delivery (28$ US billion) and 10 drugs are approved for clinical use [25]. Microfabricated needles, chemical enhancers, devices for iontophoresis and electroporation can improve passive delivery requirements, e.g. increasing rates of

transport. Implantable devices can be preferred for therapies that require many daily or weekly injections. They usually require micro pumping mechanisms.

Among MEMS for therapy, swallowable drug delivery systems constitute a new trend. They can achieve major patients acceptance with respect to implantable subcutaneous devices because oral route of administration is the most common.

As far as tissue engineering is concerned, it applies the principles of biology and engineering to develop substitutes which restore, maintain, or improve the function of human tissues. MEMS are used in some major fields of application such as nerve regeneration or the development of artificial organs, bone or vessels.

One example is given by microelectrodes for electrical stimulation and recording of neural activity that can be interfaced to peripheral nerves. A large quantity of solutions have been developed as electric interfaces and recently also magnetic solutions are being explored [10, 11].

Finally, surgical applications include minimally invasive surgery and endoscopy.

Micromechatronics opens the field to miniaturized medical robots. Traditional medical robots in fact operate from the outside inside the body; a miniaturized robot can operate from inside, entering the body through natural orifice or small artificial punctures, avoiding surgery and resulting in less trauma and faster recovery time; in addition, it also enables new therapies.

As part of Minimally Invasive Therapy (MIT), Minimally Invasive Surgery (MIS) aims to provide a better quality of care reducing pain, medical complications and time of hospitalization.

Micromechatronics in MIS can give advantages over human operations such as geometrical accuracy, constant performances, low cost and safety [12].

MIS would incorporate microsensors and miniaturized instrumentation to give feedback perception to the surgeon and to measure physical parameters. Limited visual information is a major issue that is overcome with 3D vision systems.

Another branch in which it is desirable to reduce pain and trauma is endoscopy, that is the field of interest of this work of thesis. Micromechatronics, in fact, can provide microrobots that are particularly suitable for the gastrointestinal system due to its shape and size.

Attempts for minimally invasive examination started in ancient time and evolved through centuries (fig. 3).

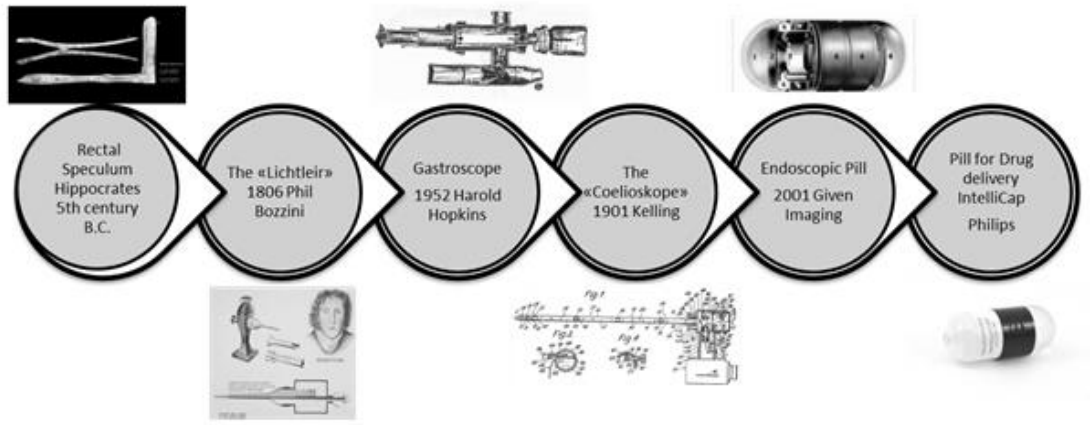

Figure 3*Evolution of endoscopy, from ancient rectal inspection to swallowable capsules for drug delivery.*
The first optical instrument was inserted into the gastrointestinal tract by Philip Bozzini . These devices included an external light source. Air insufflation was first used by George Kelling in 1901 in order to expand the field of view [17]. The flexible fiber optic gastroscope was invented by Harold Hopkins in 1951. At the beginning of the 21th century, capsule endoscopy (CE) appeared, thanks to the development in CMOS technology.

Traditional endoscopes introduce long flexible instruments into natural orifices or small incisions. They usually have CCD cameras or fiber optics for visualization, but their main drawback is the lack of dexterity.

Wired endoscopes, that are introduced through oral or rectal orifices make it possible to view stomach, upper small intestine and colon, leaving part of the small intestine a dead zone. Such traumatic procedures result in poor toleration by patients. Disadvantages of the procedures are mainly related to the insertion process, that necessitates the inflation of air in the channel that might require sedation. Consequent pain or problems with sedation make patients reluctant to undergo endoscopy, limiting pervasiveness of mass screening campaign that could largely benefit the discovery and treat of asymptomatic pathologies.

As an example, the American Cancer Society estimates that only 26% of eligible patients have decided to undergo screening [13]. Data show a still small penetration of the colon cancer screening in the population if compared to other screening

programs, such as mammography for breast cancer (70% adoption rate) and Pap smears for cervical cancer (80 % adoption rate) [14].

Nowadays, endoscopic technologies still comprise traditional flexible endoscopy but they also enclose some example of Wireless Capsule Endoscopes (WCE).

From a historical perspective, research activities in the field of smart pills (in the following also called swallowable capsules) started in 1950s (Fig. 3) [15][16]. The first swallowable capsule was able to measure the pressure in the small intestine of patients suffering from dysentery [17].

Since then, the possibility of integrating miniaturized sensory systems (e.g. vision, pressure, pH and/or temperature) has been investigated. However, swallowable capsules have been hardly applied in clinic, because of limitations related to the lack of adequate electronics, low integration level, low performance, and prohibitive costs.

In 1981s, Iddan conceived the first wireless camera pill for imaging the entire GI tract but a swallowable camera capsule could not be realized because of technological limits. In recent past the availability of low power and low cost miniaturized image sensors based on CMOS technologies, and miniaturized light emitting diodes (LEDs) enabled the realization of a swallowable capsule, and in 2000 Given Imaging Inc., thanks to Iddan's patents, introduced WCE [18].

Screening of the GI apparatus is a common medical practice but it still presents some limitations such as the capability of achieving exact control over position, active locomotion and camera orientation.

The development of technical solutions to localization and navigation issues, as well as novel power management systems, will improve WCE performance and allow integration of diagnostic and therapeutic capabilities [19].

2.3 Endoscopic capsules

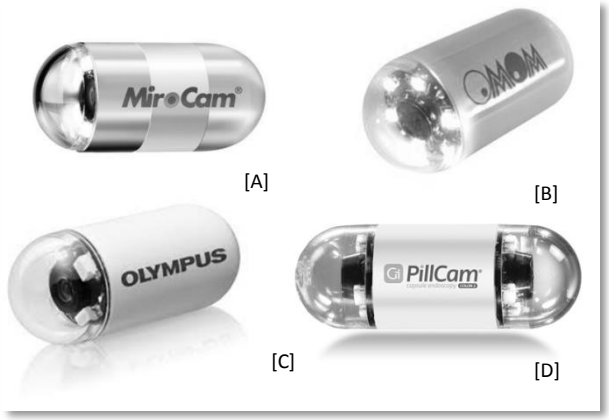

Figure 4 *Commercial endoscopic capsules: A: MiroCam by Intromedic Co ; B: OMOM of Chongqing Jinshan Science and Technology Group; C: EndoCapsule by Olympus Inc.; D:PillCam Colon2 by Given Imaging Inc [19].*

Existing capsules, especially considering commercially available devices, are mainly diagnostic imaging tools.

Some common features can be identified by analyzing their characteristics.

The first commercial endoscopic capsule (M2A by Given Imaging (Fig. 5)) can give an idea of the salient characteristics of endoscopic capsules. The same features have also been implemented and ameliorated on next generations of capsules.

M2A presents a radiofrequency transmitter, an antenna and an external workstation. The capsule has a cylindrical shape, with a diameter of 11 mm and a length of 26 mm. It has two domes, one of them being the optical one with white LEDs.

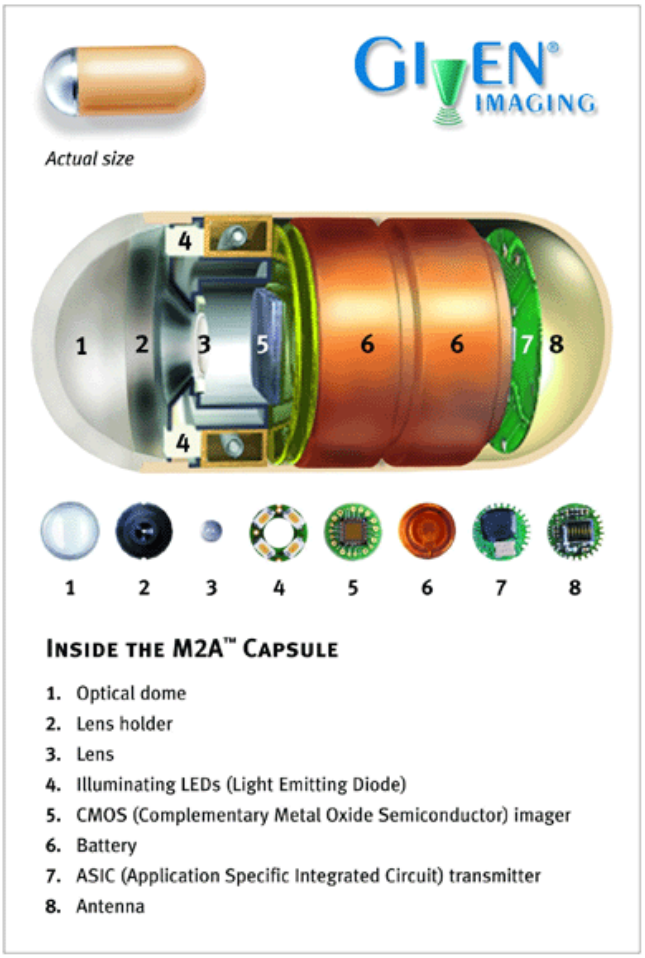

Figure 5 *M2A capsule by Given Imaging*

This capsule discloses the salient advantages and problems of using endoscopic capsules.

In many cases WCE does not need sedation and bowel preparation, reducing risks and discomforts that can be associated to laxative and allergies to other medications used.

But WCE may expose patients to the risk of retentions, in particular in cases of suspected GI obstruction.

In 2004 Given Imaging re-branded M2A as PillCamSB. In 2005 PillCam evolved in two devices PillCam SB, specific for the small intestine, and PillCam ESO, specific for the esophagus together with Bravo pH for identifying the presence of acid reflux and PillCam COLON specific for the colon.

PillCam COLON aims at the visualization of colon mucosa and the detection of polyps. Its second generation version (PillCam COLON2) has two image sensors on both ends. PillCam COLON has been FDA approved only recently. In fact it was firstly rejected by the FDA in 2008 because, unless costs advantages and safety, during a trial of 700 patients the capsule failed to identify polyps in one third of the time. FDA recommended the use only in those patients for whom a traditional colonoscopy cannot be completed (e.g. cases of abdominal surgery, diverticular disease, or other colon conditions).

Considering also other capsules such as MiroCam by IntroMedic Co., Ltd, Endocapsule by Olympus Co. Ltd or the Chinese OMOM by Chongqing Science & Technology (Group) Co., Ltd., and all the different applications, camera, transmission of images, communication system, batteries life time are the key elements of endoscopy capsules design and a central point for research [20,21].

As an example, major efforts are made to enlarge the field of view and to improve the CMOS image sensors design.

Enlarging the field of view is desirable because it means having a complete view of the internal environment and improve the diagnostic capability of the capsule that is autonomously moving into the digestive tube. A 100% screening in fact cannot be guaranteed by capsule endoscopes because having only one camera the orientation of the capsule view in the intestine is not necessarily forward and some studies have showed that the capsule is actually not constant in its facing direction and will often unpredictably turn around its diagonal axis. As a direct solution does not exist, the problem is mostly addressed by having very wide viewing angles of the cameras, or using more than a camera. M2A had a 140° field of view, PillCam's was improved to 156°, MiroCam 150°, OMOM can reach 160°, finally PillCam COLON2 with two cameras can provide a near 360° view of the colon.

Autonomy is a focal topic too, because time of navigation may vary from subject to subject and it is heavily influenced by peristalsis.

Usually the time needed to explore the entire bowel is variable from 6 to more than 8 hours, batteries can usually guarantee 8-10 hours of autonomy [22]. By the way, none of the commercial devices implement internal active locomotion but the majority is moved by external control.

As far as transmission is concerned, it is worth mentioning the system used in MiroCam.

MiroCam is the first endoscopic capsule that exploits electric field propagation and uses the human body itself as a communication medium [23].

Standard CE systems consider the human body as a nonconductor and use RF module to send information from the image sensor through living tissue to the outside. But free electrons and ions can block the signal and attenuate their energy by consuming the electric field by drift currents. The innovation is that MiroCam uses the human body as a semiconductor (poor conductivity compared with a metal wire) in which the electric field can be inducted and produce drift currents. So using "electric-field propagation" no antennas or high frequency circuits for remote communication are needed and the battery lasts longer for lowest energy consumption. The system has passed preclinical tests, in particular it is capable of 9 to 11 hours of operating with two serial silver oxide batteries.

The last EndoCapsule from Olympus shows the same intent in improving those mentioned characteristics, such as a wide field of view (160°) together with an optimal lightening, brilliance and clarity of images.

Attention is also given to the software design in order to enrich usability of the device, allowing to capture images at any time and to play back downloading of them in a workstation.

The recorder is constitute by a belt style antenna and a recording –viewing system so that images are always available for medical analysis [24].

Specifications of the endoscopic capsules analyzed are listed in the table below (Table 2).

	M2A	**PillCam**	**Endocapsule**	**OMOM**	**MiroCam**
Dimensions (mm)	11x 27	11 x 27	11x 26	13 x 27.9	11x 24.5
Weight (g)	3,7	3,45	3,8	6	3,3
Frames/s	2	2	2	2	3
Sensors	CMOS	CMOS	CCD	CMOS	CMOS
Field of view	156°	156°	160°	140°	170°
Power Supply	Battery	Battery	Battery	Battery	Battery
Company	Given Imaging, Yoqneam, Israel	Given Imaging, Yoqneam, Israel	Olympus Ltd., Tokyo, Japan	Chongqing Science & Technology (Group) Co., Ltd	IntroMedic Co., Ltd, Seoul, SouthKorea

Table 2 *List of the* ***e****ndoscopic capsules and their specifications*

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Chapter 3

Smart Pills

3.1 A definition

A smart pill is an ingestible capsule that integrates miniaturized electronics. The concept of smart pill has evolved from capsule endoscopy improving clinical performances and enhancing the functionalities of the devices.

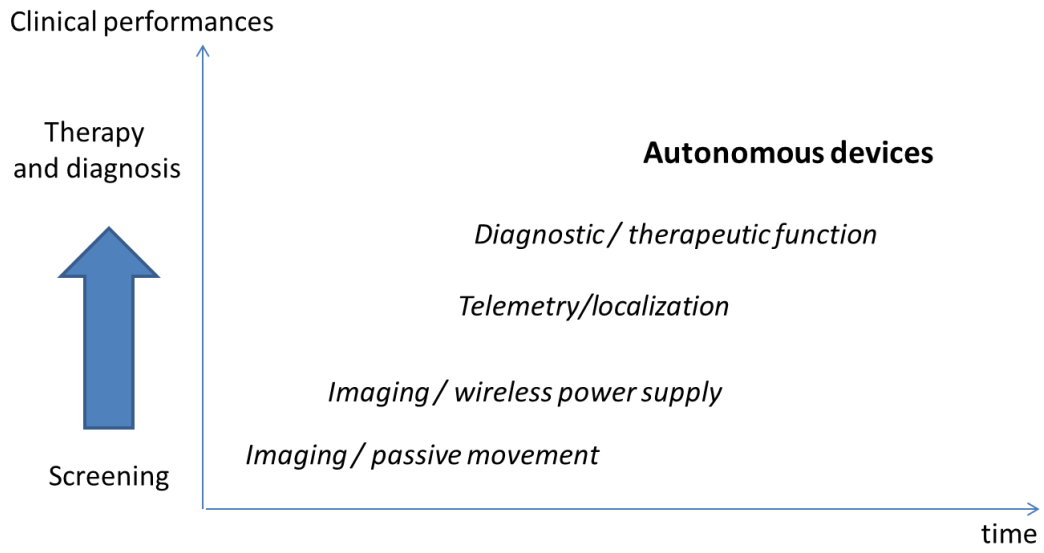

Figure 1 *Evolution of the concept of smart pill*

So smart pills are a point of convergence between technology, modern medicine and health care (pharmaceutical) industries. In fact, a successful smart solution can merge only from a synergic combination (Fig. 2) of competences and facilities from different compartments, such as pharmaceutics for drug, biology and engineering for device and micro technology. In fact, each of these compartments can contribute to give access, analyze and manipulate the body from the inside providing miniature chips, sensors, cameras, robots and medications .

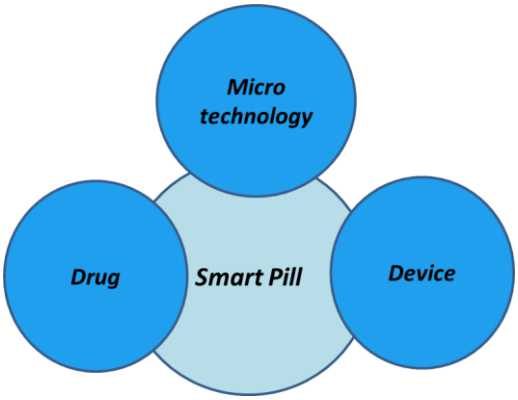

Figure 2 *Smart Pill: a solution emerging from a synergetic combination of different compartments*

As camera pills, since their introduction in 2000s to today, diffused in medical practice and replaced the standard tethered endoscopes in gastrointestinal apparatus monitoring and video recording because of all the advantages we mentioned in chapter 2, smart pill are emerging full-featured medical devices promising solutions for diagnosis and treatments and medication adherence to patients (i.e. personalized treatment) thanks to sensors embedded on-board. They would become widely used *theragnostic* devices.

Theragnostics is an emerging concept compound of "thera" for therapeutics and "gnostics" for diagnostics that well explains the double essence of a smart pill aimed to the identification and treat of specific pathologies.

As therapeutics aspects are concerned, smart pills can bring advantages in a variety of applications; firstly, drug delivery through smart pills can be a successful approach in comparison to others such as intravenous or subcutaneous drug delivery systems because the oral route of administration is the preferred due to convenience, costs and not least patient acceptance [1]. In fact, even if to accept to swallow chip and electronics is not yet considered "natural" it is well comparable to traditional drug administration.

Smart pills, that have also been used to develop new drugs, have also the potential to create innovative new therapies. In fact the combination of functions (drug and

devices) available from smart pill, enables therapies not possible with conventional means.

As an example, smart pills allow the treatment of locally active diseases such as esophageal cancer, intestinal cancer and inflammatory bowel diseases (IBD) [2]. In fact, local delivery can reduce toxicity from systemic exposure to anti-inflammatory drugs, corticosteroids or all the drugs that are used but have a critical therapeutic index.

As biological drugs have been introduced to overcome conventional therapies inefficacy and side effects, smart pill are useful in order to reduce the doses of biologicals that are very expensive and require large doses for intravenous administration. As an example infliximab, the most used biological drug, is administered through intravenous infusion of 5 mg per kilogram of body weight from every 2 to 8 weeks [3]. Smart pills can drastically reduce the doses and consequently the costs of therapy and so lower costs to health system.

Swallowable drug delivery systems for local treatment bring many advantages and opportunities for personalized treatments (e.g. the region of interest can vary from patient to patient and for the same patient overtime), effectiveness (e.g. specific dose), better management of disease (e.g. site-specific drug delivery with minimal side-effects). The programmable nature of an electronic pill allows the target site and the dose to be personalized.

Clinical studies show that smart pills can provide more cost–effective solutions per same performances in respect to standard procedures.
As an example, a study in [4] showed that the incremented cost effectiveness compared with no screening of colonoscopy was $ 16,165 and of capsule endoscope $29,244 per life-year saved.

Moreover, a smart pill can become a key element of a larger connected care environment: on-board sensors measurement can be transmitted to an external platform for monitoring and tracking in long term therapy and eventually communicate wireless with external devices such as smartphones for long distance care-giving, especially for elderly people.

It must be considered in fact, that elderly people are at a higher risk of acquiring various gastrointestinal diseases such as ulcerative colitis and IBD.

The World Health Organization (WHO) has estimated that by 2050 world's geriatric population will reach around 2 billion. Thus, rising geriatric population will accentuate the growth of smart pill technologies market globally. Also, changing lifestyle (including shift in diet pattern) will augment the growth of smart pill technologies market.

According to the Centers for Disease Control and Prevention (CDC), prevalence rate of inflammatory bowel diseases (IBD), in 2012 was estimated to be approximately 396 per 100,000 people in the U.S. Similarly, prevalence rate of Crohn's disease (a type of gastrointestinal disease) in 2012, ranged from 0.1 to 16 per 100,000 people in the U.S. [5].

The report in [6], that gives an overview of smart pills technology market, cites a fast growing market from $442 million in 2012 to estimated $965 million in 2017. Generally such analyses are segmented based on specific applications and geographical areas, i.e. North America, Europe, Asia Pacific and rest of the world.

North America in 2012 accounted for the largest share of total smart pill technologies market and is expected to grow at a steady CAGR (Compound Annual Growth Rate) during the period 2013 to 2019. Asia-Pacific is expected to grow at the highest CAGR followed by Europe, during the period 2013 to 2019. The growth in these regions is attributed to the presence of large patient population coupled with increasing awareness about gastrointestinal diseases, and their diagnostic and treatment methods.

3.2 Gastrointestinal apparatus pathologies

Along the apparatus, specific diseases can occur at every point of the gastrointestinal tract (Fig. 3).

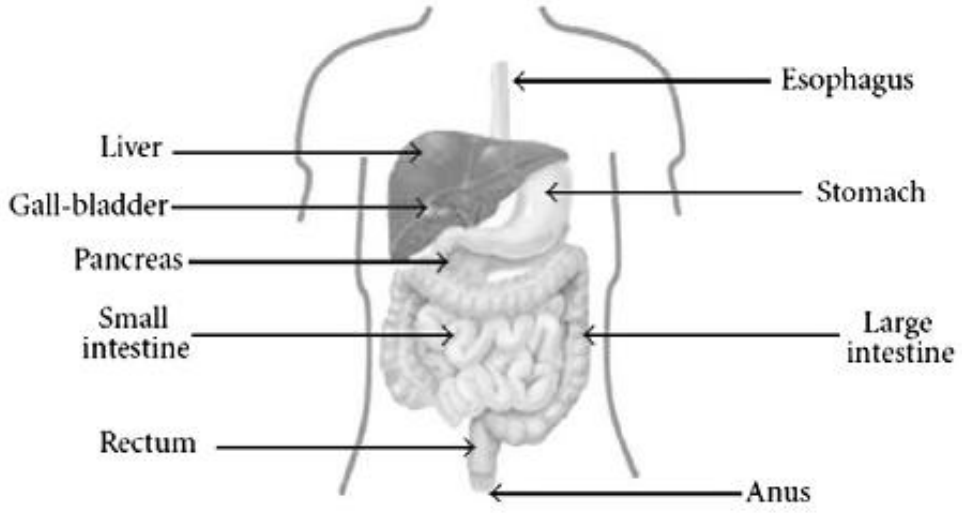

Figure 3 *The digestive tube is a 9 meters long musculomembranous tube, lined throughout its entire extent by mucous membrane. Its commencement is the mouth. The organs of deglutition, the pharynx and the esophagus (25-30 cm in length 2 - 3 cm in diameter) convey the food into the stomach (an about 25 cm wide collapsed saclike chamber, with an expandable volume from 0.1 liter to 4 liters). It is followed by the small intestine (6 m in length, 3 cm in diameter, about 600m in surface^2) The small intestine ends in the large intestine (1.5 m in length surface of 150 m^2) followed by anal canal ending in the anus[93][19].*

Gastroesophageal reflux disease (GERD) is the most common esophageal pathology; gastric acids ascend from the stomach irritating the esophageal wall and causing heartburn [7].

Peptic ulcers, crater-like lesions in the mucous membrane are the most common stomach disease [8].

Small intestine pathologies include a quite wide range of chronic disorders including food intolerances (lactose intolerance) that can result in most serious illness. Among them, are celiac disorders, in which the mucosal wall is damaged by gluten resulting in nutrients absorption inability.

In Western countries about half of the population is affected by diverticular disease. It consists of the formation of pouches in the colon. Diverticular disease is made up of two conditions: diverticulosis and diverticulitis. Diverticulosis is when pouches occur, diverticulitis when they get inflamed [9].

Bowel tumors may be asymptomatic at early stages or be present with abdominal pain and weight loss. The great part of tumors affects jejunum and ileum [10]. Diagnostic methods for small bowel tumors include enteroclysis, computed tomographic scanning, magnetic resonance imaging, arteriography and enteroscopy.

Large intestine can be affected by chronic inflammations such as Crohn's disease and ulcerative colitis. Inflammatory bowel diseases (IBD) are considered an interesting field on which focus research in CE and eventually localized treatments because of the advantages that this type of devices can bring to diagnosis and treatment of regions otherwise difficult to access. So, we will examine a bit in detail these pathologies, tools of diagnosis and their diffusion.

Ulcerative colitis (UC) causes inflammation and ulcers in the inner lining of the large intestine (colon and rectum). The inflammation causes loss of the lining of the colon and as a consequence bleeding and production of pus, diarrhea, and abdominal discomfort.

Crohn's disease (CD) causes inflammation or irritation of any part of the gastrointestinal (GI) tract. Inflammation can extend deeply into the lining and can result in scars and strictures of the intestine.

It can be difficult to diagnose because its symptoms are similar to other intestinal disorders. Because of strictures the passageway is narrowed and the transit of the food through the intestine causes pain and cramps. The same symptoms are caused by ulcerative colitis and irritable bowel syndrome.

Causes are unknown but it is thought to result from an immune system reaction. The immune system does not protect anymore the body from dangerous bacteria but attacks bacteria, foods and substances that are harmless and beneficial; as a result white blood cells accumulate in the lining of the intestine producing chronic inflammations which lead to scars and ulcers [11].

In medical practice there are many tests for diagnosing Crohn's disease but, surprisingly, all of them are affected by a low success rate. Usually, it is diagnosed by performing blood and stool tests and imaging tests [12].

An established method for detecting and evaluating the presence of the CD in the small bowel is called "Small bowel follow through" (SBFT).

An alternative is enteroclysis, based on the ability of the evaluator to channel the constant media into the bowel areas rather to have the patient to ingest it as the SBFT.

Barium enema is a special X-ray exam used to detect changes or abnormalities in the large intestine. There are two types of barium enema exams: Single contrast barium enema (SCBE) and air contrast barium enema (ACBE).

Computer tomography (CT) offers the ability to decipher the various types of patterns in which the disease may present and it is useful for showing the site and the cause of high–grade obstruction in the patient.

Magnetic resonance imaging (MRI) has a limited role in the valuation of initial CD in part due to the limited accessibility of the colon and high costs.

Serology is often reserved as a supplemental tool to help rule-in or rule-out CD in cases that are questionable. The two mainly used tests rely on detecting serum antibodies.

Colonoscopy is the classic endoscopic examination of the large bowel and the distal part of the small bowel with a CCD camera or a fiber optic camera on a flexible tube passed through the anus. Together with classical colonoscopy there is WCE that is less invasive and overcomes all the problems of discomfort such as intubation, insufflation and sedation of flexible endoscopes.

Some complications are linked to capsule endoscopy in patients with known strictures or swallowing disorders. The analysis of experimentations on humans and of clinical cases evidences that capsule retention is a major cause of capsule endoscopy failures [13].

Cases of retention are reported as related to particular anatomical sites or pathological conditions such as Crohn's disease, small bowel cancer, and various types of duodenal, small bowel and large bowel diverticula, and suspected GI obstructions [14].

For patients with Crohn's disease, retention may happen in 6.7% of cases [15].

In medical practice in case of retention, confirmation is given by radiographic imaging and surgical intervention is needed [16]. To date, the only commercial device that tries to prevent retention is Agile, a patency capsule by Given Imaging [17]. The capsule has the same dimensions and shape of standard capsule (12 x 26 mm). It consists of an external body made of absorbable material (lactose) that surrounds a small identification tag detectable by radiofrequency; it also contains a reservoir for barium for detection by fluoroscopy. The capsule can remain intact for

30 hours after ingestion, after this period, if it is still in the body, it spontaneously disintegrates except from the identification tag that can pass through stenosis of reduced lumen size thanks to its small dimensions (3 x 13 mm) [88]. But such kind of devices that can be a non-invasive tool to identify if patients with suspected stricture can ingest standard capsules [89], cannot avoid problems linked to diverticula where capsule may stop.

3.3 Smart pills for drug delivery

3.3.1 Requirements

An ideal swallowable capsule would be fully autonomous and able to position itself, to perform diagnosis, to transfer data and to receive commands by wireless communications for performing drug treatments [18].

With regards to medical impact, for administrating therapeutics in the GI tract in a safe and effective manner anatomical features are to be taken into account and possibly exploited.

The anatomy of the GI tract imposes constraints in terms of device size and transit time through specific tracts. For instance, the large surface area of the small intestine (about 600m^2) enhances its capacity of drug adsorption but this tract is also quite long and tortuous, which makes the passage of the capsule difficult. Constraints on capsule dimensions are mainly imposed by the smallest diameter in the GI tract, i.e. the esophagus, with a mean diameter of 2 cm.

Typical dimensions of swallowable capsules are about 10mm in diameter, 25 mm in length with a volume of about 3.0 cm^3. Transit time varies from tract to tract and changes as an effect of pathological conditions or age [19]. To control the transit time of a capsule it is desirable to have anchoring and stopping mechanisms onboard the device.

A key improvement in WCE allowing the shift from endoscopic capsule to therapeutic devices is the integration of active locomotion systems to ensure reliable control of the device during navigation, reducing uncertainty of passive, peristalsis induced, movements.

Another key issue is power management. In particular, devices with moving parts,

e.g. endowed with locomotion capabilities and active therapeutic tools, such as pumps, have higher power requirements than passive devices.

Localization systems are important to evaluate position and orientation of the capsule and to have a closed loop control during intervention. Another important issue regards the compatibility of active devices with imaging systems [20].

The choice of materials, which impacts robustness and biocompatibility, as well as the strategies to implement drug delivery (e.g. pumps, valves) are crucial.

Capsules are made of bioinert polymers or coated with films made of biocompatible materials that remain physically and chemically stable during drug storage and are impermeable to gastric fluids (e.g. gelatine, lactose, cellulose [21]). Also internal components are made of biocompatible materials (e.g. Polydimethylsiloxane (PDMS), Polimethylmethacrylate (PMMA), parylene, gold) or encapsulated in polymeric films.

Whereas vision is crucial for screening capsules, it is not similarly essential when focusing on therapy.

In fact, a non-viewing capsule can save room to host other subsystems such as those for drug delivery, locomotion and batteries. Furthermore, non-viewing capsules can simplify systems specifically designed for long time drug administration (e.g. in case of Crohn's disease) for example saving on battery consumption.

Overall, swallowable capsules for drug delivery require technological advances in several fields: micromachining, microactuation, sensorisation, localization and teleoperation [21] [22].

3.4 Drug release mechanisms

Drug can be passively released or dispensed by active mechanisms.

Passive drug delivery systems only expose the drug to the environment. They involve mainly physical (e.g. diffusion) or chemical interactions, triggered in response to certain conditions of the environment, such as the temperature and pH. The release relies on specific conditions at the target location.

Conversely, active mechanisms refers to the capability of the capsule to expel drug out of a reservoir once the release mechanism is activated. An overview of actually used mechanisms is briefly reported in figure 4 while some details are provided in

the next paragraphs.

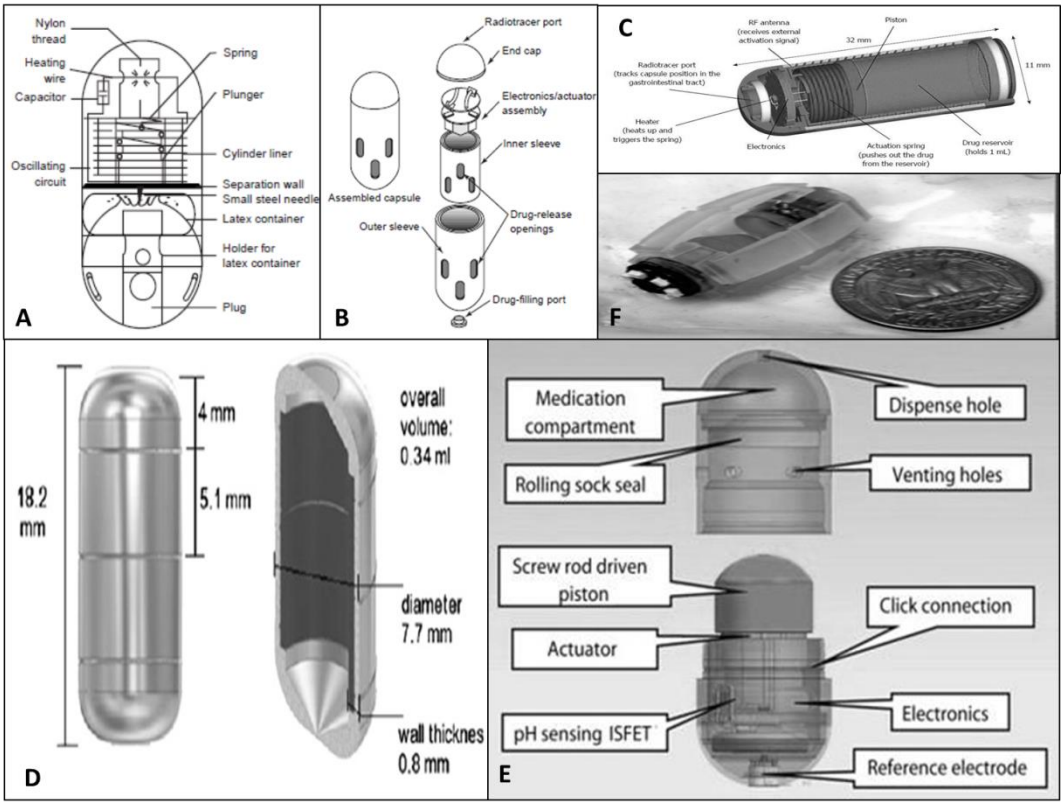

Figure 4 *A: HF CAPSULE by Battelle- Institute V, Frankfurt am Mai , Germany, activated by RF signal B: InteliSite by Scintipharma Inc., electromagnetic activation C: Enterion by Phaeton Research activated by an external electromagnetic signal D: MAARS: Magnetic Active Agent Release System Capsule E:IntelliCap by Philips Research activated by pH measure F: MASCE: Magnetically Actuated Soft Capsule Endoscope.*

3.4.1 Passive release mechanisms

The early swallowable capsule developed for drug delivery in 1980s is the High Frequency capsule (HF Capsule) (Fig. 4A) by Battelle-Institute V, Frankfurt am Main, Germany) [23]. It is activated by a RF signal, generated by an external high frequency generator. The heat generated by the RF wave [24] melts a thread and releases a needle which in turn pierces a latex balloon and allows drug to passively flow from ports in the wall of the capsule.

InteliSite by Scintipharma Inc.(Fig. 4B) consists of two main parts: an outer sleeve and an internal cage that fits in the outer sleeve. Liquid or powder diffusion can occur through the two slots. The released volume is about 1 ml. The inner cage is spring loaded and held in compression by two shape memory alloy (SMA) wire clips. An externally provided electromagnetic wave provides energy, activating the

capsule. In particular, the warming of the wire clips allows the release of the spring, which allows the inner cage to move out the external body. Thus the drug is dispersed through the slotted sides of the capsule body [25]. The main issues with this technique are the slow activation and the possible activation failures if the capsule is particularly deep in the body. In addition, drug leakages can occur before reaching the target areas in case of non-perfect sealing around the sleeves. Out of the total volume of 2.75ml, about the 30% is occupied by the drug reservoir.

Another way of releasing drug is by exploiting magnetic fields. An example is given by MAARS (Magnetic Active Agent Release System) by Matesy GmbH (Fig.4D) .

The drug release mechanism comprises a magnetic carrier for the transport of the drug and a system for the drug release initiation. The wall of the carrier consists of separate magnetic semi-hard and soft components. The two parts are magnetically attracted to each other keeping the capsule closed during navigation. Once the target is reached an external magnetic field is used to open the capsule and release its content. Both powder and liquid medication can be released [26]. The reservoir volume is 0.34 ml over a total volume of 0.847 ml.

3.4.2. Active release mechanisms

Active release mechanisms allow a better control over drug delivery. Solutions used often include pistons to push the drug out of a reservoir.

In the IntelliCap by Philips Research (Fig. 4E) [27] a piston, driven by a stepper motor via a screw-rod mechanism, pushes the drug out of its reservoir through a dispensing hole. The pill can deliver the full payload in about 10 minutes (burst release) or over a prolonged period of time (extended release), with a medication compartment of 300 µl. The delivery is precisely controlled using pH sensors along the gastrointestinal tract to achieve personalized treatment.

Another mechanical platform for delivering a controlled dose of medication has been developed by Woods et al. [28]. It includes an holding mechanism and a needle positioning mechanism. Such a needle positioning system can target the area of interest and deliver liquid medication when the target has been localized. Drug volume is 1 ml, about one third of the overall device volume.

Another device exploiting magnetic actuation is the Magnetically Actuated Soft Capsule Endoscope (MASCE) (Fig.4F) [29]. It exploits the interaction between an external permanent magnet and an on-board permanent magnet (Fig. 4F). When the external magnet moves close to the soft capsule, the capsule is axially compressed by magnets. Because of the axial magnetic attraction, the drug chamber between two internal magnets is compressed and the drug is released through holes at when a critical pressure is achieved. The drug delivery chamber has a volume of 0.17ml [30]. The advantage of this system consists in its possibility to release multiple doses and in a better control over drug release rate. To achieve a successful release it is necessary to carefully align internal and external magnets up to a maximum distance of 100mm.

Enterion capsule by Phaeton Research (Fig. 4C) uses a release mechanism based on piston/spring actuation (Wilding, Hirst, & A., Development of a new engineering-based capsule for human drug absorption studies, 2000) with a drug reservoir volume of 0.8 ml.

The drug release methods reviewed in the article are summarized in Table1.

As it regards fabrication aspects and sealing of the dispensing-hole different solutions have been investigated and implemented. Common solutions make use of valves (e.g. membrane valves, cantilever, disc-single valves, V-shape valves) [31]. However, valves may be not robust in long-term cyclic use. An alternative is represented by a medicine reservoir, as in [32], comprising a drug reservoir, a hole for dispensing and a plug. The latter is made by a non- rigid biocompatible material. The adoption of non- rigid materials allows the sealing of the dispensing hole while, when required, pressure can push the plug out for dispensing the drug.

Materials usually used are PDMS, PMMA, parylene and other bioinert polymers [33]. Polymeric stretchable films can be used also to protect electronics from the acid environment of the stomach [34]. Also other materials, commonly used in surgery and for implantable medical devices (e.g. austenitic 316 and 440 and 420 martensitic stainless steel, gold) can be adopted [35].

The major issue with active drug delivery systems are associated with the need to develop compact moving mechanisms without subtracting too much to drug reservoirs. Therefore, miniaturization of electronics, sensors and actuators is highly

required.

Active drug release mechanisms implies also the use of proper strategies for power supply. On board batteries can be adopted for autonomous robots but they can subtract room to drug reservoirs. Alternative solutions, such as magnetic devices or wireless power transmission systems, still lack the capability to transmit the required power. Furthermore safety of live tissues is a major issue [36].

Device	Capsule dimensions	Drug reservoir volume	Mechanical release mechanism	Powered by
HFCapsule	-	–	Passive	-
InteliSite	35 x 10 mm	0.8 ml	Passive	Battery
MAARS	18.2 x 7.7 mm	0.34ml	Passive	Battery
IntelliPill	26 x 11 mm	3ml	Active	Battery
MASCE	15 x 40mm	0.17 ml	Active	Magnetic field
Enterion	32 x 10 mm	1ml	Active	Magnetic field

Table 1 *Drug delivery solutions*

3.5 Capsule navigation: active and passive locomotion

With regard to locomotion, capsule endoscopes can be either active or passive, depending from the presence or not of controlled locomotion strategies.

Passive capsules do not require an active mechanism for halting the capsule neither a telemetric system to control the navigation. Devices exploiting active locomotion, on the contrary, require physicians supervision during the entire procedure [37]. Active locomotion enables teleoperation thanks to telemetry [38].

3.5.1 Passive locomotion

Passive locomotion, exploiting natural peristaltic contractions of the bowel, dominates the existing Wireless Capsule Endoscopy (WCE) market. Unfortunately, peristaltic movements are unpredictable and result in unreliable diagnoses in 20% of the trials [39]. Consequently, passive locomotion can hardly enable therapeutic

functionalities, such as drug delivery [40].

3.5.2 Active locomotion

Since active locomotion aims at providing the ability to move or stop the device for diagnosis and treatments, it holds promise to allow the physician to control the device during operation [41]. The main challenge in developing an active locomotion system regards the difficulty in integrating the locomotion mechanisms into the capsule while keeping the size of the pill compatible with the oral use. Indeed, smart pills using active locomotion are still at a research stage.

A locomotion system should be able to [42]:

- Adhere on the tissue, so that locomotive forces can be transmitted;
- displace the contact points in order to produce locomotion.
- swim in case of liquid media (e.g. water/gastric juice in the stomach).

There are three main locomotion methods:

One uses internal miniaturized locomotion means; the second approach exploits external magnetic fields; the third approach applies proper (i.e. electric) stimuli to GI tissue to control peristalsis. Combination of these methods can be used [28].

3.5.2.1 Internal locomotion

Internal locomotion may rely on different principles.

Earthworm-like robots have also been developed, usually exploiting Shape Memory Alloy (SMA) actuators. For example, the contraction-extension of agonistic-antagonistic muscles pair of earthworms have been reproduced using a SMA spring actuator placed inside a silicone bellow [43].

SMA actuators exhibit up to 30% stroke, with a ϕ20 mm actuator [44]. This type of actuators suffers from a typically low efficiency (<5%), whose upper bound is set by the ideal Carnot machine operating between the same extremal temperatures, and relatively slow response time, as the SMA element has to be heated up to obtain a phase/geometry change [45]. Menciassi et al. in [46] compared the locomotion performance of earthworm-like robots and real earthworms, resorting to a purposely

developed friction model taking into account design parameters such as number of segments, body mass, special friction enhancement appendixes. Their experiments indicate that the maximum speed of the robotic crawler is 2.5 mm/s, and that 3-segment crawlers have almost the same velocity as earthworms having the same weight (and about 330% their length), whereas 4-segment crawlers have the same velocity, expressed as *body lengths/s*, as earthworms with the same mass (and about 270% their length).

A locomotion technique inspired by inchworms has also been explored. In this case, linear (e.g. SMA) actuators work in synergy with clampers [47].Both earthworm and inchworm locomotion are not continuous but step-wise, since each locomotion cycle is obtained through a sequence of clamping and elongation steps (Fig. 5).

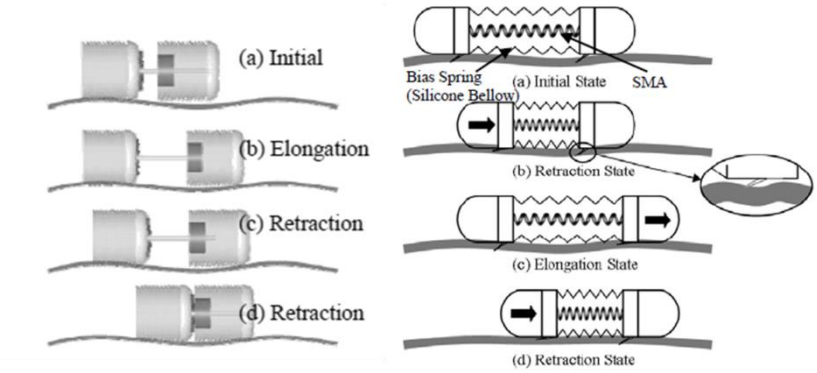

Figure 5 *Crawling locomotion mechanisms: SMA based Inchworm (left) and Piezo actuator based earthworm (right) locomotion principles by Kim et al.* [48].

A nearly continuous motion is achieved in the crawling mechanism presented in [49], exploiting a long stroke (up to 11 mm) piezo actuator arranged to form a Tiny Ultrasonic Linear Actuator (TULA) [50]. In this case the ceramic actuator periodically moves back and forth while a mobile element follows the actuator when moving forward and keeps the same position when the ceramic actuator comes back to the base position.

Other bioinspired locomotion solutions exploit artificial legs, e.g. inspired by cockroaches [51].

Legged locomotion provides the ability to control the position and orientation of the pill, anchoring and releasing the capsule as desired. The most used actuators are SMA springs or fin-type electromagnetic actuators.

Anchoring is a critical aspect because of the difficulty of designing a mechanism capable of anchoring to the tissue without damaging it, while still applying the right amount of force necessary to propel. This is why legged solutions are technically more complex in terms of hardware and control but some advantages they exhibit, in terms of the above-mentioned maneuverability but also safety, justify the development of this solution.

In medical terms safety means that the contact of the capsule with the gastrointestinal wall does not damage the tissue, at least not more than a traditional endoscope. Whereas in earthworm locomotion the capsule is sliding on the tissue and cannot avoid damaged areas, legs theoretically allow a better control of the navigation and, if needed, the passage over a lesion without further damaging the tissue. Furthermore, legged locomotion can simplify adhesion and improve adaptability to the environment: higher contact pressure can be reached producing significant local deformation. Since the main exploitable friction mechanism in the GI tract is based on tissue hysteresis [42], high friction coefficient can be reached in the contact points [52]. Adaptability to the environment makes systems suitable for biomechanically different areas, such as stomach, small and large intestine. The main drawback is related to power supply and space constrains.

Some criterion can be identified to design legged locomotion systems [53]. After having defined force requirements, usually with experimental testing and modeling, and selected the actuator, the number of legs, the gait, and their position on the capsule have to be designed.

Glass et al. presented a locomotion mechanism constituted by three actuated legs with compliant feet lined with microcapillar adhesives able to withstand axial peristaltic forces at a fixed location [54].

Increasing the number of legs helps distributing the contact force over a higher number of contact points, thus reducing the risk of damaging the tissue. In addition, a large number of contact points is supposed to improve the effectiveness of propulsion. In detail, successful locomotion is possible with two sets of legs, one in the front and one in the rear, with a total number of 12 legs (Fig. 6) [55].

The capsule designed by Woods et al. [56] implements a holding mechanism capable of resisting the peristaltic pressure. The advantage is mainly constituted by the

possibility of exploiting the peristalsis during the navigation when the drug delivery is not active and it is not necessary to stop the capsule (Fig. 6)

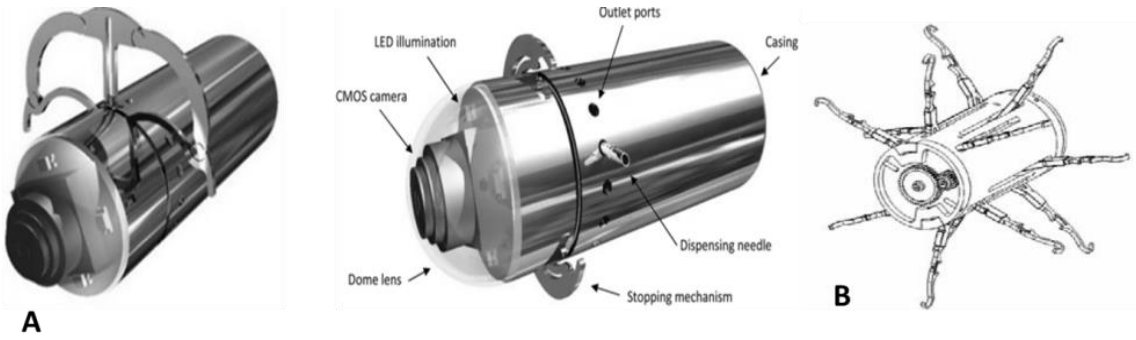

Figure 6 *Active locomotion mechanisms:* ***A.*** *Capsule for drug delivery by [56] and* ***B.*** *12-legged active locomotion solution by [55].*

Legs are opened only when the target is reached. The opening and closing of the legs brings the risk of trapping the tissue into the mechanism but the orientation of the legs combined with their smooth rounded ends prevents the collapsing of GI walls. Furthermore, to secure the robot in place when the holding mechanism is open, an increase in the circumference of the robot is implemented (Fig. 6).

Swimming requires a liquid medium. Therefore, such locomotion modality cannot be adopted along all the gastrointestinal tract, but only in the stomach, which can be easily filled with water. Magnetic swimming capsules have been developed, such as the one by Morita et al. [58] with a permanent magnet in the fin. The fin is moved by the alternating magnetic field produced by an electromagnetic coil. A swimming speed of 50 mm/s is reported. Guo et al. [59] proposed a hybrid swimming capsule integrating fish-like motion with spiral motion.

Overall, internal locomotion systems are very promising in terms of maneuverability and safety, but their development and actual use in the clinical practice has been hindered by a number of drawbacks, mainly related to mechanical complexity, which makes miniaturization difficult, and high power demand. For these reasons, external locomotion has been approached by many research groups.

3.5.2.2. External locomotion

External locomotion exploits magnetic fields that interact with magnetic components

mounted on-board the capsule. Both electromagnets and permanent magnets are being explored.

Electromagnets are used in the Norika capsule, developed by the Norika Project team (RF System Lab, Nagano, Japan). The capsule is provided with three internal electromagnets (rotor coils) interacting with three external electromagnets (stator coils) integrated in a vest-like jacket. Thanks to this configuration the capsule can rotate while in the GI [58].

Olympus Inc. developed a capsule that integrates an internal permanent magnet interacting with three pairs of external electromagnets. The capsule is provided with a spiral ridge and can be propelled bidirectionally thanks to a rotating external field [62].

Another interesting way of achieving external locomotion consists in using electromagnetic guidance with a very low flux density. MGCE (Magnetically Guided Capsule Endoscope) is a prototype system jointly developed by Olympus Medical Systems Corp. and Siemens Healthcare [59]. The system includes a guidance magnet designed by Siemens to generate a magnetic field of low intensity to steer a capsule endoscope with two cameras in the stomach.

The guidance magnet consists of an assembly of electromagnetic coils surrounding the working volume (Fig. 8).

This approach is different from the MRI guidance that has also been sometimes used for such kind of applications. In fact, the necessary magnetic flux density is about 30 times smaller than that of a conventional MRI system (3T), which significantly reduces the risks of typical MRI systems in presence of ferromagnetic objects. Furthermore, MRI has a fixed and unchangeable direction of the base field so it is not useful for the control of the capsule orientation.

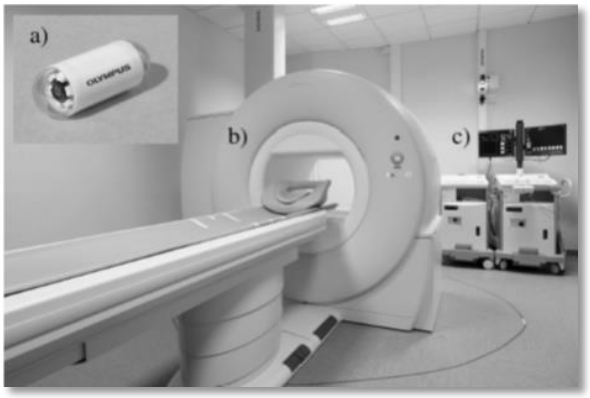

Figure 8 *Magnetically Guided Capsule Endoscope with a) capsule endoscope b) magnet guidance c) user interface [61].*

External Magnetic locomotion can fail when the GI walls are collapsed because friction may prevent effective control [64]. A combination of magnetic and legged locomotion can be beneficial to circumvent this issue. A novel solution proposes the use of hybrid active locomotion, defined as the combination of external and internal locomotion means [61]. In this case, external locomotion can be obtained by using magnets inside the capsule coupled to an external magnetic field generated either by coils or permanent magnets. Magnetic shells can also be used [62]. The legged mechanism is actuated whenever the capsule gets trapped in a collapsed area of the GI tract. Hybrid locomotion can improve navigation along the heterogeneous gastrointestinal environment (e.g. in [58]). Furthermore, it can address power consumption issues: a combination of passive and active locomotion means reduces the overall energy expenditure. On-board energy saving can also be achieved by alternating external and internal active locomotion means. Anyway, the integration of different principles may not be trivial, e.g. when the interaction among internal magnetic parts (e.g. in electric motors) and external magnetic guidance means is unavoidable.

3.5.3 Peristalsis inhibition

As already mentioned, the third solution involves the applications of a proper stimulus to inhibit peristalsis.

Sang Hyo Woo et al. [63] proposed a stopping mechanism for endoscopic capsules

involving an electrical stimulus provided externally. The Authors applied stainless steel electrodes on a M2A capsule (Given Imaging, Israel). The proposed approach induces the contraction of the small intestine using electrical stimuli. The contraction of the GI walls increases frictional force, which can stop the capsule otherwise pushed by natural peristalsis. Electrostimulation could be used also to control locomotion.

Despite some open critical issues, active adhesion regulation is one way to control the navigation along the GI.

In vivo small intestine mucosal adhesivity on the surface of robotic capsules has been investigated. The mucosa adhesivity is quantified by the energy required to separate the two adhering surfaces [64]. Terry et al. measured the adhesivity of the proximal, middle and distal portion of the small intestine on typical engineering materials, such as stainless steel, polycarbonate, micropatterned PDMS, used in the construction of robotic endoscopic capsules [65]. Estimated energy values required to overcome mucosal adhesivity at the leading and trailing edges, due to mucosa-mucosa separation and mucosa-capsule separation, are Wle = 25.9 mJ and Wte= 13 mJ respectively [65].

A new adhesion control technique has been presented by Accoto et al. [66]. It consists of a system capable of adjusting adhesion force on a wet substrate, such as the GI mucosa. A grooved PDMS surface is covered by a fluid that is immiscible with the gastrointestinal mucus (silicone oil, Sigma-Aldrich). The surface adhere onto the wet substrate according to the wet-adhesion principle [67]. Interdigitated electrodes, placed beneath the grooved surface, generate an electric field that changes the wettability of the silicone oil, thus modifying the adhesion force. Experimental results show that adhesion force can be reduced by acting on the voltage applied to the interdigitated electrodes. Adhesivity reductions up to 80% were measured [68].

3.6 Telemetry and localization solutions

Telemetry allows the communication with the robotic endoscope, e.g. to track and remotely control the capsule. Radio frequency (RF) telemetry is often used.

The HF capsule is tracked using X-Ray fluoroscopy. When the target is reached, activation of the drug release system is triggered by RF pulse emitted from an external high frequency generator [26].

Some commercial capsule endoscopes exploit RF wireless telemetry, for example Given Imaging capsules exploit a commercial RF transmitter custom chip with a carrier frequency of 402-403 MHz.

Other techniques implemented to remotely control capsules include scintigraphic methods: the Enterion capsule by Phaeton Research presented a sealed compartment filled with a radioactive marker for localizing the capsule [71].

InteliSite capsule by Scintipharma exploited gamma scintigraphy to track the capsule in the intestine and acquire absorption data. Incorporating two short half-life gamma isotopes (indium and technetium) sealed in the radiotracer port, while keeping physiological parameters unaltered, the capsule itself and the drug release were tracked simultaneously using gamma cameras with dual isotope detection capabilities. Thanks to a continuous monitoring of the capsule location, when the target region is reached, drug release can be remotely triggered by applying an oscillating electromagnetic field. Gamma scintigraphy limits the locational accuracy because capsule orientation cannot be determined.

Many custom solutions for wireless telemetry have been used to send the signal from inside the body to external devices [72]. But the majority of these systems, especially when in their early stages, were bulky due to large electronic components and batteries; they presented inhomogeneous performances (data rate, power efficiency) [73]. Finite energy supply available from batteries mainly limits telemetry. Large power for continuous motion can be provided with real-time energy transfer.

An alternative is ultra-wideband communication (UWB),usable at low energy levels for short ranges. Important parameters of UWB are: low power transmitter design, low interference effect in medical environment and high data rate transmission. Yuce et all. [74] proposed the use of a one-direction UWB transmission, in which only information from the capsule are recorded to save on electronic complexity and battery lifetime.

Another strategy, proposed by Intromedic Co. and integrated on the commercial capsule MiroCam, is based on electric field propagation, using the human body as a conductive medium for image data transmission.

In active locomotion bidirectional communication is very useful if control commands are given by an external controller. Otherwise, one direction communication can be adequate to transmit monitored in-body parameters or images. In the case of a completely autonomous device the use of the communication systems may not be mandatory, since data can be stored on-board to be retrieved after navigation.

The solution proposed by Susilo et al. [75] integrates a ZigBee communication protocol. Such a solution is characterized by low data rate (250 Kb/s) in bidirectional communication, high networking capability and low power consumption according to the protocol standards.

Localization acquires great importance for capsules with therapeutic purposes, in particular for drug delivery. The information about position and orientation of the capsule allow the localization of lesions to be treated. It gives also indications about the distance travelled, the anatomical district in which the capsule is located and the transit time.

Many localization methods have been proposed in literature [76] other than the mentioned wireless signals [77].

Magnetic tracking [78] has been adopted to localize the capsule MAARS. A 3D magnetic monitoring system called 3D-MAGMA (Innovent technology, Germany), determines the position of the magnetic pill, it adopts 27 magnetic field sensors for collecting individual measurements with a control time loop of 20 ms and an overall accuracy of 5 mm and 2° [79].

Many magnetic tracking strategies have been developed but most of them are not applicable when an external magnetic locomotion system is used (Sec. III) as the magnetic field would affect the external sensors array measurement and such interferences are difficult to be avoided. Despite, various methods and optimization algorithms to determine the capsule position and orientation were proposed [80].

A localization approach, compatible with external locomotion is based on a triangulation algorithm able to detect the capsule in the GI traced by recording and processing external magnetic field measurements through a custom on-board tri-axial

magnetic sensor [81]. An alternative consists in using radioactive emission markers. In [82] authors proposed a novel method based on tracking of three positron emission markers embedded in a capsule. An advantage of the system is the compatibility with any actuation mechanism as there is no interference between gamma rays and electromagnetic fields used for actuation.

Research on localization methods is very active. Some new methods have been presented, such as visual odometry [83]. By the way, such methods can be adopted only on viewing capsules because they are based on visual information from capsule endoscope recordings. New odometric solutions should be implemented for non-viewing capsules that also need spatial information to define the travelled distance and the position within the anatomical districts in order to deliver, for example, localized therapy.

3.7 Future trends

The main challenge for the development of smart pills consists in integrating in a single device an effective and robust locomotion system, taking into account characteristics of the operating environment, which is poorly accessible, tortuous and slippery, and a reliable drug delivery system, whose performances must be controllable in terms of release rate, number of doses and amount of drug released.

The overview of the state of the art suggest that research studies should aim to the development of autonomous pills. Active locomotion should be preferred to passive one because it ensures reliable control of the position in the GI tract and limits undetermined movements. Furthermore, internal locomotion is preferable because it does not require extra instrumentation, thus reducing maintenance costs and patients' exposure to magnetic fields.

Bioinspired solutions are promising for dexterous positioning and orientation, anchoring and releasing of the capsule. Legged locomotion allows to optimize performances thanks to the flexibility of the mechanical design (number and position of the legs, gaits parameters). Anyhow, further miniaturization of the mechanics and of power supply systems should be pursued.

Externally controlled systems are more promising in the medium-term. External power can solve consumption issues and physician supervision may guarantee a

higher safety (e.g. in steering control and drug delivery activation).

Hybrid locomotion can help in the development of autonomous smart pills [61], for example combining passive, but modulated, and internal active locomotion.

In fact, a smart pill should have the smallest impact on the patient's body: the design of the capsule should avoid as much as possible the implementation of complex mechanisms on-board and exploit environmental characteristics too. To this respect, peristaltic forces can be modulated controlling mucosal adhesion to reduce the time of use of the locomotion mechanism. So, power consumption and possibility of damaging the tissue are reduced and external instrumentation is not needed.

Future smart pills will need very good localization and positioning capabilities. Moreover, the energy demand should be reduced to allow batteries or energy harvesting solutions to provide the necessary energy, even during long interventions.

On the side of drug delivery, the possibility of tailoring the dose on the patient and on tissue local conditions is desired. There is not a only device capable of doing that but studies on mechanical solutions, reservoirs dimensions and materials are moving toward the achievement of the result.

Tailoring of the treatment is hardly achieved by externally controlled release mechanisms, such as HF capsule, Enterion, EnteliSite capsule, because of the difficultly of activation deep in the body or the use of isotopes. In the case of MAARS, the capsule is well targeted by the external guidance but only one shot release is possible. That limits local and personalized treatment according to specific needs.

Therapeutic properties of the capsule rely on the monitoring of physiological parameters with sensors on-board. Continuous sensing of body's conditions can trigger the drug release according to pre-programmed profiles in correspondence of real time measurements. It is done by IntelliPill with pH sensors.

The scientific state of the art would be improved by the integration of drug delivery systems more and more capable of delivering personalized treatment with sophisticate, but not too much complex, autonomous navigation systems. Besides all the solutions illustrated, some other issues still need to be solved. In particular, the analysis of experimentations on humans and of clinical cases evidences that capsule retention is a major cause of capsule endoscopy failures [86].

Cases of retention are reported as related to particular anatomical sites or pathological conditions such as Crohn's disease, small bowel cancer, and various types of duodenal, small bowel and large bowel diverticula, and suspected GI obstructions [87].

Based on these considerations, we foresee an increase in the diffusion and use of the capsules if proper methods to predict and avoid retention will be developed and implemented. Among such methods, active locomotion mechanisms appear quite promising.

Another issue that deserve further attention is site identification. To this purpose, different levels of motility in different parts of the gastrointestinal tract could be detected for site identification purposes, since motility is characteristic of different tract and conditions [88]. As an example, the pylorus is a critical passage point for the capsule, especially for passive capsules moved by peristalsis. In many cases much of the navigation time is spent for passing from the stomach to the duodenum [63].

In this context, localization systems can provide a feedback control on the active motion that also speeds up examination and greatly reduces the risks of retention [89].

It is therefore expected that future systems will include novel localization means in order to improve the efficacy of combined local treatments and diagnosis. Moreover, new odometer methods to be directly integrated with locomotion mechanisms on non-viewing capsules specific for treatment purposes, should be implemented.

In the next years, smart pills will integrate different functions, such as endoscopy, drug delivery, biopsy.

Currently, the use of capsules for biopsy is not very widespread. For such kind of capsules, the requirements on positioning and localization capabilities are quite demanding. Furthermore, the execution of bioptic procedures through swallowable devices is still in need of adequately sophisticated miniaturized tools from robotic surgery [90]. The development of such tools requires in fact the miniaturization of articulate mechanisms and resistant to loads structures.

Anyway, the implementation of different functions (e.g. endoscopy, drug delivery, biopsy) on a single device can make the device quite complex and prone to failures.

The idea to realize not a unique complex capsule, capable of screening, diagnosis and treatment but a platform including three different devices that can be used for specific medical needs or in consecutive steps, screening diagnosis and therapy has been pursued, for example by Versatile Endoscopic Capsule for Gastrointestinal Tumor Recognition and Therapy (VECTOR) project [91].

In this perspective, the STORM Lab developed a modular open source architecture for Medical Capsule Robots aiming to provide a tool for shortening the design and development time for capsule robots. It consists of hardware modules, firmware and software libraries that can be integrated for specific purposes [92].

In this context, as described in the next chapters, this work of thesis aimed to the development of a smart pill specific for drug delivery with the intention to provide a device for localized treatment of pathologies active along the gastrointestinal tract. The capsule architecture is simple and can be adapted to specific needs in terms of type and quantity of drug, it is disposable and can be naturally expelled. The capsule is sensorized in order to achieve targeted therapy. At this first stage, passive locomotion is implemented but active locomotion can compatibly be integrated on-board.

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Chapter 4

UCBM Capsule Architecture

4.1 Overview and aims of the UCBM capsule

The UCBM capsule is a smart pill for local drug delivery in the gastrointestinal tract. It is a non-viewing capsule capable of monitoring physiological conditions of the gastrointestinal tract thanks to on-board sensors, and of consequently performing local therapeutic actions thanks to the on-board drug delivery system (Fig. 1).

Figure 1 *Main features of the UCBM smart pill*

The need for developing a capsule for drug delivery comes from the medical considerations and healthcare trends, as presented in Chapter 3.

The UCBM capsule is in particular addressed to chronic inflammatory diseases that have a patchy nature.

As a matter of fact, local drug delivery brings many advantages to the therapy of these locally active pathologies: firstly, local drug delivery allows dose reduction for medications that or can produce large side effects, due to large doses of systemic

administration (i.e. anti-inflammation medications, cortisone and steroids) or are very expensive and require large intravenous infusions (i.e. biological drugs) [1].

As a consequence of doses reduction, also costs are reduced in terms of direct medical costs and indirect costs of hospitalization, time out of work and mortality (USA Costs: $141.8 billion (2004) $97.8 billion, direct medical costs (2004) $44 billion, indirect costs (2004) [2]. The total health-related cost in 2004 was estimated to be about $142 bn [3]).

Local drug delivery can also help to achieve personalized treatment.

The concept of personalized treatment is a key element of the evolution in healthcare. Personalized treatment refers to the idea of tailoring the therapy on specific patient's needs. It is also referred to as individualized or patient-specific therapy.

Combination of diagnostics with therapeutics is also an important component of personalized medicine.

A personalized drug delivery system on a swallowable pill could be able to:

- Tailor the dose level to suit the individual needs
- Adjust dosage over time in line with treatment response or disease progression
- Select a precise location for drug delivery within the gastro-intestinal tract
- Measure and monitor the conditions of the gut by means of built-in biosensors
- Vary treatment according to collected data

As shown by general requirements asked to a smart pill for drug delivery in chapter 3, the development of the capsule has address some technological challenges:

- Size, dimension of the capsule must be contained in an ingestible size, comparable for example to a vitamin tab.

- Choice of the components, considering electronic circuits, batteries, in terms of dimensions, isolations and, RoHs compliance.

- Power management. Power consumption of all the on-board components and operations of the capsule must be estimated.

- Material toxicity and reliability. The choice of biocompatible and mechanically resistant materials for coating or building components is a fundament step.

- Device control, the device is autonomous thanks to sensing capabilities embedded on-board and batteries, but passive. The drug delivery system is capable of delivering a controlled amount of drug.

In the next paragraphs the architecture of the system is illustrated in order to provide an overview of the capsule features. Details on the design and development of every component will be provided in the dedicated chapters.

4.2 UCBM capsule features

In order to develop a device that could address the requirements and the abovementioned technological open challenges, a capsule has been developed according to the concept showed in figure 2.

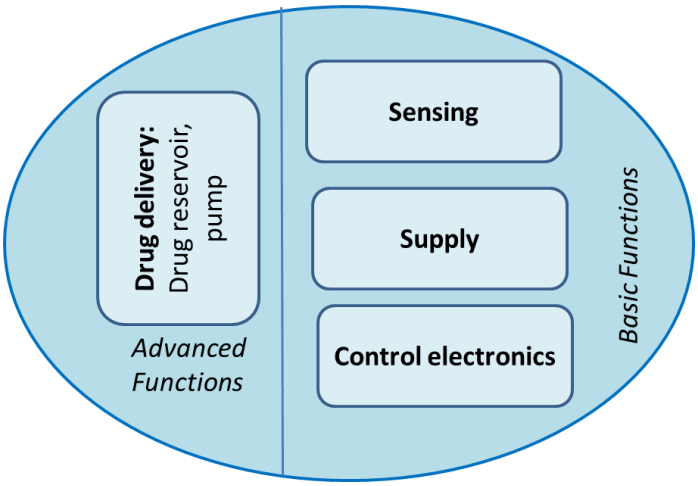

Figure 2 *Basic scheme showing the UCBM capsule concept*

The capsule is basically constituted by a unit for drug delivery interfaced to electronics for the sensing of the physiological conditions during navigation and for the control of the drug delivery system.

A prototype of the capsule has been realized with the techniques of rapid prototyping (3D printing) in acrylic resin (EX200 and S100 Visi Jet, HD3000 Projet, 3D Systems) as shown in figure 3.

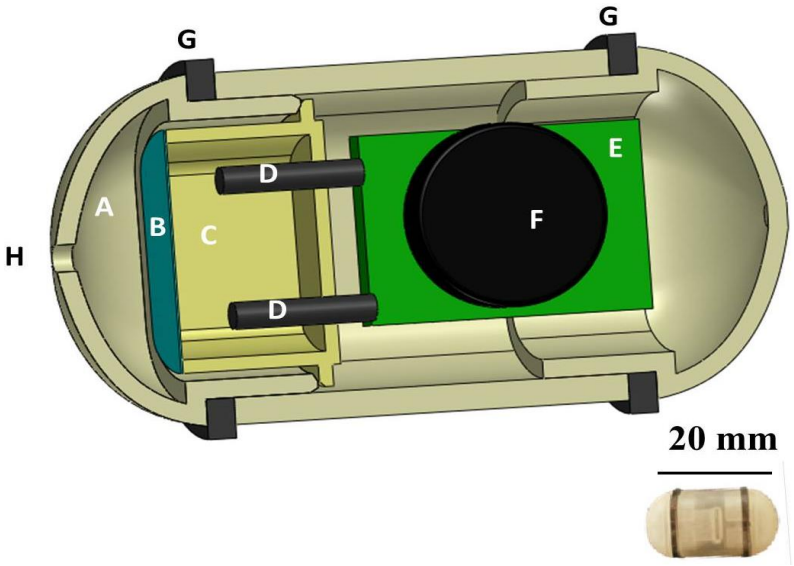

Figure 3. *3D printed mock up and cross section of the capsule.* ***A****. Drug Reservoir,* ***B****. PDMS membrane* ***C****. Electrolyte reservoir,* ***D****. Electrodes* ***E.*** *Electronic board,* ***F****. Battery (LIR1025, GMB Power),* ***G****. Electrodes for impedance measurement* ***H****. Nozzle. Capsule dimensions are 21 x 14 mm (length x diameter).*

The overall dimensions of the capsule are 21mm x 14 mm, and they are comparable to existing commercial endoscopic capsules. The total volume of the capsule is about 1300 mm^3.

The capsule houses the drug delivery system, the impedance sensor, the control electronics and the battery.

The front and the rear lobes are assembled together with a central body and two circular electrodes are wrapped around the capsule in order to contact the mucosa tissue and the electronics inside.

The front lobe is dedicated to the drug delivery system.

The drug delivery system is constituted by the following parts:

- Drug reservoir
- Electrolytic solution reservoir
- Electrodes for electrolysis
- Nozzle
- Diaphragm between the two reservoirs

The remaining place is devoted to the control electronics and power source.

The capsule has an internal power source, in particular battery, that is a LiPo battery (LIR1025 GMB srl).
Biocompatible materials have been selected for the development of the capsule: as an example the pump used in the drug delivery system is an electrolytic pump made of Polydimethylsiloxane (PDMS), the electrolytic solution is a saline non-toxic solution, electrodes are in platinum.
In the basic version, the capsule is passive but it can be equipped with active internal locomotion. Details of the mechanisms that can be implemented are given further on.

4.3 UCMB capsule sensing capabilities - The impedance sensor

Localized drug release can be triggered based on the measurements performed by the sensing system, which relies on an impedance sensor able to monitor gastrointestinal tissue conditions. The sensor has been developed and validated on esophageal tissue. Impedance measurement is known to be a useful tool for tissue characterization [4]. The measure of the alteration of the impedance is used to assess diseases of the esophagus. The impedance, combined with pH measurement, is used in medical practice to assess gastroesophageal reflux diseases (GERD) through naso-gastric probe.
The impedance sensor has been developed to provide the possibility of monitoring impedance values along the whole gastrointestinal tract and a miniaturized version

designed in order to be integrated on the swallowable pill that allows the exploration of inner part of the gastrointestinal apparatus. The novelty in respect to the present state of the art is that impedance can be used as a diagnostic parameter not only in the esophagus but along the whole gastrointestinal tract.

The sensing system exploits electrodes mounted on the capsule surface to measure the impedance of the tissue (fig. 3 G). The surface electrodes are thin Pt rings (thickness 1 mm). Each electrode partially protrudes inside the capsule, where they are connected to the electronics.

Conventional endoscopic capsules have a cylindric shape, UCBM Capsule has a flat shape in order to increase the contact area between the capsule and the tissue during navigation, for a continuous monitoring of the tissue impedance. As a matter of fact, the miss contact between the electrodes and the tissue can influence the value of the impedance measured. As an example, air insufflation during the in vivo test of the developed sensor produced a substantial increase of the value of resistance measured. The increase of the read impedance value over a set threshold may stop the acquisition.

4.4 Therapeutic solution- the drug delivery system

The drug delivery system comprises two reservoirs respectively for the drug and the electrolytic solution, separated by an elastic membrane. The two reservoirs occupy one lobe of the capsule (Fig. 4).

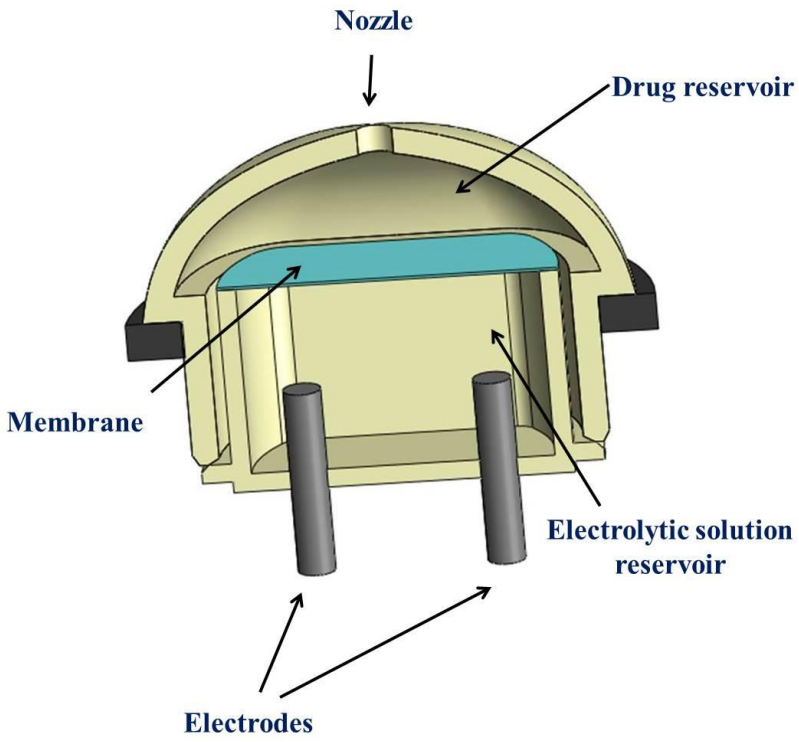

Figure 4 *The drug delivery system*

The drug delivery system is actuated by an electrolytic micropump. This kind of device uses the generation of gases, resulting in volume expansion, to actuate a membrane and displace a fluid.

Electrodes are polarized only when a variation of the impedance is detected, so the electrolytic reaction starts, bubble gas are produced, the membrane is displaced and the drug is pressurized.

The drug is delivered through a nozzle on the frontal part of the capsule (ϕ 1 mm). The nozzle is normally closed by a pre-stretched paraffin membrane (Parafilm "M", Pechey Plastic Packaging). Two through holes on the membrane (ϕ 0.5mm), placed on both sides of the nozzle, allow the drug to flow out of the nozzle only when the paraffin membrane is deflected by the pressurized drug (Fig. 5). It must be noticed that no valves have been used because structural simplicity is necessary and a top coating guarantees no leakage and a good sealing.

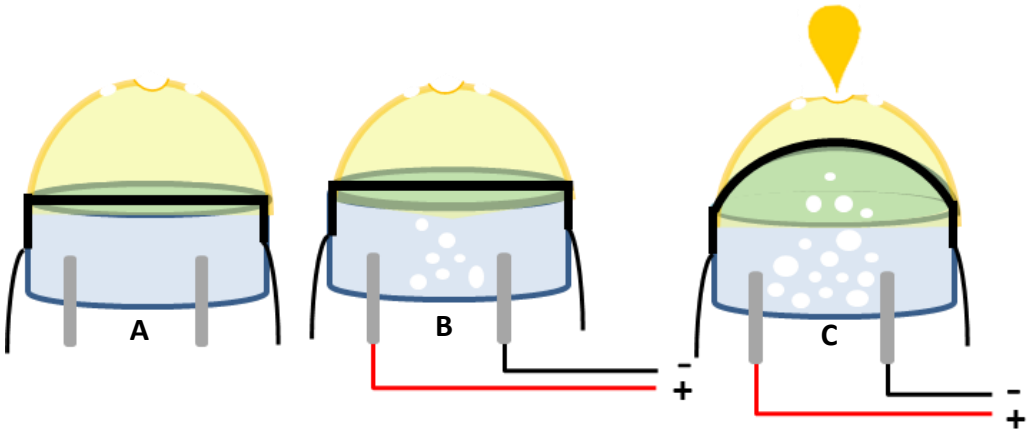

Figure 5. *Schematic of the drug delivery. The two reservoirs are separated by an elastic membrane (A). When current flows through the electrodes, electrolytic reaction starts (B), the membrane deforms and drug is released through the holes (C).*

The volume of both the drug and electrolytic solution reservoirs is 120 µl. The expected volume of drug to be delivered is about Vd = 50 µl (i.e. about half of the volume of the drug reservoir).

Electrodes are Pt wires, 1 mm in diameter. The area of the membrane separating the two reservoirs is about 40 mm^2. The membrane is in Polydimethylsiloxan, (PDMS, Sylgard 184, Dow Corning, Midland, MI). For fabricating the elastic membrane, PDMS was mixed with curing agent at 10:1 mass ratio. The mixture was degassed for 30 minutes, and poured on the electrolytic solution reservoir that had been prefilled with the saline solution. The assembly was cured at 60°C in an oven for 30 minutes. The thickness of the membrane is about 0.1 mm.

Before realizing the PDMS membrane different materials and micro-fabrication techniques have been empirically tested (e.g. Parafilm membrane, acrylic membrane, lattice membrane) but none of them was mechanically robust.

The choice of PDMS is justified by the characteristics of the material that is biocompatible and largely used in medical applications. Furthermore it can be easily adapted to the design of the micropump and can elastically bear repeated membrane deformations, maintaining unaltered its mechanical properties.

As can be seen from figure 5, the PDMS membrane supports a sensor fixed on it. The sensor is a novel strain sensor prepared to monitor the membrane deformations. It consists of thermoplastic elastomer loaded with graphite. The strain sensor

provides an indirect measure of the pressure produced in the electrolytic solution reservoir. So, a closed loop control over the drug delivery is achieved.

The electrolytic solution used to fill the electrolyte reservoir is a 0.5 M solution of NaCl.

4.5 Mechanical assembling of the capsule

The system is mechanically assembled according to the following steps:

- The drug reservoir is filled from the bottom while the dispensing hole on the drug reservoir is sealed.

- The pre-filled electrolytic solution reservoir is fitted in the drug reservoir that constitutes the frontal lobe of the capsule.

- The assembly is locked by clamping a thin collar that avoids the electrolytic solution reservoir to slide backward. External electrodes are fixed on both sides of the central part of the capsule body.

- The capsule is closed by locking the second lobe on the rear part of the central body. The electronic board and the battery are put in place before closing the capsule.

The sealing of the system is very important and not trivial. As the drug delivery system is concerned, the drug release depends on the capability of the membrane to transfer all the pressure produced by the gases in the lower chamber to the upper one. So no relative displacement of the two reservoirs and no leakage are allowed. In particular, the two reservoirs have to be fixed and hold in position. The interface of the frontal lobe with the central part must be leak tight too.

To address these sealing issues, first of all, the electrolytic reservoir has to be fixed to the capsule in a way that it is always in contact with the drug reservoir above.

Different mechanical solutions have been investigated to guarantee the sealing, and in particular:

- crown stop

- interlock

- collar at the bottom edge

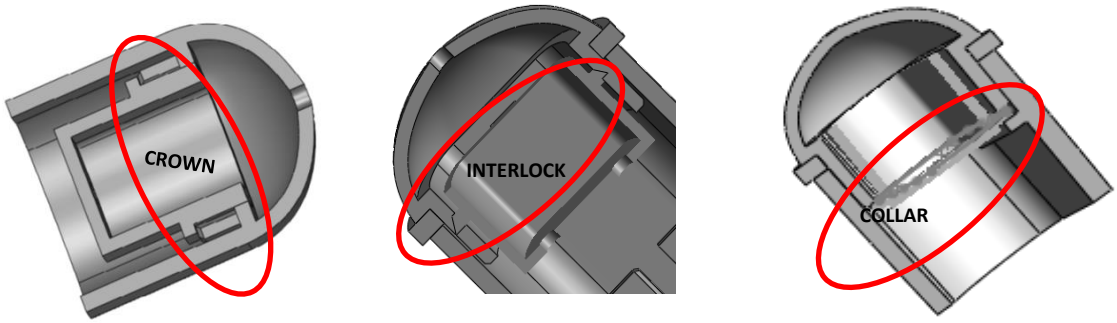

Figure 6 *Mechanical solutions for reservoirs assembly*

The first one only prevented the electrolytic solution reservoir to penetrate the drug reservoir but did not prevent the reservoir from slipping backward.
As an alternative, a mechanical interlock between the two parts to connect (drug delivery reservoir and electrolytic pump) was added but the mechanical interlock was too brittle because the capsule prototype is made of acrylic resin and a new solution was explored. A collar at the bottom of the electrolytic reservoir was designed to fix it to the frontal lobe of the capsule. Furthermore, the internal wall of the central body blocks the reservoir avoiding backward slippage. This solution can guarantee the drug delivery system is leak thigh. When the upper dome is fitted in the central body and the electrolytic reservoir is locked to it the drug delivery system constitutes an isolated sub system. Only the electrodes can contact the electronics.

4.6 Power

Power issues are important in capsule endoscopy and various methods have been implemented to power up devices. Generally, power source can be internal or external. Powering is still a major field of investigation because performances of devices depend on it. Nowadays a maximum of 10 hours of functioning have been achieved by commercial devices [5].

Consumption analysis of the electronics will be investigated further on. By the way key elements to consider when programming electronics are :

- Sensors consumption;
- Microcontroller's clock frequency;
- Programming mode as alternation of sleeping and activation mode for microcontrollers and sensors;
- Frequency of acquisition (e.g. reducing frequency of acquisition doesn't save energy but reduces rate at which it is consumed);
- Type of communication (e.g. I_2C with pull-up resistances).

The drug delivery system can also be power demanding, especially because of the pump. The choice of the electrolytic micropump is due to low voltage and current (~ 3V, 2 mA) required by this kind of actuator.
For the prototype LiPo batteries have been selected. As commercial batteries can be adopted, flexible thin batteries are a solution.

4.7 Future works –Locomotion

We stated as diagnostic and therapeutic functions can be integrated on a swallowable device. The swallowable capsule is the vector for the therapeutic action exploited by the drug delivery system that itself is available thanks to the sensor for the monitoring of physiological conditions. Such interaction of elements makes the device a complex system, a smart pill.
A further element that is important for the improvement of such a device is the integration on-board of a locomotion system.
Considering the classification of locomotion solutions provided in chapter 3, as an autonomous robot the UCBM capsule should embed internal locomotion. A locomotion system on-board allows autonomous navigation of the capsule and the possibility to improve control over capsule's position along the gastrointestinal tract.

A solution that can be integrated on the capsule is the "pinch locomotion" that has been developed by Accoto et al. [6].

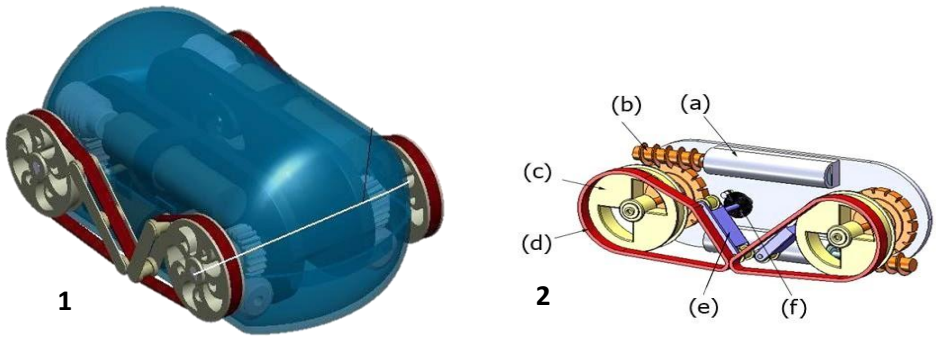

Figure 7 1. Concept of the pinch locomotion integrated on a capsule. **2.** The Mechanism**. a** + **b**. motor; **c** + **d**. pulleys and belts; **e.** Oscillating arm; **f.** Torsional spring **2**.

The pinch locomotion principle exploits simple mechanics: two counter-rotating wheels are connected by an elastic element that allows the adjustability of the distance between their axes. When the two wheels counter rotate the outer layers of the tissue are forced to enter the space between the wheels, which is thus pinched. A translation is obtained when the wheels rotate in the same direction. Each capsule mounts a pair of identical modules, one per side (Fig. 7). In this way, turning in place and steering is achieved when the two modules are driven at different speeds (Fig. 8) [7].

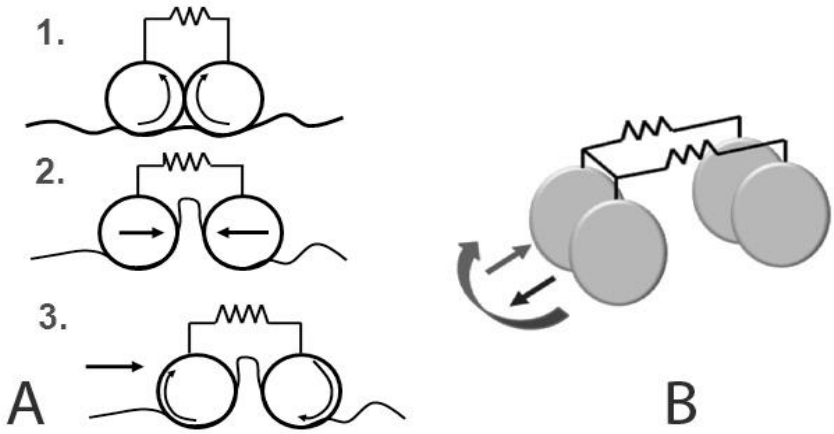

Figure 8 A. *Pinch Locomotion Principle: 1) two counter-rotating wheels connected by an elastic element pinch the tissue. 2) An elastic force maintains the pinch while allowing the passive adjustment of the distance between the wheels. 3) The same direction of rotation produces the translation.* ***B.*** *Turning/steering is achieved when the two modules are driven at different speeds.*

The theoretical maximum locomotion speed is 86 mm/s, which allows a complete inspection of the GI tract in 30 – 35 min.

Such a solution can be integrated on the UCBM capsule because it saves about the 60% of the internal volume of the capsule that can be allocated to the drug delivery system, the battery and the electronics described.

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Chapter 5

The impedance sensor

5.1 Electrical properties of the tissue

Impedance measurement is a useful tool for tissue characterization [1] and monitoring of pathological conditions so it is diffusely used together with other tools to achieve a complete diagnosis.

Electrical properties of the tissue are determined by the type of cells and by physiological structure of the tissue [2]. The plasma membrane of the cells determines electrical properties of the tissue. In particular, it regulates the ions transport between intracellular and extracellular media, acting as a capacitor. For this reason biological tissues have different responses to different frequencies of stimulation and types of tissue can be discriminate according to their response. To this respect, the correlation between pathological conditions and alterations of the tissue electrical impedance have been investigated. In particular, it has been shown that cancerous tissue has different electrical characteristics compared to normal tissue. So, electrical impedance measurement has emerged as a diagnostic tool [3].

As an example, electrical impedance sensing has been used on biopsy needles for prostate cancer [4], or electrical impedance spectroscopy (EIS) has been used to detect acute ischemia [5] or old infarction scar [6] and rejection in transplanted heart [7].

Recently, impedance measurements have been used as a minimally invasive replacement of standard biopsies, in the so-called *electrical biopsy* and also tested on intestinal tissue of rats [8].

5.2 Impedentiometry in medical practice

Real-time monitoring of biomedical parameters is essential to the diagnosis of several affections [9] and as a matter of fact, impedance measurement is becoming a new testing paradigm.

Intraluminal impedance measurement (MII) technique has been recently introduced in medical practice to detect intraluminal bolus movements without the use of radiations and for evaluating esophageal functions and gastroesophageal reflux disease (GERD).

The presence of a bolus or a reflux episode produce changes in resistance between the metal electrodes used for the measurement. Variation is usually measured by a naso-gastric probe equipped with multiple metal rings (multichannel impedance measurement) or combined with a pH sensor. Usually probes for reflux monitoring use a single pH electrode, located 5 cm above the lower esophageal sphincter (LES) and multiple couples of impedance electrodes located 2 cm apart from each other (fig. 1). The exam lasts 24 hours during which the patient is asked to maintain a daily routine.

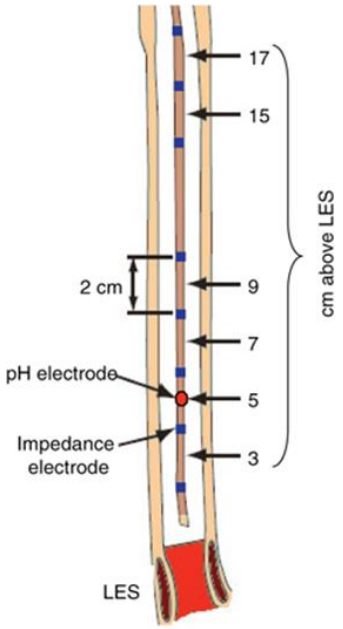

Figure1 *Schematic representation of a multichannel intraluminal impedance and pH (MII- pH) catheter. Classical pH-Impedance probe configuration incorporates 6 impedance measuring segments (each comprising two impedance electrodes spaced 2 cm apart) and one pH electrode. A pH electrode is placed 5cm above the proximal border of the lower esophageal sphincter (LES), with impedance measurements 3,5,7, 9, 15 and 17 cm above the LES [10].*

In an empty tubular organ (i.e. esophagus or small intestine) the electrical current between the two rings is conducted by the few ions present on the mucosa. Liquid

containing bolus with a large number of ions, has a higher conductivity and when entering the impedance measuring segment lowers the impedance value.

The impedance stays at its bottom value as long as the bolus is present in the segment, returning to baseline once the bolus is moved on by a contraction. The contraction produces a slight increase in impedance above the baseline due to a decrease in luminal cross-section.

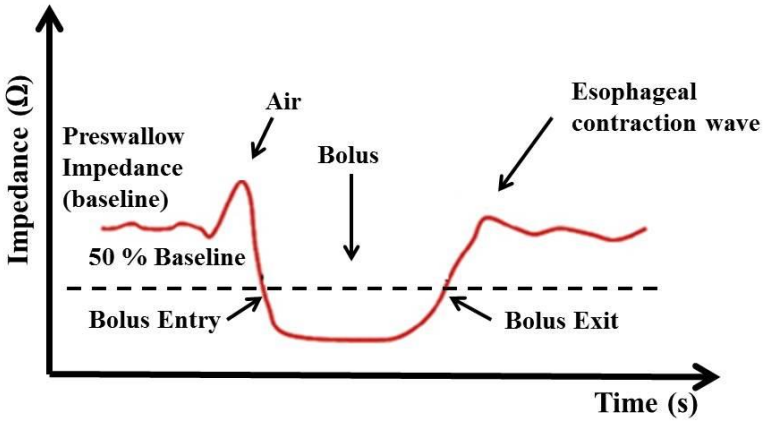

Figure 3 *Typical trend of impedance during swallowing*

Measuring impedance at multiple sites (multichannel) permits the determination of the direction of bolus movement based upon temporal differences in bolus entry and exit.

Intraluminar impedance measurement is still used in combination with esophageal manometry (MII-EM) and barium or radioisotope esophagram for esophageal function testing providing information about both pressures and bolus transit within the esophagus. For GERD testing, in combination with ambulatory pH-metry (MII-pH), impedentiometry permits detection of both acid and non-acid gastroesophageal reflux [10]. Traditional pH recording, in fact, only records acidic pH reflux episodes. Whereas non-acid reflux is poorly diagnosed by pH only testing, producing 70% false negative results. Regardless, also in the case of acid reflux pH testing can result in 32% false positive results [11]. In MII-pH test, reflux is no diagnosed by pH-metry but is primarily detected by MII and then characterized as acid and non-acid based on pH measurement [12].

The growing importance of impedentiometry and mostly due to the large diffusion

of GERD, that is estimated to be the most prevalent disease affecting the gastrointestinal tract [13]. GERD has been reported as one of the major risk factors for adenocarcinoma of the esophagus, an often incurable tumors with a rapidly rising incidence rate. It also has an economic importance, contributing to the expenditure in the United States of US$4–5 billion per year for antacid medications [14].

GERD results from the failure of the normal antireflux mechanisms to protect against frequent and abnormal amounts of gastroesophageal reflux (GER), that is, the effortless movement of gastric contents from the stomach to the esophagus. GER is not itself a disease but a normal physiological process that may occur multiple times in a day without producing either symptoms or signs of mucosal damage.

In contrast, GERD is a disease usually producing symptoms of heartburn and acid reflux. Most patients have no visible mucosal injury at the time of endoscopic examination (nonerosive GERD), whereas some have esophagitis, peptic strictures, Barrett's esophagus, or evidence of extraesophageal diseases such as chest pain.

A system able to monitor the tissue's conditions and consequently provide a diagnostic tool can facilitate management and treatment of patients.

Usually esophageal reflux produces a decrease of the baseline impedance value (usually from about 4 kΩ to less than 1 kΩ [19]), then during the 24 hours test, particular events can produce variations that are monitored and registered.

GERD patients are often treated with Proton Pump Inhibitor (PPI) medication, but non-acidic reflux can still cause symptoms.

Combined Impedance-pH recording is clinically useful in the evaluation of symptoms under PPI therapy, as well as for hoarseness, unexplained cough, and applications of particular interest.

5.3 Capsules for impedance monitoring: state of the art

The explosive growth in semiconductors industry is enabling the development of a new class of affordable, low cost products, which can be considered as *smart*

medical systems. Moreover the diffusion of high performance electronics enables the development of compact, low power and portable measurement units.

Consequently, a new emergent approach for Impedance-pH monitoring devices is based on wireless communication instead of tethered probes to increase patients comfort level. Studies show that of 520 ambulatory procedures 4% of patients couldn't tolerate the intranasal catheter and do not complete the exam. 10% of the patients to whom the test is recommended, refuses to take it [15]. Moreover, despite the recommendation of maintaining a normal daily routine during the test period, the majority of patients alters their eating habits due to the discomfort caused by the catheter. So the quality and accuracy of the exams are jeopardized.

To improve the reliability of the exams, different monitoring devices have been proposed and in particular ingestible capsules have been proposed also for this purpose. An example is the capsule for pH and impedance monitoring in the esophagus by Gonzalez-Guillamin [16].

The capsule developed is an impedance-pH wireless capsule capable of discriminating between acidic and nonacidic reflux. The capsule is magnetically hold in position. The magnetic holding is an alternative to surgical affixation and is capable to overcome peristalsis.

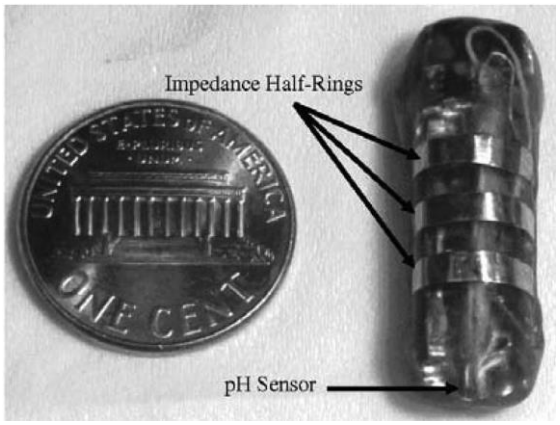

Figure 3 *Capsule for Impedance and pH monitoring in the oesophagus [16]*

Another device proposed by Hung Cao et al. [17] is an implantable batteryless and wireless capsule with integrated impedance and pH sensors.

This device claims to overcome the problems presented by the only commercially available capsule for esophageal acid reflux monitoring, the Bravo Capsule by Given Imaging.

The capsule only monitors pH. It presents a pH sensor at the bottom and a radiotransmitter with a insertion needle to attach the device to the esophageal wall. The capsule is not capable of detecting individual reflux episodes because it identifies variations between samplings. Furthermore, sampling is conducted discretely, to save battery.

Some solutions have also been patented. As an example, in patent US2011/0306897 a capsule for diagnosing diseases of the intestinal tract is shown. The patent claims a method to map the sensed impedance from the pass of the capsule in order to diagnose inflammatory disorders.

5.4 Impedance sensor

Considering that intraluminal electrical impedance measurement is used widely in medical practice for esophageal exams and that recent studies show how electrical impedance measurement is a useful tool for the monitoring of physiological conditions of different tissues, and in particular of different regions of the gastrointestinal tract, our aim has been to design and develop an impedance sensor for the monitoring of the tissue conditions along the gastrointestinal tract.

The sensing system has been developed and tested on large scale and then scaled to be integrated on the smart pill. Thus, the measurement can be exploited to trigger the drug delivery system implemented on the capsule.

5.4.1 Sensor calibration

The sensor has been developed and calibrated and then validated on esophageal tissue.

Baseline impedance values of healthy and pathological tissues (e.g. affected by GERD) are known from literature. For instance, the impedance of the esophageal tissue in healthy adults is about 4 kΩ [18] and decreases in GERD [19].

The developed sensory system is capable of continuously monitoring tissue impedance through the electrodes mounted on the surface of the capsule.

The measure of an impedance value far from the physiological baseline can be used to trigger the activation of the drug delivery system of the capsule.

The large scale version of the sensor has been developed and tested *in vitro* and *in vivo* before miniaturization and integration in the ingestible capsule.

The system consists of a 12 bit impedance converter (AD5933 Analog Devices), connected through an I_2C protocol to a microcontroller (PIC18F25K20, Microchip). The impedance is measured in real-time and transmitted to the microcontroller. A custom-made circuit has been fabricated over a 63 x 50 mm^2 PCB. The system is connected to and powered by a PC, through a USB port (Fig. 4).

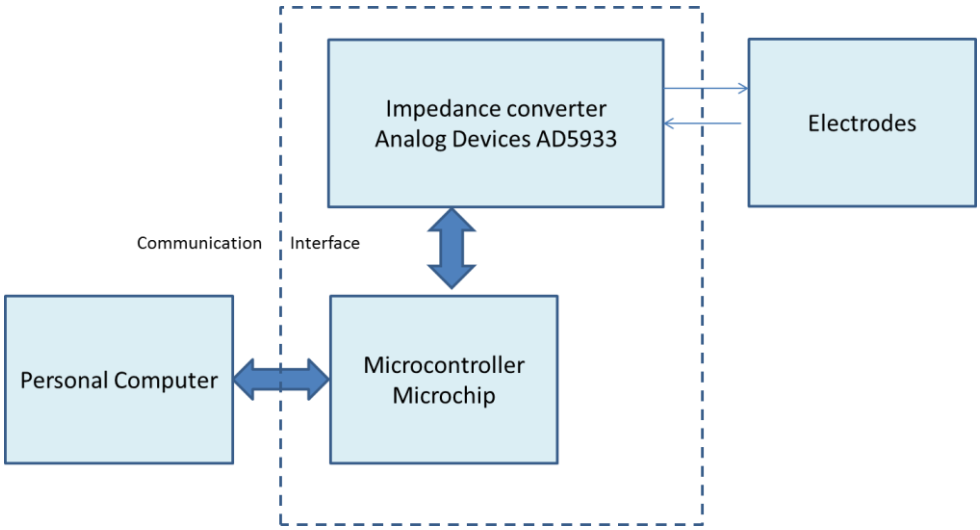

Figure 4 *Block Diagram of the electrical impedance system*

The system can alternatively be powered by a 3.3 V miniature Li-Po battery. The block diagram of the AD5933 impedance converter is shown in Fig. 5. A frequency generator provides the system output V_{OUT} with a wave input. The impedance (Z) of interest is measured between V_{OUT} and V_{IN} pins (Fig. 5). Frequency is set to 30KHz; the system clock is provided by the internal oscillator with a typical frequency of 16.776 MHz [9]. The current through the test load depends on the impedance Z. Current analogic signal is transformed into a voltage analogic signal and hence into a digital signal by the A/D converter.

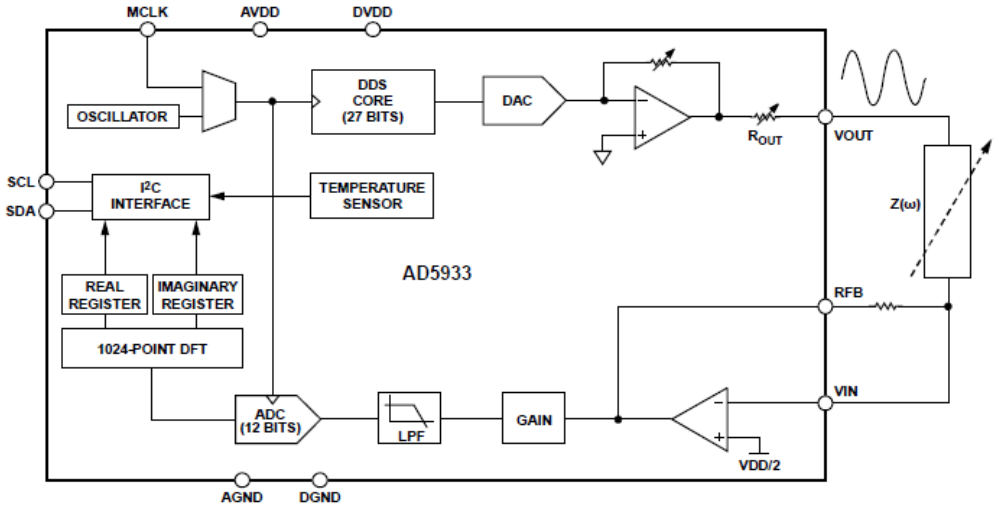

Figure 5 *AD5933 Analog Devices block diagram[20]*

A DFT processor computes the discrete Fourier transform of the signal and returns both real and imaginary parts of the test load admittance A, scaled by the amplifier gain factor G.

Thus, the impedance Z is calculated as follows:

$$Z = \frac{1}{G \cdot A} \tag{1}$$

The gain factor G has to be chosen according to the measurement range of interest, being proportional to the calibration impedance Zcalib, which has to be set as close as possible to the measured impedance.

The gain factor is defined as $G = \frac{1}{Zcalib} \cdot \frac{1}{M}$ [20], where the magnitude (M) ($M = \sqrt{R^2 + I^2}$) is calculated reading real data register R and imaginary data register I. Z_{calib} is set to 3.8 kΩ, according to the esophageal baseline impedance value. Therefore, G is set to 8.6·107.

The impedance sensor was firstly tested by measuring a set of known resistances, within the range 100Ω - 10kΩ. The relative estimated error between the measured value and the real one is lower than 6%. The absolute (ΔR) and relative errors (R%) were calculated according to the following equations:

$$\Delta R = R_t - R_M \text{ and } R_{\%} = \frac{\Delta R}{R_M},$$

where R_t is the theoretical resistance and R_M is the measured resistance. Error results to be approximately linear with the measured impedance (fig. 6).

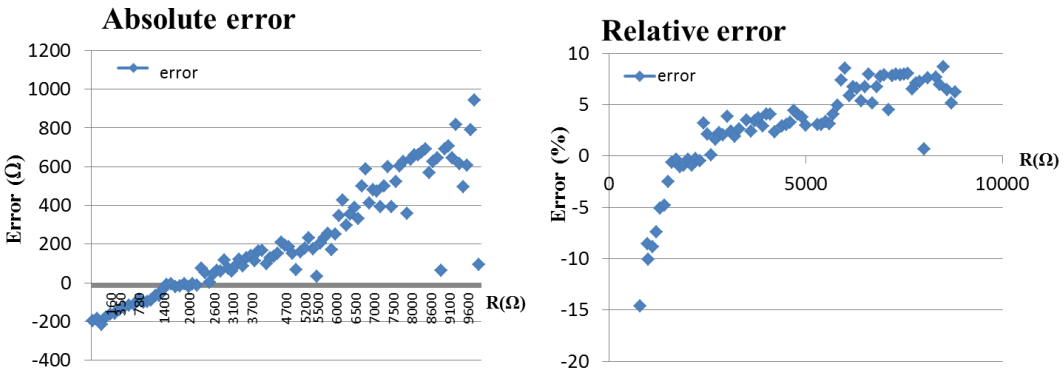

Figure 6 *Absolute and Relative errors*

Thus, the absolute error can be evaluated from the measured impedance values. To this purpose, a software correction has been introduced in order to increase the accuracy of the measurements.

Using Matlab (R2012a, Mathworks) curve fitting tools, the error has been linearly fitted to compensate the measurements (fig. 7). The corresponding correction factor has been implemented in the firmware. The post-acquisition correction is implemented on five small subsets of impedances from 10Ω to 10kΩ.

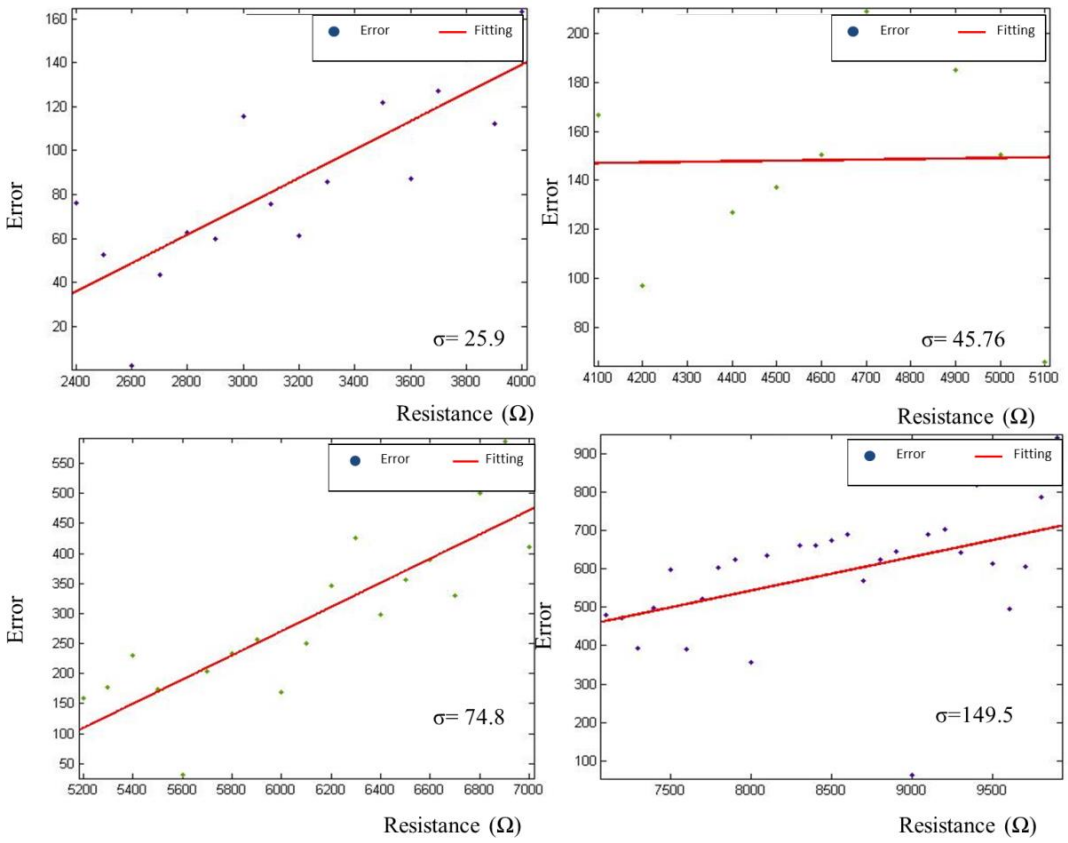

Figure 7 *Error fitting on the intervals (2.4.kΩ – 4kΩ 4kΩ -5kΩ; 5kΩ -7kΩ; 7kΩ-10kΩ)*

Consequently, the error results acceptable (< 6%) over an extended range of impedances without the need for extra circuitry devoted to the measurements outside the optimal range (1 kΩ - 10 kΩ) around Z_{calib}. A second set of measures were conducted using a circuit comprising a variable capacitance (0.1nF, 10nF, 100nF) and a 2.2 kΩ resistance, connected in series and in parallel. Real and imaginary parts have been correctly measured (error <6%) using the same correction factor previously defined.

5.4.2. In vitro and in vivo tests

After calibration, the impedance sensor has been tested *in vitro* measuring the impedance of a wadding stripe soaked with NaCl solution at different concentrations (20 - 350 mg of NaCl in 100 ml of water).

Two electrodes of a naso-gastric probe (Sandhill, mod. ZANBG-44), used in medical practice for esophageal impedance/pH monitoring, have been connected to the sensor

and inserted in the cotton support. Figure 8 shows the sensor response during in vitro test.

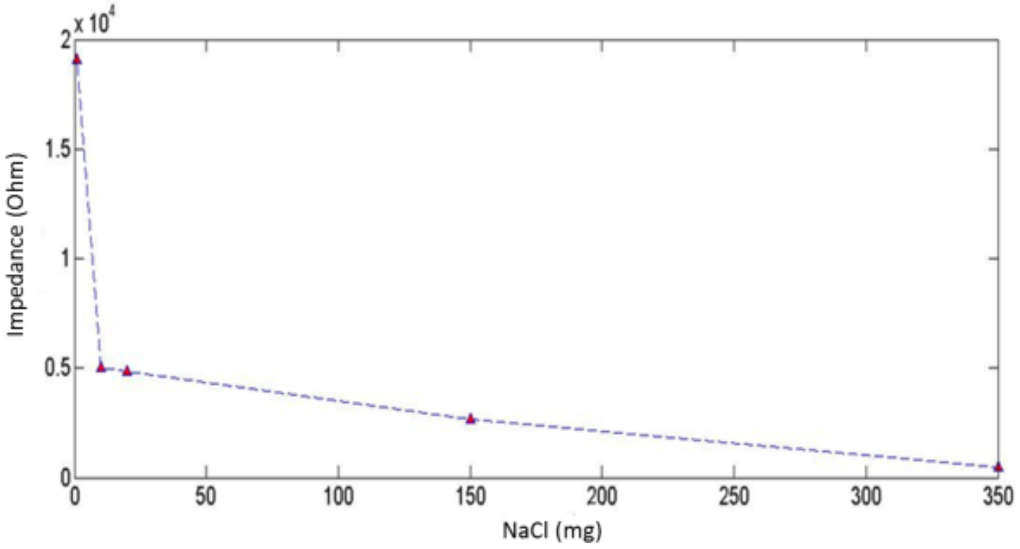

Figure 8 *Sensor response to different NaCl concentrations*

The signal is proportional to the tissue impedance for concentrations between 0.2% P/V and 0.02% P/V. Out of that range, the signal reaches its saturation value.

The sensor has been also tested *in vivo* on a GERD patient. The diagnosis on the patient had been previously made with traditional ambulatory instrumentation.

At the end of the medical exam, the probe was connected to the developed electronics and, as for in vitro test, a couple of electrodes used to read the impedance. Compliance with the standard IEC60601-1 (0.1mA in normal conditions, 0.5mA in single fault condition) was verified before in vivo testing.

The electrodes impedance is normally negligible but the interruption of contact between the electrodes and the tissue causes sharp increases in the value of impedance.

During the test, impedance values between 600-700 Ω were measured, as shown in Figure 9 (mean value: 645Ω; standard deviation: 31.8 Ω, 4.9% of the mean value, data acquisition every 500 ms).

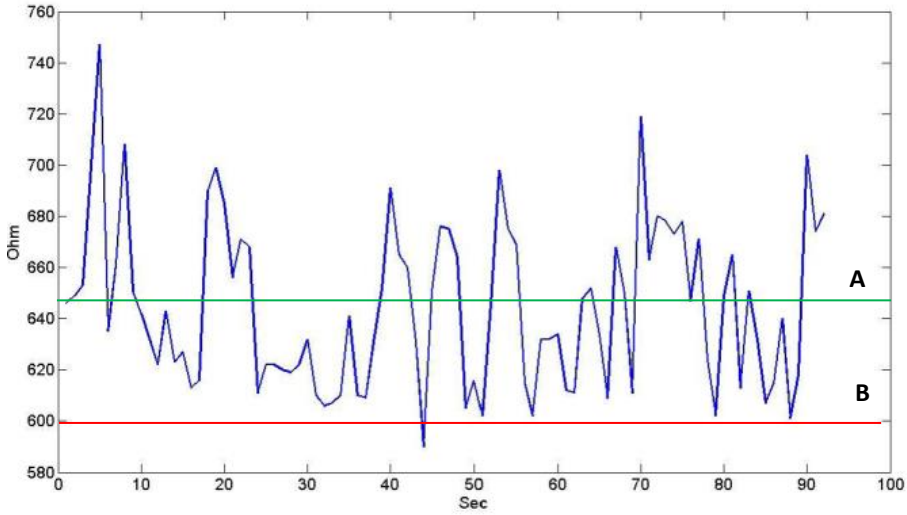

Figure 9*Oesophageal impedance profile on a period of 93 s.*

A: 645Ω, impedance mean value measured with the proposed system.

B: 600 Ω, impedance mean value measured with ambulatory instrumentation (Sleuth, Sandhill).

Measured impedance was in agreement with literature data related to GERD patients [19]. Moreover, the developed sensor provided measurements in good agreement with those made with the ambulatory instrumentation.

5.5 Discussion

The tests perfomed demonstrated that the developed sensor is a good candidate for electrical measurements on the human in-body tissues.

The possibility of measuring a wider range (1kΩ-10kΩ) of impedance values than that characteristic of the esophagus makes the sensor a good candidate for impedance measurement along the whole gastrointestinal tract.

In medical literature a complete database of values of the intestinal mucosa impedance baseline is not available neither all the gastrointestinal pathologies are correlated to electrical impedance alterations. But, as the state of the art shows how impedance alterations can be used to discriminate normal tissue from cancerous tissue during biopsy, we claim that alterations of the impedance value can be a diagnostic mean also for other pathologies.

Some studies show that the impedance spectroscopy can be successfully used to measure tissue injury. Experiments on anaesthetized rabbits are reported [21] and data obtained by impedance spectroscopy using an intestinal catheter, with results of tonometric pH.

Another study by Imam [22] shows that, as MII is used to study esophageal physiology and pathology, small bowel motor functions can be studied with the same means. The study shows that impedance measurement can be used to study intestinal flow in combination with videofluoroscopy and manometry.

This work of thesis aims to translate on intestine the impedance sensor tested on the GERD patient and to exploit the impedance sensor developed to trigger the activation of the drug delivery system.

The use of sensors on smart pills for the activation of the drug delivery system is testified by existing capsules as for example IntelliCap by Philips that exploits a pH sensor. Regardless, impedance measurement has been preferred because it is estimated to be less susceptible to external factors such as food or drink that pH measurement.

The developed capsule at a first stage can allow to record data from healthy gastrointestinal tissue and pathological one along the entire gastrointestinal tract in order to enrich medical knowledge, then the pathological values can be exploited to trigger the activation of the device.

Activation of the drug delivery system is programmed in the microcontroller, according to the following scheme (Fig. 10):

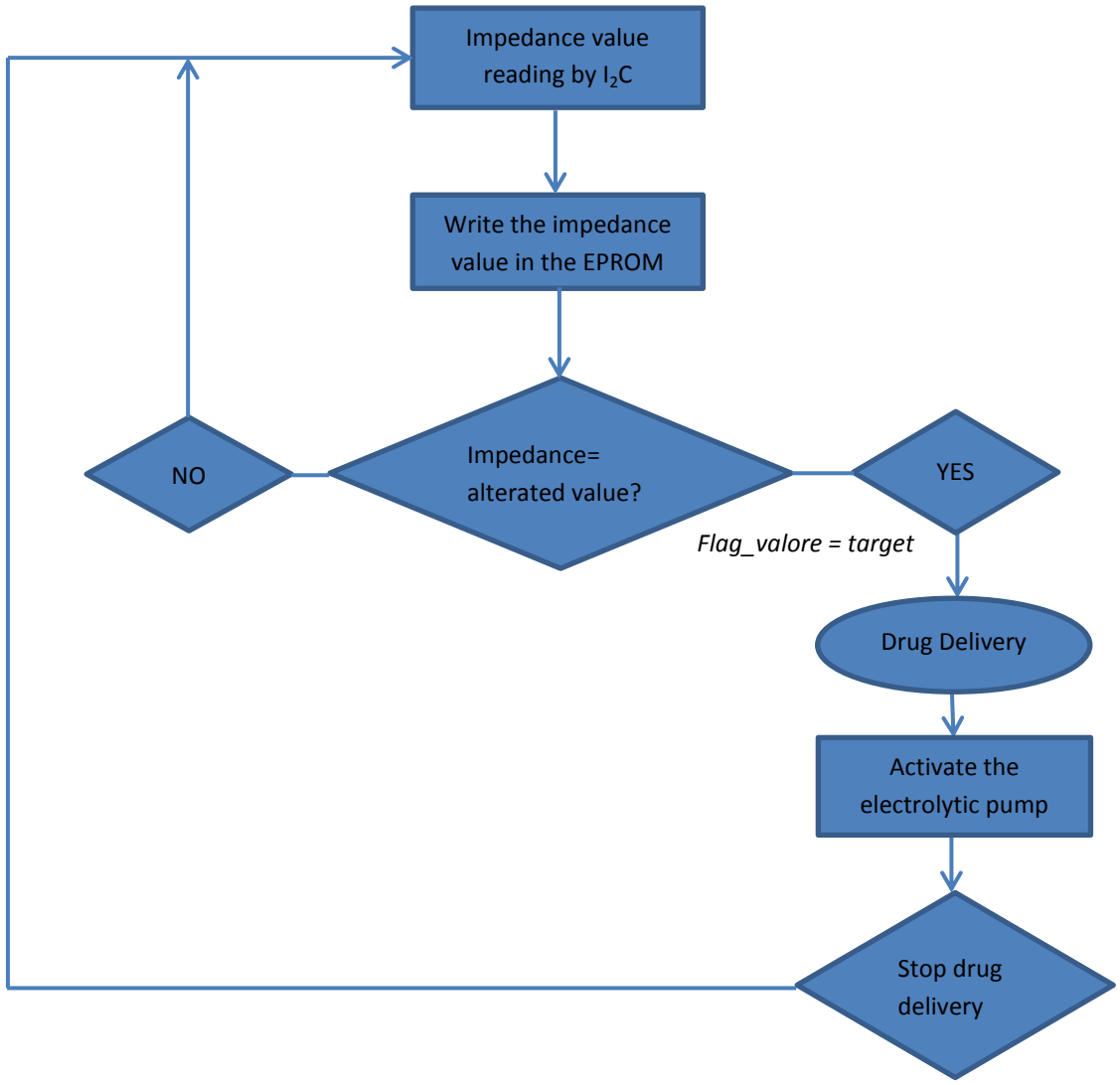

Figure 10 *Block Diagram of the electronics control*

To this aim, miniaturized electronics has been designed by scaling the dimensions of the tested one. Electrodes are mounted on the capsule surface. Microelectronics on board includes a microcontroller (PIC12f1822, Microchip), the impedance sensor (AD5933, Analog devices), an EPROM memory (24AA64, Microchip) where data read by the impedance sensor during navigation are stored, the battery (LIR1025, GMB Power), activated by a magnetic reed (MEDER MK24B2OE, Shukat Electronic). The magnetic reed is normally closed, once the capsule is removed from the magnet the reed switch opens and activates the battery, applying power to the circuitry, and the impedance sensor is activated. The PCB designed is 10 mm x 10 mm.

Figure 11 shows the large size prototype (top), the schematic of the related electronic board (bottom left) used for testing and the design of the miniaturized PCB (bottom right).

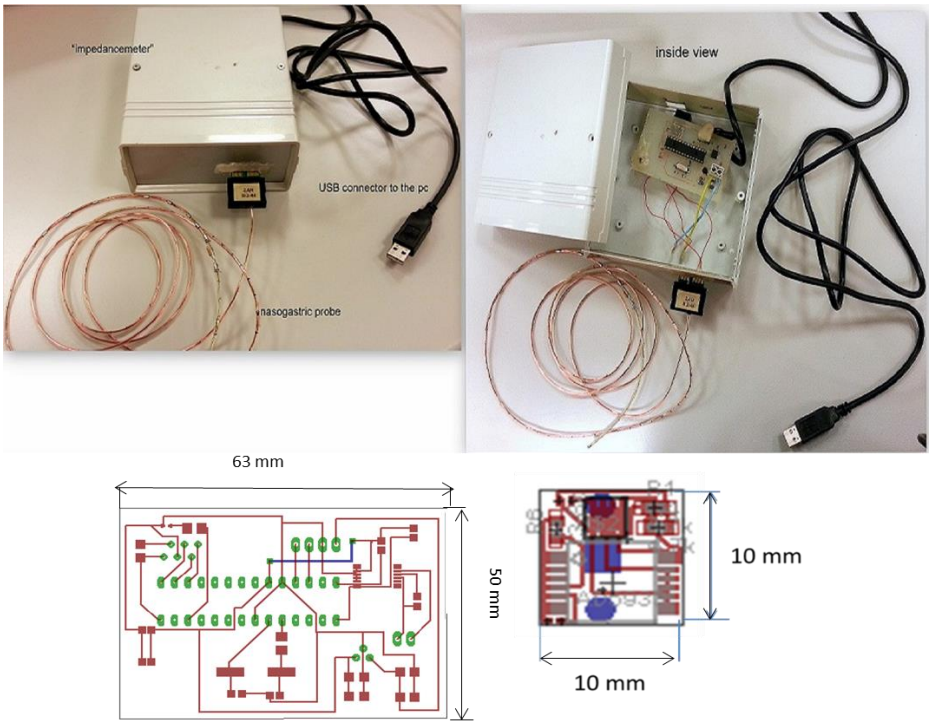

Figure 11 *The impedancemeter tested (top); Electronics design (bottom left), miniaturized electronics (bottom right).*

5.6 Power management

One of the main challenges for swallowable capsules is to design an internal power source than can fulfill the power requirements [27] despite the variable duration of procedures. To date, to overcome this issue, most robotic capsules use external power sources, which do not limits the duration of the procedure. As a drawback, external powering requires extra instrumentation (e.g. magnetic fields sources in the case of magnetic induction).

External power sources include mainly wireless power transfer, such as magnetic induction, or energy harvesting from the environment, while batteries are the most used internal power sources.

Wireless transfer of energy by induction is limited by the small distances due to the fast decay of magnetic field and its attenuation in the body. Other wireless techniques for transmitting electric power are electric-field induction, radio-frequency, microwave radiation and piezoelectric ultrasound systems [25]. Another solution are super capacitors, they are characterized by high power density but low energy density.

A new and emerging family of power generators based on energy harvesting includes nanobiogenerators, which exploit blood flow, muscle contraction, body movements, as mechanical energy can be converted into electric energy for powering in-body devices [26]. Energy harvesting systems can use natural body vibration or external ultrasonic sources.

Many commercially available capsules use silver-oxide coin batteries, that provide approximately 8-10 hours autonomy at a voltage of 3V with a capacity of 55 mAh and an average power of 20 mW. Silver-oxide batteries are widely used because they are the only type approved for clinical use, although Li-ion batteries are a potential power source because of their high energy density of approximately 200 Wh/kg [24]. The high power and the small package make also LiPo batteries good candidates for being integrated on-board swallowable capsules. As it regards battery-operated pills, a maximum battery life time of about 10 hours has been achieved with commercial capsules.

In order to define the requirements of a power supply system it is necessary to take into consideration three main parameters: power density, energy density and battery capacity [23].

Consequently, to select an appropriate power supply, power consumption of all the components was calculated. As the pill is meant to be an autonomous device we decided to use batteries integrated on-board.

Energy density, defined as the amount of energy stored in a given system or region of space per unit volume, is $d = \frac{E}{V}$, where E is the energy and V the volume.

E is defined as $E = Q \cdot V$, where Q is the electric charge [C] and V is the voltage.

Plate data for the components are:

Device / ***Current***	**Microcontroller PIC18f1822, Microchip**	**Impedance sensor AD5933, Analog Devices**	**Eeprom memory, 24AA64 Microchip**	**Electrolytic pump**
Standby current	30 µA	0.7 µA	1 µA	-
Operating current	75 µA	10 mA	3 µA	2 mA

Considered that when the electronics is not operating (standby mode) power consumption is kept very low (µA), it is possible to estimate the system power requirements estimating an average time of activation for the sensing system and for the pump.

If we consider an activation time for the sensing system for a maximum of about 3 hours and for the electrolytic pump of about 15 minutes and a volume of the capsule $V_{capsule}$ = 1300 mm^3, energy densities required by each component can be estimated. The energy density developed by a selected LiPo battery is calculated too:

Eeprom memory, 24AA64 Microchip

$$E = 3\,\mu A \cdot 3.3\,V \cdot 3h = 29.7\,\mu Wh$$

$$d = \frac{29.7 \cdot 10^{-6}}{0.0013} = 22.8\,\frac{mWh}{dm^3}$$

Impedance sensor AD5933, Analog Devices

$$E = 10mA \cdot 3.3\,V \cdot 3h = 99\,mWh$$

$$d = \frac{99 \cdot 10^{-3}}{0.0013} = 76 \frac{Wh}{dm^3}$$

Microcontroller PIC18f1822, Microchip

$$E = 75\,\mu A \cdot 3.3\,V \cdot 3h = 0.74\,mWh$$

$$d = \frac{0.74 \cdot 10^{-3}}{0.0013} = 0.56 \frac{Wh}{dm^3}$$

Electrolytic pump

$$E = 2mA \cdot 3.3V \cdot 15\,min = 1.65\,mWh$$

$$d = \frac{1.65 \cdot 10^{-3}}{0.0013} = 1.26 \frac{Wh}{dm^3}$$

LiPo Battery, LIR1025, GMB Power

$$Vd = \pi \cdot r^2 \cdot h = 3.14 \cdot 25 \cdot 2.5 = 196mm^3 = 0.000196\,dm^3$$

$$E = 5 \cdot 10^{-3}\,Ah * 3.3\,V = 16.5\,mWh$$

$$d = 84.18 \frac{Wh}{dm^3}$$

So, it results that the selected LiPo batteries lir1025 can be used on board. The major energy consumer is the impedance sensor. Regardless, it must be considered that, as the capsule is passive, time of activation has been over estimated in order to consider cases in which the transit is slower because of specific patient's conditions.

Power consumption depends mainly on:

- Sensors
- Clock
- Sleeping mode
- Acquisition frequency (reducing don't save energy but reduces rate at which it is consumed)

- Pull-up resistances (I^2C)

So, it has been important to implement strategies to optimize power consumption in the firmware. In particular, as all the electronic components can be programmed in standby and activation mode, the alternation of periods of activation and standby is defined in the firmware. An alternative to coin batteries can be flexible thin batteries, with the same characteristics, that can adapt to the capsule surface saving space on-board.

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Chapter 6

Drug delivery system

6.1 Drug delivery system: main features

The term drug delivery system (DDS) refers to a device used to deliver drug. The device is an interface between the patient and the drug that enables therapeutic actions in the body introducing a control on the rate, time, and place of release of the drugs and improving medication efficacy and safety (low toxicity). An efficient system could be capable of monitoring patients physiological conditions and deliver the necessary quantity of drug to treat the specific pathological condition at any given time [1].

The progression in microfabrication technologies has enabled the introduction of drug delivery systems overcoming conventional solutions [2]. Improvements in MicroElectroMechanical Systems (MEMS) have made devices miniaturization possible and have opened the path to the development of microfluidic systems, producing devices in the micrometer scale that can sense, pump, mix and monitor fluids at volume as low as microliters. Firstly, diagnostic tools have been provided, now MEMS technology is focusing on the development of microdevices for therapeutic applications.

For example, one of the main challenges for pharmacy and medicine is the delivery of drug locally at the right time and in a safe and reproducible way. Most of the time, drugs are administered through oral route or injection but dosage and rate of delivery on target area are not exactly controllable. In fact, usually, the initial concentration of drug peaks to values above the toxicity level and diminish over time to an ineffective level. Most of the time, therapies require high dosages of non-targeted drugs to achieve an effective blood concentration. MEMS, with implantable or ingestible devices allow targeted therapy and so many advantages in terms of doses, toxicity and costs.

A microfabricated device for therapeutic applications should be able to:

- monitor the physiological conditions inside the patient body and convert them to electronic signals by means of physical and chemical transducers;
- receive the electronic signals, analyze them and make proper control regulations by means of a microcontroller;
- release the appropriate amount of drugs by means of microactuators.

So a smart solution comes from the merge of micropumps, microvalves, physical and chemical microsensors and control electronics. In this way, it is possible to obtain functional integration, as for example the integration of diagnostic and delivery methods on a single device. That means that an appropriate drug volume must be incorporated into the device for controlled long term release of drug to a specific pathological areas in response to monitored physiological parameters.

The smart pill developed is an example of how that can be achieved.

Characteristics of an ideal drug delivery system can be summarized as follows:

1. It should increase the bioavailability of the drug.
2. It should provide for controlled and triggerable drug delivery.
3. It should transport the drug intact to the site of action while avoiding the normal tissues.
4. The product should be stable and delivery should be maintained under various physiological variables.
5. The same method should be applicable to a wide range of drugs.
6. It should be easy to administer to the patients (size and shape of the device must be controlled) .
7. It should be made of biocompatible materials (e.g. Polycarbonate, PDMS, gold, surgical stainless steel) and so safe and reliable.
8. It should be cost-effective.

Main design requirements are reported in figure 1 and further explored in the next paragraphs.

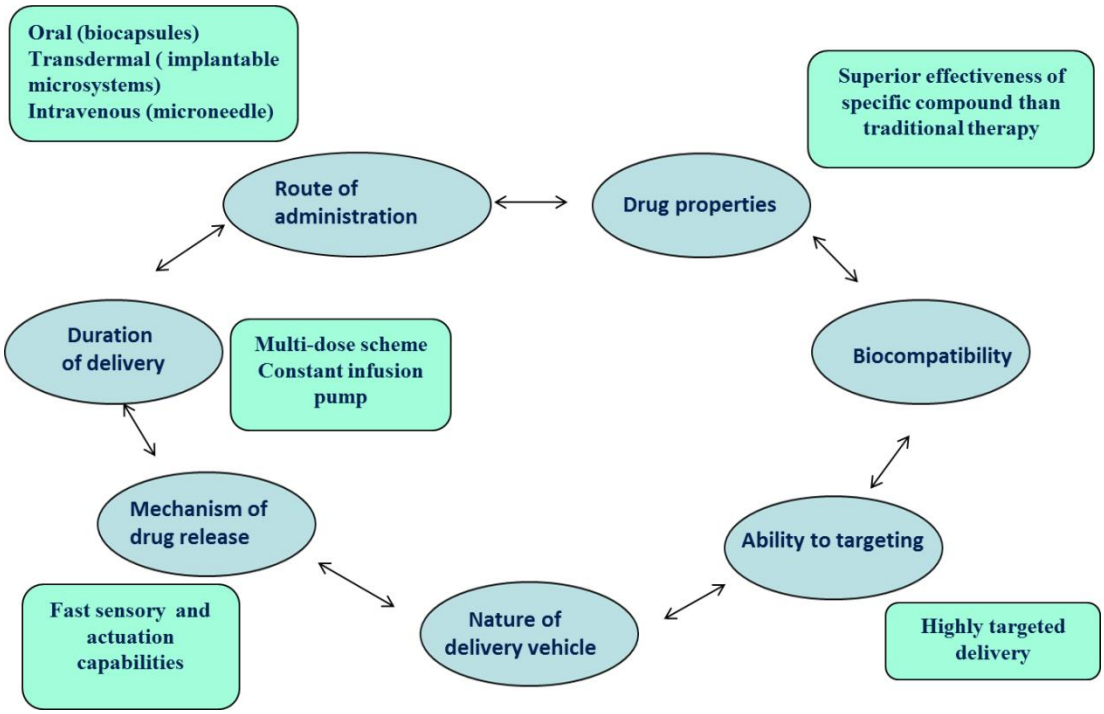

Figure 1 *Design requirements of a drug delivery system*

Challenges that still need a solution in DDS production are as follows:

1. Drug delivery technologies require constant redesigning to keep up with new methods of drug design and manufacture.
2. As the costs of drugs are rising, drug delivery aims to reduce the costs by improving the bioavailability of drugs so that smaller doses are necessary.
3. New materials that are being discovered, such as nanoparticles, need to have safety studies and regulatory approval.

6.2 Controllability

The control of a drug delivery system can be active o passive.

Active control is where an external stimulus, such as an electrical signal, radio frequency or magnetic wave alters the behavior of the drug delivery device and causes it to disperse the drug.

In passive control the device is preprogrammed to release a certain drug dosage profile. Diffusion of biological substances can be used as environmental biological stimulus to control the device.

A responsive drug delivery system would allow the drug dosage to be specifically tuned according to the type and state of disease within the individual, providing personalized drug delivery, that means to maximize the therapeutic effects of the drugs and to reduce the overdose induced side-effects.

To this respect, methods of release are also distinguished in sustained release and controlled release.

Sustained release is referred to as "long acting" or "delayed release" when compared to conventional release preparations. The term sometimes overlaps with "controlled release," which implies more sophisticated control. Sustained release is developed in order to extend the duration of action of the drug and reduce the frequency of dosing, in order to reduce side-effects.

In **controlled release** delivery of a drug is usually regulated by a device.

The control is aimed at delivering the drug at a specific rate for a definite period of time independent of the local environments. The periods of delivery are usually much longer and variable than in case of sustained release. Controlled release may also incorporate methods to promote localization of drug at an active site. Site-specific and targeted delivery systems are classified as controlled release methods.

The drug delivery system developed on the smart pill provides controlled release.

6.3 Biocompatibility and properties of materials for Drug Delivery

When developing devices for drug it is very important to consider materials used and their interaction with the operating environment that is the human body.

In particular, the biocompatibility is a major requirement for BioMEMS.

Materials used have to be selected in order to resist particular conditions of the environment in which they operate, as for example the acidic environment of the stomach. Examples of polymers used are PDMS, PMMA and polycarbonate, also inert metals as gold, platinum or surgical stainless steel are used.

6.4 Drug Delivery Routes

Drug delivery may exploit such a wide range of methods according to the region of interest and its accessibility [3].

Drugs may be intended for systemic effects or targeted to various organs and diseases.

Various methods of drug delivery can be classified by anatomical routes, as the oral one mainly direct to the gastrointestinal system, the transdermal, the transmucosal or the parenteral one, including subcutaneous injection, intramuscular injection, intravenous injection, intra-arterial injection.

As new technologies for DDS are concerned, devices for drug delivery have been developed and can be divided into implantable or ingestible.

Implantable devices are classified according to the area of interest and the type of control. The use of devices enables localized therapy with all the advantages linked to local administration in respect to the systemic administration. To this purpose mainly implantable devices are used but the oral route can be exploited as well for ingestible devices.

Table 1 summarizes principal types of drug delivery devices.

Surgically implanted devices for prolonged sustained drug release
Drug reservoirs
Surgically implanted devices for controlled/intermittent drug delivery
Pumps and conduits
Transdermal/transmucosal implants for controlled release of drugs (nonbiodegradable)
Implantable biosensor-drug delivery system
Microfluidics device for drug delivery
Controlled-release microchip
Swallowable smart pills

Table 1 *Classification of drug delivery devices*

Subcutaneous implantations have been widely used to administer controlled drug release from biocompatible polymeric materials in response to specific stimuli such as electric and magnetic fields, ultrasound, light and enzymes.

Various amounts of chemical substances in solid, liquid, or gel form can be released either in a pulsatile or in a continuous manner or a combination of both.

Transdermal delivery is very diffused as it provides the possibility of achieving localized treatment delivering drugs through the skin. It includes the following categories of drug administration:

1. Local application formulations, e.g., transdermal gels
2. Penetration enhancers
3. Drug carriers, e.g., liposomes and nanoparticles
4. Transdermal patches
5. Transdermal electrotransport
6. Use of physical modalities to facilitate transdermal drug transport
7. Minimally invasive methods of transdermal drug delivery, e.g., needle-free injections.

Transmucosal delivery is also diffused because mucous membrane covers all the internal passages and orifices of the body, and drugs can be introduced at various anatomical sites.

Penetration of drug is by diffusion. Delivery of biopharmaceuticals across mucosal surfaces may offer several advantages over injection techniques, which include the avoidance of an injection, the increase of therapeutic efficiency, the rapid absorption when compared with oral administration, an higher patient acceptance and a lower cost when compared with injectables.

Mucoadhesive controlled-release devices can improve the effectiveness of transmucosal delivery of a drug by maintaining the drug concentration between the effective and toxic levels, inhibiting the dilution of the drug in the body fluids, and allowing targeting and localization of a drug at a specific site.

6.4.1 Oral Drug Delivery

Historically, the oral route of drug administration has been the one most used for conventional as well as novel ingestible drug delivery.

In fact, despite all the new implantable solutions developed, oral route of administration is still the preferred one because of the ease of administration, widespread acceptance by patients, convenience and costs. Major limitations of oral route of drug administration appear in systemic administration because drugs have variable absorption rates and variable serum concentrations which may be

unpredictable. But novel devices overcome these limits with sustained release and controlled-release systems. Novel drug delivery devices, such as smart pills, for oral administration have merged as a combination of functions (drug and devices) [4], and they may be used in a wide range of applications and enable therapies not possible with conventional means. As in the case of the treatment of locally active diseases along the gastrointestinal (GI) tract, such as inflammatory bowel diseases (IBD), intestinal cancer and irritable bowel syndrome to whom the UCBM capsule is addressed.

6.5 Drug reservoir size and loading volume

Relevant features for DDS are also the size of the device and the drug payload that the device can carry [5]. The volume can usually range from microliters to a few milliliters.

Size of the device is important in case of implantation because it must be as small as possible to allow easy implantation with minor surgical inteventions and local anesthesia. In the case of ingestible devices, limits are given by the dimensions of the esophagus (2 mm of diameter).

Minimizing overall size can produce low drug payload volume, so some solutions have been implemented such as employ an external reservoir, use transdermal delivery, use a refillable reservoir.

Regardless, it is very useful in the mechatronic design to consider all the elements on-board and their sizes (e.g. power source (internal microbatteries, Li-Ion batteries, film batteries), actuating mechanisms) to allow more space for increasing the loading volume of the device.

6.6 Micropumps and dosing systems

Micropumps in medicine have been applied in a wide range of cases, allowing for significant enhancements in healthcare especially in long term treatments as for example insulin administration or chronic inflammatory diseases.

By their nature, pumps for biomedical applications have to comply with stringent requirements in terms of reliability and flow-rate control [10], especially when implanted or used in long time treatment.

The delivery method is the core technology of a BioMEMS drug delivery device, as it provides the driving force to dispense the drug.

Many methods exist, most popular are actuators that pressurize the drug reservoir and release the drug formulation from a delivery port. But also actuation–less solutions are used.

Actuation-less methods utilize passive methods such as diffusion to perform drug delivery. These methods rely on a controlled microvalve that opens and closes the drug reservoir and are controlled by external stimuli [6].

On the other side, actuation methods can be distinguished in single chamber and multi-chamber actuation methods.

In a single chamber actuation method, the actuation system is housed within the same chamber as the drug reservoir. In a multi-chamber actuation system the actuation system is separated from the drug, isolating the two components and preventing cross contamination.

Microfluidics, including microchannels, microvalves and micropumps, are disegned as active elements for dispensing therapeutic agents.

Advantages of drug delivery through micropumps are as follows:

1. The rate of drug diffusion can be controlled.
2. Relatively large amounts of drugs can be delivered.
3. The drug administration can be changed or stopped when required.

Miniaturization should ideally reduce costs and facilitate the integration of micropumps on platforms and eliminate the need for additional specialized or bulky equipments [7].

Micropumps, as pumps in general, can be divided into two major categories [8]:

- Mechanical: this type of pumps need a physical actuator or mechanism to perform pumping functions.
- Non-mechanical: these micropumps have to transform certain non-mechanical energy into kinetic momentum so that the fluid in microchannels can be driven.

Many pumps are micromachined using tools and techniques originally developed for integrated circuit industry or resembling such tools and techniques, as for example photolithography and etching. They are integrated on microdevices and have length scales of order 100 μm or smaller [9].

Figure 2 shows a schematic classification of micropumps.

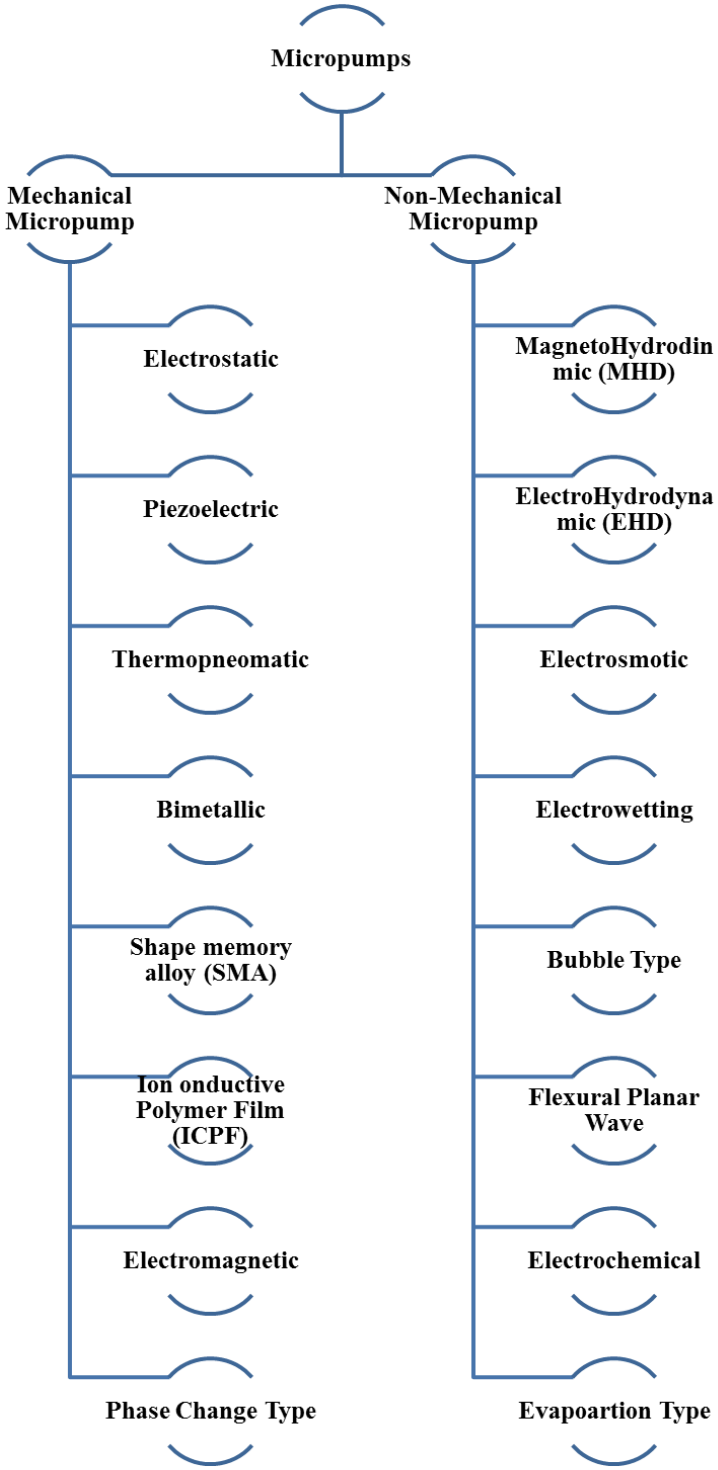

Figure 2 *Classification of micropumps*

6.6.1 Mechanical Micropumps

Mechanical micropumps can exploit different actuation principles, in the following, the most common are explored. Principal features of micropumps are disclosed.

6.6.1.2 Piezoelectric micropumps

Piezoelectric micropumps consist of a piezoelectric disk attached to a membrane, a pumping chamber and valves.

The piezoelectric micropump is actuated by the deformation of the piezoelectric disk. Piezoelectric actuation involves the strain induced by an applied electric field on the piezoelectric materials. Typical characteristics of piezoelectric actuators include large actuation force, fast response time and simple structure. However fabrication is complex as piezoelectric crystals are not easily processed.

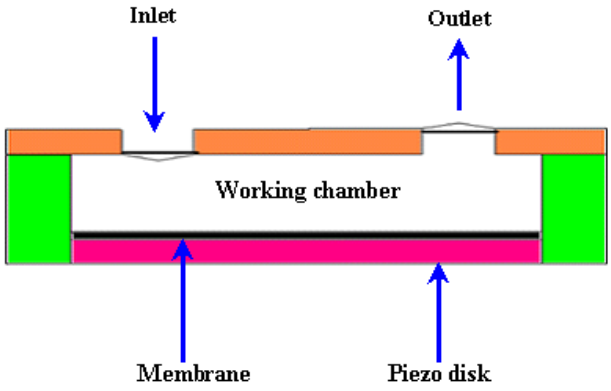

Figure 3 *Piezoelectric micropump[11]*

6.6.1.2 Electrostatic micropump

The actuation mechanism of these micropumps is based on electrostatic forces. The membrane of the electrostatic pump is moved by the appropriate controlled voltage that is applied to the two opposite electrostatic plats. The membrane deformation will be recovered if the applied voltage is shut off. The chamber volume inside the micropump is changed by the switching of the applied voltage. The chamber volume is thus changed alternatively by every half cycle of periodical switching of applied voltage. The fluid in the reservoir is forced to flow in the microchannel due to the pressure difference induced by the membrane momentum.

Electrostatic actuators have a small stroke (10 µm), they have low power consumption and fast time response.

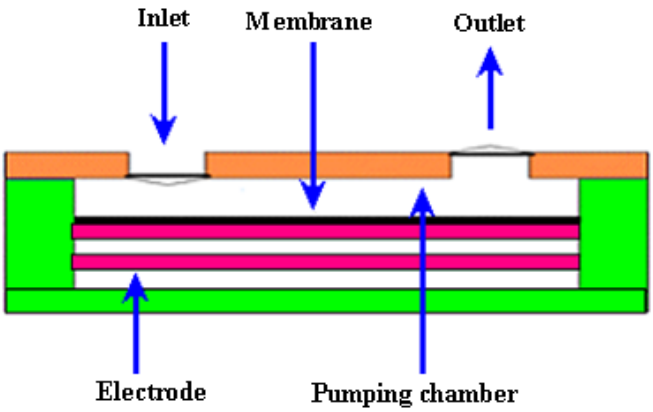

Figure 4 *Electrostatic micropump[11]*

6.6.1.3 Thermopneumatic micropump

In thermopneumatic micropump air is expanded and compressed periodically by a pair of heater and cooler in a chamber. The change in volume of chamber actuates the membrane with a regular movement that allows the fluid flow.

Thermopneumatic actuation involves thermally induced volume change or phase change of fluids sealed in a cavity with at least one compliant wall.

These pumps generate large induced pressure and displacement of membrane but suffer from high-power consumption.

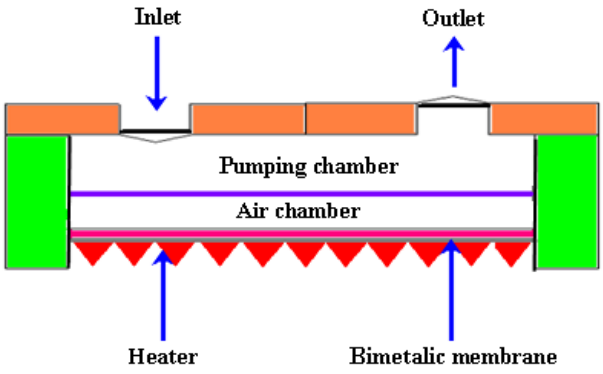

Figure 5 *Thermopneumatic micropump[11]*

6.6.1.4 Electromagnetic micropump

Electromagnetic pumps consist of soft magnetic cores and are activated by currents in energized coils. Alternatively, they can use permanent magnets. The force of Lorentz generated by a magnetic field on a wire carrying a current is large but electromagnetic actuation requires external magnetic field usually in the form of a permanent magnet.

An electromagnetic micropump typically consists of a chamber with inlet and outlet valves, a flexible membrane, a permanent magnet and a set drive coils. Either the magnet or the set of coils may be attached to the membrane. When a current flows through the coils the resulting magnetic field creates an attraction or repulsion between the coils and the permanent magnet which provides the actuation force. This type of actuation can provide large force over long distance as compared to electrostatic actuation and requires low operating voltage. Anyway the miniaturization of such devices is limited by a cube scaling factor of the electrostatic force with size. Moreover, they have high power consumption and heat dissipation.

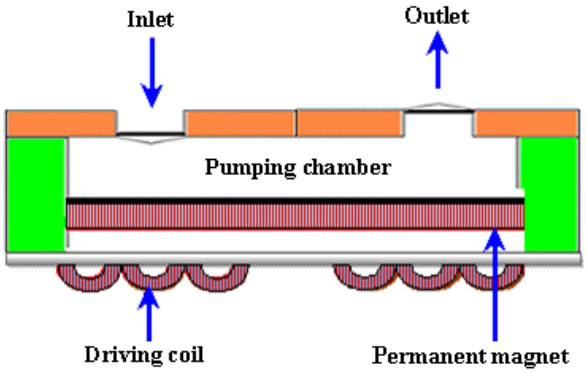

Figure 6 *Electromagnetic micropump[11]*

6.6.1.5 Bimetallic micropump

Bimetallic actuation exploits the difference of thermal expansion coefficients of materials. When dissimilar materials are bonded together and subjected to temperature changes, thermal stress are induced and different thermal expansion in the two materials causes deformation. The implementation is simple and the force generated can be large but the deflections of the membrane depend on the thermal expansion coefficients of materials involved. Bimetallic micropumps require low voltages compared to other solutions but are limited by low frequencies of operation.

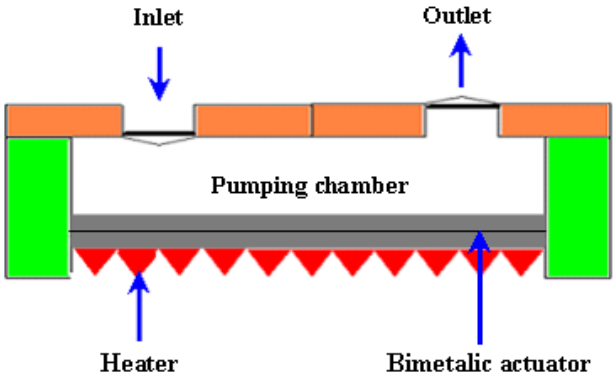

Figure 7 *Bimetallic Micropump[11]*

6.6.1.6 Ion Conductive Polymer Film (ICPF)

Polymer MEMS actuators can be actuated in aqueous environment with large deflections and require less power input than conventional MEMS actuators. Are actuated by stress gradient generated by ionic movement due to electric field. These pumps are composed of poly-electrolyte film with both sides plated with an inert metal. An electric field induces ions movement. The ICPF are called artificial muscles because of their large bending displacement, low actuation voltage and biocompatibility.

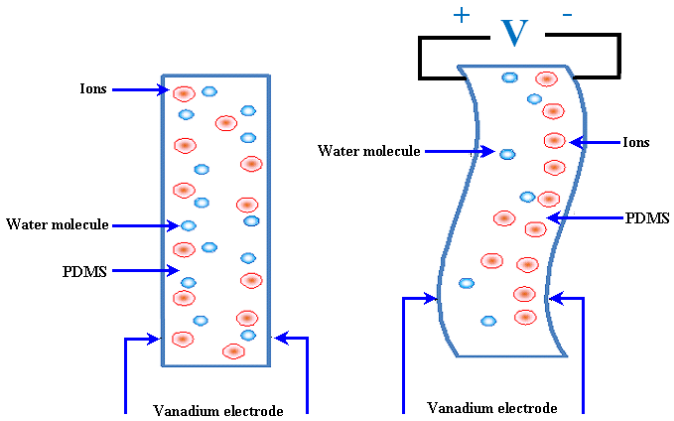

Figure 8 *Ion Conductive Polymer Film (ICPF)[11]*

6.6.1.7 Phase change micropump

This type of micropump exploits vaporization and condensation phenomenon.

Phase change pumps consist of a heater, a diaphragm and a working fluid chamber.

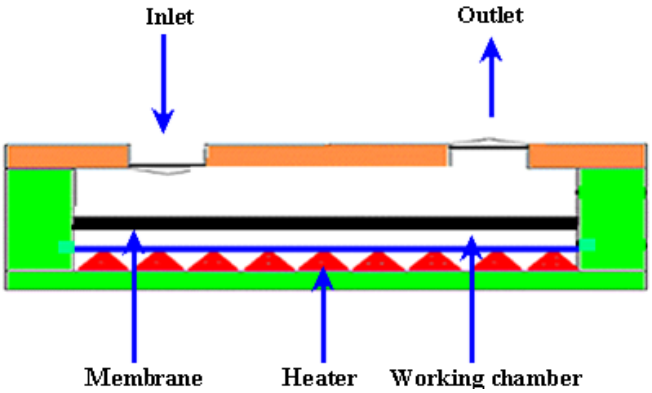

Figure 9 *Phase Change mciropump[11]*

6.6.1.8 Shape memory alloy

These micropumps make use of the shape memory effect of SMA materials such as titanium and nickel. The shape memory effect involves a phase transformation between two solid phases (austenite phase at high temperature and martensite phase at low temperature). In SMA materials, the martensite is much more ductile than austenite and this low temperature state can undergo significant deformations by selective migration of variant boundaries in the multi variant grain structures. When heated to the austenite start temperature, the material starts to form single variant austenite. When the material do not undergo mechanical constrains it will return to the pre-deformed shape.

This phase transition produces mechanical deformation that is used for actuation. High power consumption is required and the response time is slow.

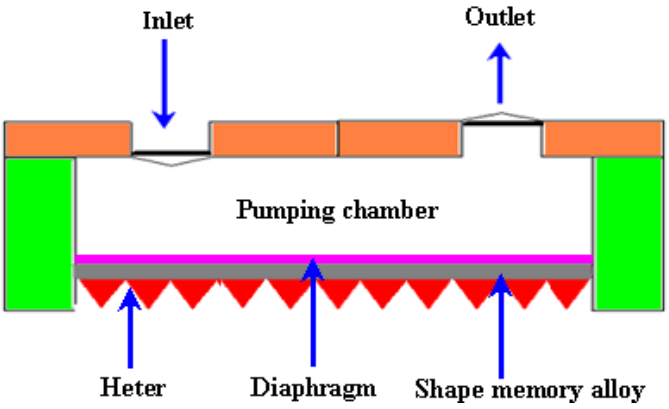

Figure 10 *Shape memory alloy[11]*

6.6.2 Non-Mechanical Pumps

Non-mechanical micropumps convert non-mechanical energy into mechanical energy. In general, they do not need physical actuation components so their design is simpler in respect to mechanical pumps. However their performance are comparable to those of mechanical micropumps.

Non-mechanical can include for instance electrowetting, electroosmotive, these methods depends on the properties of the fluids.

6.6.2.1 Electroosmotic micropump

In this kind of pump an electrical field is induced upon the channel walls, so the fluid, that is electrically conductive, is driven. The voltage potential is induced at the interface between the silica capillary walls and electrolytic solution.

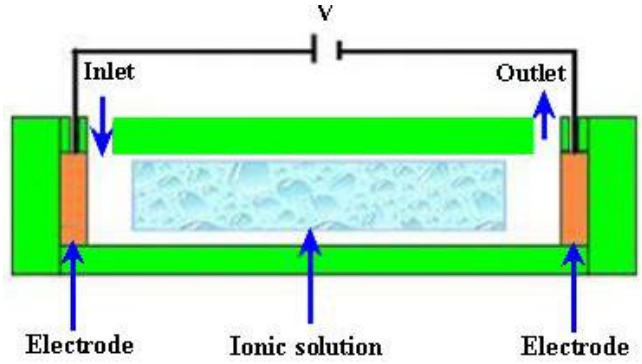

Figure 11 *Electrosmotic micropump[11]*

6.6.2.2 Electrowetting micropumps

In electrowetting micropumps an electrostatic force controls the surface tension between two layers of immiscible or two-phased materials that could be solid/liquid or liquid/liquid. They can operate in continuous or digital mode.

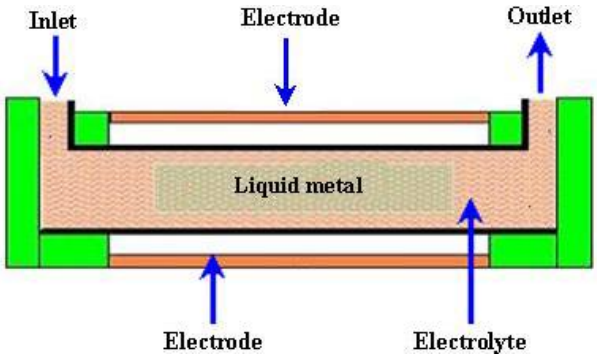

Figure 12*Electrowetting micropump*

6.6.2.3 Electrochemical micropumps

The most common feature of electrochemical micropumps is the generation of bubbles by electrolysis in which the decomposition of the electrolyte occurs into its constituents, such as hydrogen gas (H_2) and oxygen gas (O_2), when the electrolytic solution is water.

The key component is a bubble reservoir filled with a redox electrolytic solution. Applying a voltage at the electrodes, usually made of inert metals, the gas production is activated.

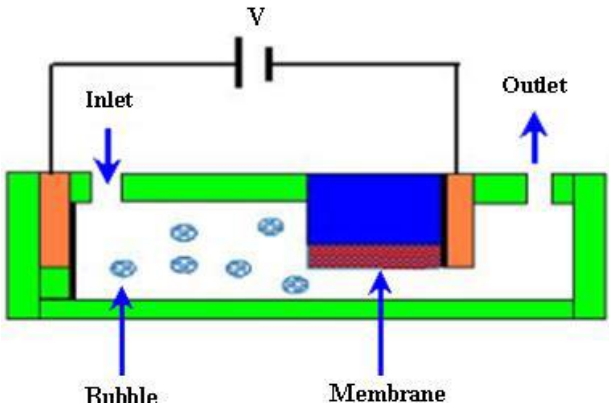

Figure13 *Electrochemical micropump[11]*

6.6.2.4 Evaporation micropump

In evaporation micropumps, the actuation is based on the controlled evaporation of a liquid. The conversion from its liquid form to vapor form (evaporation) and its reverse, condensation are used to actuate a membrane.

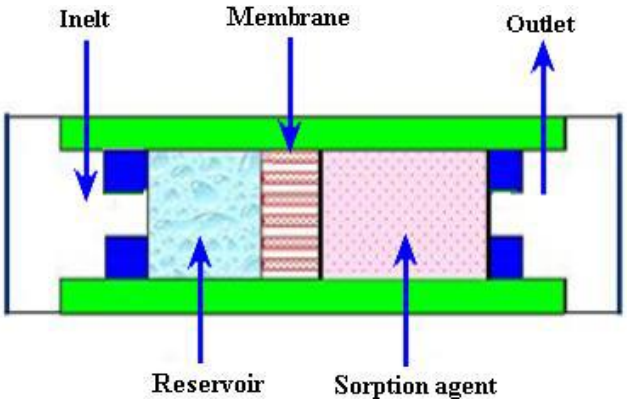

Figure 14 *Evaporation Micropump [11]*

6.6.2.5 Bubble micropump

Bubble micropumps are based on periodic expansion and collapse in the volume controlled by voltage input. The volume change in chamber is incorporated with the diffuser/nozzle mechanism that is used to determine the direction of fluidic flow. The bubbles are generated by heating process.

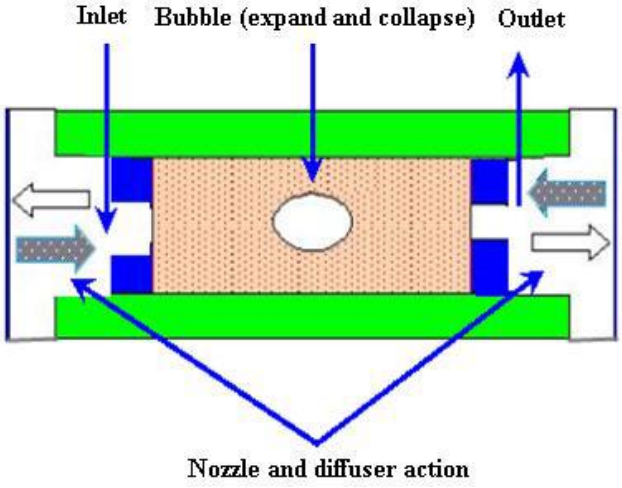

Figure 15*Bubble micropump[11]*

6.6.2.6 Magnetohydrodynamic pump

The functioning principle of magnetohydrodynamic micropumps is based on the dynamics of electrically conducting fluids. The driving force is the Lorentz force.

A schematic of the MHD micropump is shown in figure 16.

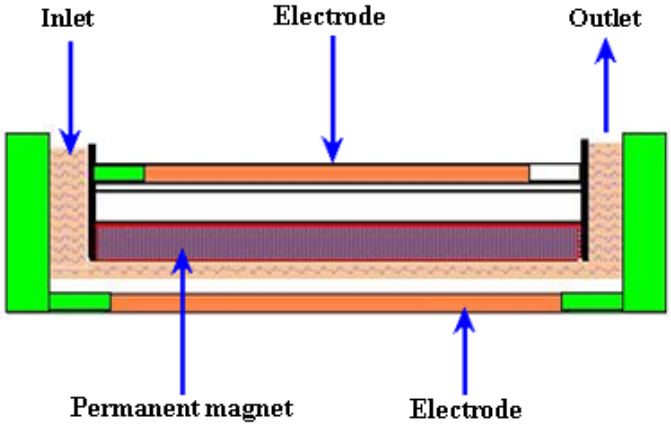

Figure 16 *Magnetohydrodynamic pump[11]*

6.6.2.7 Flexure planar wave micropump

These micropumps are driven ultrasonically. The wave induces fluid's motion in the direction of its propagation. The speed is proportional to the square of acoustic amplitude. These pumps require low operating voltage.

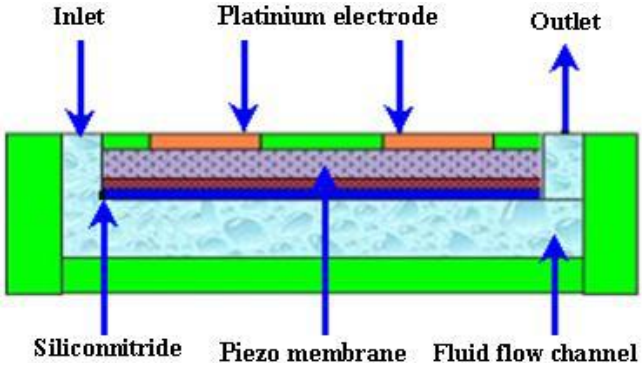

Figure 17 *Flexure planar wave micropump[11]*

6.6.2.8 Electrohydrodynamic micropump

In electrohydrodynamic micropumps the actuation force is generated by the interaction of electric field and ionised particles in the fluid. These pumps have emitter and collector electrodes that are regularly spaced along a microchannel. They require no moving parts such as impellers, bellows or valves. The electrical charges

generated from the electrodes mobilize according to the direction of the electric field that is built up by the electrodes. The surrounding liquid molecules move together dragged by the ion dragging force.

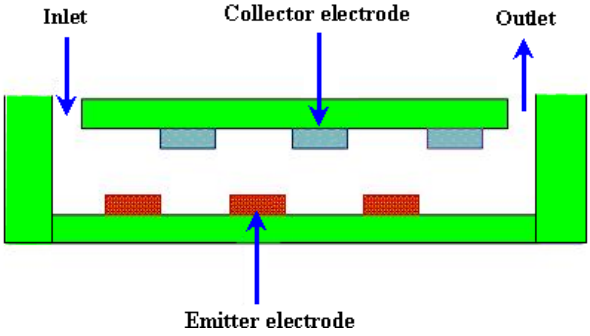

Figure 18 *Electrohydrodynamic pump[11]*

6.7 The smart pill's drug delivery system

6.7.1 The DDS features and motivations

In order to develop a proper drug delivery system to be integrated on the smart pill the solutions described have been explored considering requirements imposed by the gastrointestinal system.

Swallowable drug delivery systems for gastrointestinal applications must be small in size, should operate at low voltages (~ 3V) and with low current intensities (~ 2 mA) [12].

Taking into account such requirements, electrolytic pumps have been identified as the good solution to be integrated on the UCBM smart pill for targeted therapy. Electrolysis-based pumps exploit gas production to deform a membrane and displace a fluid in contact with it [13].

The device developed is a low-cost electrolytic micro-pump, which is custom made to be integrated on the capsule.

Another relevant motivation for the choice of electrolytic pumps is that they can be much more easily integrated on a device in respect, for example, to electromagnetic pumps that require bulky electromagnet and electroosmotic that are sensitive to sample characteristics [14]. Furthermore, they produce larger strain at lower voltage in comparison to piezoelectric pumps [15].

Electrolytic reactions require low voltage, usually compatible with microelectronics powering systems and with small size batteries, which can be mounted on board. In our experiments the electrolytic solution was a saline solution (NaCl 0.5 M). The electrolytic reaction occurring when a voltage is applied to two inert electrodes is:

$$\text{Anode :} \quad 2H_2O \longrightarrow 4H^+ + 4e^- + O_2\,(g)$$

$$\text{Cathode :} \quad 2H_2O + 2e^- \longrightarrow 2OH^- + H_2\,(g)$$

$$\text{Net:} \quad 2H_2O\,(l) \rightleftharpoons O_2(g) + 2H_2\,(g)$$

Overall, 1 mole of electrons is needed to generate $\frac{3}{4}$ moles of gases (H_2 and O_2).

The electrolytic pump was custom made and 3D printed to fit in capsule.

Inserting the electrolytic pump in the frontal lobe of the capsule the displacement of the membrane, due to gases production, can allow the release of the drug (about 50 µl are required for the DDS) contained in that chamber in contact with the abovementioned membrane (fig. 19).

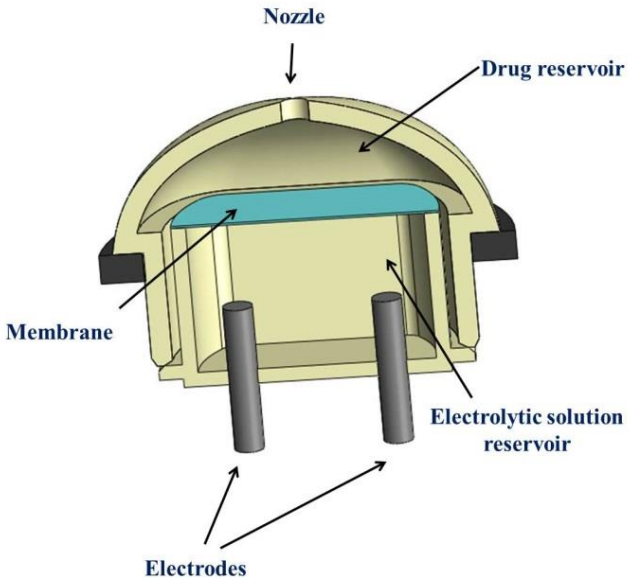

Figure 19 *Cross section view of the drug delivery system*

6.7.2 Materials and fabrication

The electrolytic pump consists of a reservoir for the non-toxic electrolytic solution. The solution used to fill the reservoir is a saline 0.5 M solution.

The reservoir volume is 120 µl. It presents a collar at the bottom edge that avoids backward and forward sliding of the reservoir.

The reservoir also presents the lodging for electrodes that are platinum wires of 1 mm of diameter.

The reservoir, as the rest of the capsule, is made of acrylic resin (EX200 and S100 Visi Jet, HD3000 Projet, 3D Systems).

The reservoir is closed with a PDMS (Sylgard 184, Dow Corning, Midland, MI) membrane. Moreover, the membrane is sensorized with a strain sensor made of a conductive nanocomposite thermoplastic elastomer (CTPE) that allows to measure the overall deformation of the membrane (fig. 20).

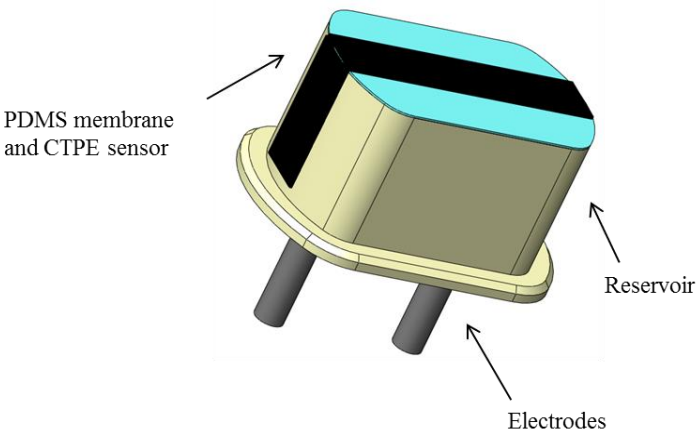

Figure 20 *Electrolytic pump (Reservoir volume 120 µl, PDMS membrane area 40mm^2, CTPE sensor area 10mm^2)*

6.7.3 Electrolytic pump membrane

The membrane of the electrolytic pump constitutes an active element of the pump because it is actuated by gas production in the lower chamber and its displacement is responsible for the delivery of the drug contained in the upper reservoir.

For fabricating the elastic membrane, PDMS is mixed with curing agent at 10:1 mass ratio. The mixture is degassed for 30 minutes, spun at 900 rpm and cured at 60°C in an oven for 30 minutes. The thickness of the membrane is about 60 µm.

Mechanical properties of the PDMS membrane allow to estimate the maximum deformations that can be reached in correspondence of the gas production in the electrolytic reservoir.

The displaced volume can be correlated to the volume of drug delivered.

In fact measuring the current flowing at the electrodes when a polarization voltage is applied it is possible to estimate the gas produced and so correlate data measured on the pump with the drug flow rate.

6.7.3.1 Elastic model for rectangular membrane loaded with a uniform pressure and FEM analysis

The membrane deformations have been modeled in order to evaluate the drug volume Vd that can be delivered by the drug delivery system.

The load deflection model is a known method for measuring the elastic properties of a membrane. Tabata [16] developed an analytical model for rectangular membrane that can approximately fit the membrane of the electrolytic solution reservoir.

Figure 21 schematically shows the membrane by approximately considering a rectangular membrane with sides 2a and 2b (a<b).

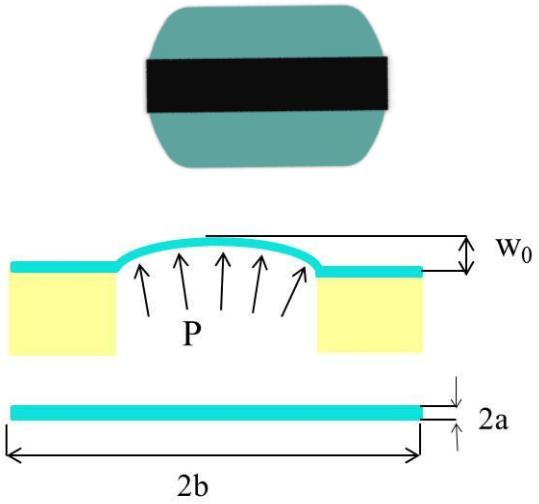

Figure 21 *Deflection of the membrane due to the applied pressure and membrane CAD*

When a pressure P is applied the membrane is deflected of w_0.

In the analytical model, a functional form of the deflected shape is assumed and the total strain energy minimized to find the load-deflection behavior of the membrane [17].

According to the model, the total strain energy of the rectangular membrane is obtained by adding the strain energy of deformation to the elastic strain energy due to internal tensile stress. In the case of large deflections (membrane deflection w_0 >> membrane thickness t) the strain energy due to bending can be neglected. Usually, the Fourier expansion of the true solution with two undetermined constants is chosen for the functional form of the displacement of a point in the membrane. Then the total potential energy of the membrane is obtained from the work input into the membrane. Energy is then minimized with respect to the two constants in the displacement equations, making use of the principle of virtual displacements, resulting in a relationship between the load and the deflection:

$$P = \frac{C_1(n)\sigma w_0 t}{a^2} + \frac{C_2(n,\nu) t E {w_0}^3}{a^4} \quad (1)$$

Where P is the applied pressure, w_0 is the center of deflection, a is the length of the short side, n is the ratio between the long side 2b and the short side 2a (n = a/b), t is the thickness, E is the Young modulus, ν the in plane Poisson Ratio, σ the residual stress; the dimensionless constants $C_1(n), C_2(n,\nu)$ are geometry and model dependent.

The equation can be rewritten as [18]:

$$\frac{Pa^2}{tw_0} = C_1(n)\sigma + C_2(n,\nu) E \left(\frac{w_0}{a}\right)^2 \quad (2)$$

the left-hand side of the equation is the normalized load, and $\left(\frac{w_0}{a}\right)^2$ is the normalized strain. Therefore equation 2 is the stress-strain curve for a membrane with σ, its intercept with the y-axis is proportional to σ and its slope is proportional to E.

At large deflection the cubic term dominate in (1) and Young modulus determines the mechanical behavior.

$C_1(n)$ and $C_2(n,\nu)$ are determined analytically to be [13]:

$$C_1(n) = \frac{\pi^4(1+n^2)}{64}$$

$$C_2(n,\nu) = \frac{\pi^6}{32(1-\nu^2)}\left(\frac{9+2n^2+9n^4}{256} - \frac{4+n+n^2+4n^3-3n\nu(1+n)^2}{2\{81\pi^2(1+n^2)+128n+\nu[128n-9\pi^2(1+n^2)]\}}\right) \quad (3)$$

Considering the membrane geometry 2a= 6mm and 2b = 9mm and assuming ν = 0.5 for PDMS, C_1 and C_2 can be calculated and result C_1= 2.21 and C_2= 1.94. Then, known C_1 and C_2, E for the membrane is estimated to be 1.4 MPa. E has been calculated considering load-deflection results previously obtained on a non-sensorized PDMS membrane (P=30 kPa, w_0= 2.2.mm) [19]. The value of the modulus of Young calculated is confirmed by the data on thin PDMS membrane in literature [20].

Analytical solution was compared with FEM analysis by Pan et al. [21], and confirmed by other authors [22] and they found that the functional form of the analytical results is similar to the FEM solution. Considered that, the membrane load-deflection behavior was modelled using finite element method. This choice allows to consider the membrane and the CTPE sensor together and to calculate the deformation of the membrane-sensor system. Furthermore, deformations can be calculated considering the true membrane shape avoiding the introduction of further approximation in the model that, by its nature, produces an approximate solution. FEM model was generated into Comsol Multiphysics and the load deflection behavior was simulated.

The membrane was clamped at its edge and uniformly loaded by a pressure P. Large deformations solver was adopted.

The parameters used in simulation were as follows. Membrane surface: 50 mm^2; thickness: 60µm; material: PDMS (Young's modulus of 1.4 MPa and Poisson's ratio of 0.49).

The membrane acts as a supporting structure for the CTPE strain sensor.

The CTPE sensor's properties and characterization will be discussed later on. By the way, in order to consider its contribute to the analysis of the membrane deformations we report the parameters adopted for the CTPE sensor in the finite elements analysis. They were: surface area 30 mm^2 thickness 0.2 mm, Poisson's modulus of 0.49 and Young's modulus 2.23 MPa. Such Young's modulus, was evaluated as the mean

value calculated from a set of stress-strain measures made on specimen of the thermoplastic nanocomposite polymer.

Mesh used consists of 23280 elements. The results in Table 1 show the central deflection of the membrane in correspondence of the load applied. Volumetric displacement was calculated by integration.

Pressure (bar)	*Displacement (mm)*	*Volume (µl)*
0.02	0.79	19.98
0.04	1.02	25.60
0.06	1.18	29.60
0.08	1.30	32.70
0.10	1.41	35.40
0.12	1.51	37.70
0.14	1.60	39.70
0.16	1.68	41.60
0.18	1.74	43.33
0.20	1.81	44.90
0.22	1.87	46.36
0.24	1.93	47.70
0.26	1.99	49.00
0.28	2.04	50.27
0.30	2.09	51.34
0.32	2.13	52.33
0.34	2.16	53.13

Table 1 *Simulation results*

The volume displaced increases linearly with the membrane deflection.

Figure 22 shows the volumetric deflection of membrane for increasing values of pressure.

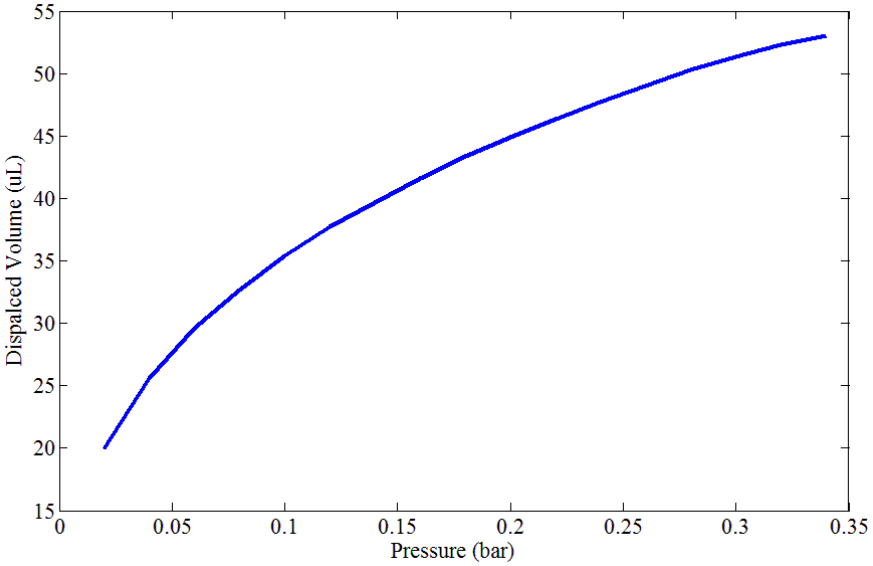

Figure 22 *Displaced volume vs. pressure applied*

The maximum membrane displacement obtained is 2.16 mm corresponding to about 53 µl that is suitable value for drug delivery application (fig. 23).

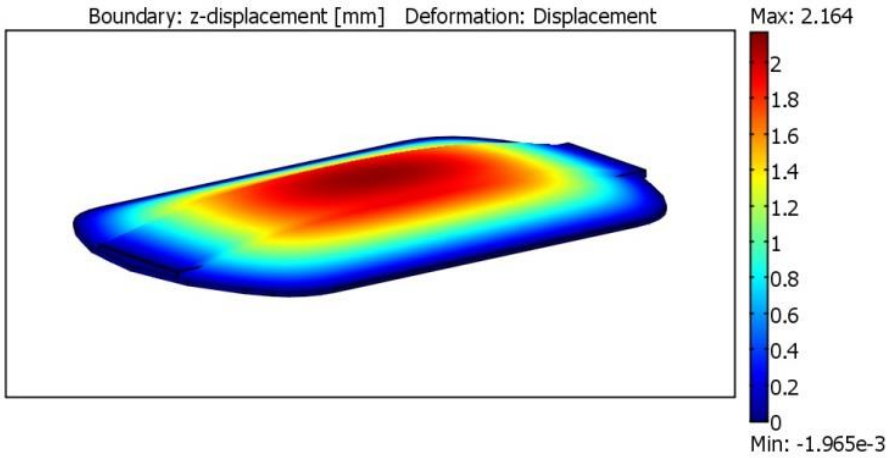

Figure 23 *Results of the simulation of the membrane deformation*

6.7.3.2 *Experimental tests*

Data from simulation are then compared with measurements on the setup in order to verify the performance of the developed system. The volumetric displacement

estimated by integration from the central displacement of the membrane are then correlated to the displacement measured on the setup.

Considering the electrolytic solution (NaCl 0.5 M), by approximating the mixture of O_2 and H_2 to an ideal gas, it is straightforward to calculate the amount of gas that at the pressure P produces the volume displacement Vd. For P = 0.34 bar such quantity is 24 µmol, corresponding to 532 µl of gases in STP conditions.

Then, gas production was measured on the system during the electrolytic reaction in the pump, to compare the performance with the maximum value expected from simulation.

Gas production in the electrolytic reservoir can be estimated using Faraday's law:

$$m = \left(\frac{Q}{F} \cdot \frac{M}{z}\right) \tag{4}$$

Where m is the mass of gases developed at the electrodes, Q is the electrical charge, F is Faraday's constant (96500 C mol^{-1}), $\frac{M}{z}$, is the mass to charge ratio of the electrolyte.

For the considered reaction, 24 µmol of gases are produced by 33 µmol of electrons, corresponding to a total charge Q = 3.2 C.

Since the electrical charge Q is the time integral of current I ($Q = \int_0^\tau I(t)dt$), the amount of gases produced can be evaluated by monitoring the current through the electrodes.

To this purpose, an interface was created in Labview (National Instrument) running on a PC equipped with a DAQ NI USB-6009 ADC/DAC converter card. An analog-to-digital line recorded the current through the pump when a constant 3V voltage was applied to the electrodes. Current flowing through the electrolytic cell is influenced by the concentration of ions and increases over time (Fig.24).

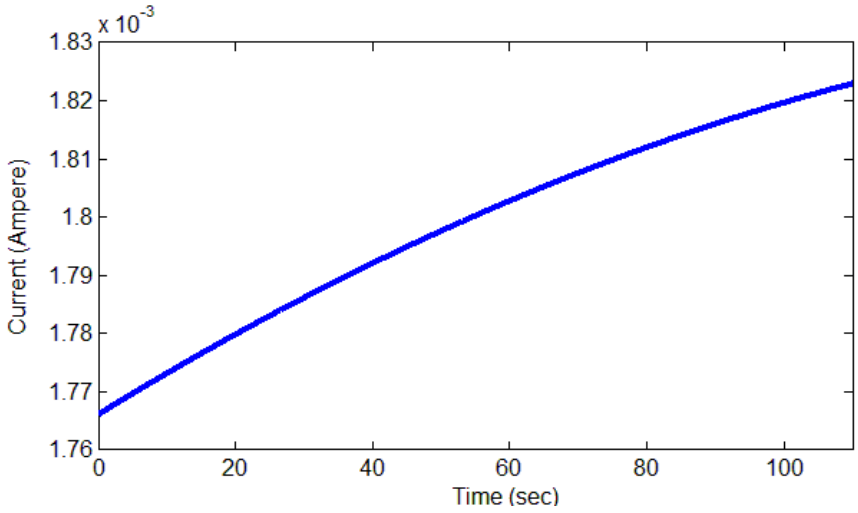

Figure 24 *Current at the electrodes vs. time*

The amount of gas produced, V_{gas}, is proportional to the electrical charge Q according to (4) and can be calculated following logical flow diagram shown in Fig 25.

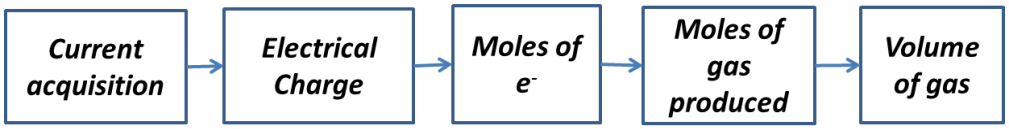

Fig. 25 *Key steps for gas production measurement.*

The number of moles of electrons produced in 120 sec, n_{e^-}, is $n_{e^-} = \frac{Q}{F} = 5.5$ µmol, corresponding to 7.3 µmol of gas (164 µl of gas in STP conditions).

The relation between the current measured at the electrodes and the flow rate of the released drug is shown in eq. (4) as a function of the time *t*:

$$Q(t) = \frac{V_{STP}}{zFt} \int_0^\tau I(t)dt \qquad (4)$$

considering the flow diagram in fig 12, the volume of gas produced is expressed as:

$$V_{gas} = n_{gas} \cdot V_{STP}$$

Then, V_{STP} = 22.414l and the moles of gas $n_{gas} = \frac{\int_0^\tau I(t)dt}{zF}$ are calculated from the Farady's law (eq. 3), taking into account that the electrical charge Q is the time integral of current I. So the flow rate calculate is 1,36 µl/s.

6.7.4 Monitoring of the drug released

Sensorization of the membrane is needed to measure the overall deformations of the membrane as needed to achieve a closed-loop control of drug delivery.

In fact, once known the information about the sensor resistance variations and the current increase due to the electrolytic reaction, the drug delivery can be controlled.

As the volume of gas produced V_{gas} is calculated from the measured current at the electrodes and the variation of resistance is correlated to the volumetric displacement of the membrane, the latter can be adopted in the control system of the drug delivery (fig. 26).

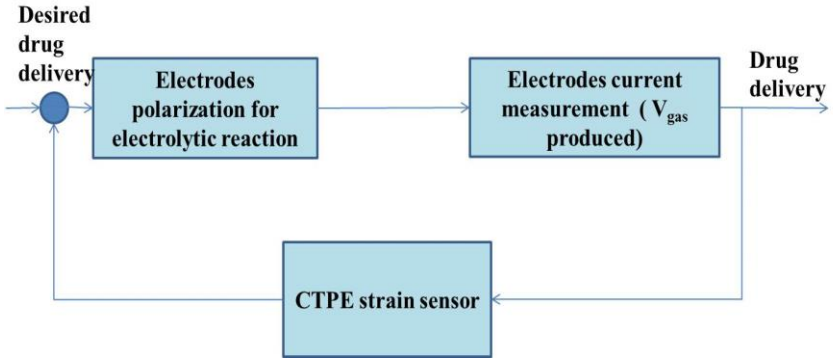

Figure 26 *Drug delivery closed loop control*

Furthermore, the integration of the strain sensor, that monitors the membrane deflection, allows to adopt such system with different kinds of liquid drugs. In fact, the measure is not influenced for example by the fluid viscosity as will happen with a control based on a direct pressure measurement inside the capsule. The closed-loop control implemented is fundament for the correct functioning of the smart pill has it is supposed to be able to reject all possible failures during navigation. Possible malfunctions could be caused by the external pressure exerted by gastric fluids on the capsule and in particular on the nozzle. The monitoring of the membrane deformation could permit to identify any cases of nozzle plugging, for example due to external pressure exerted from the intestinal wall on the capsule.

The measure of the current at the electrodes allows a double check for cases when the gas is produced in the electrolytic pump but no deformation of the membrane is

read because the nozzle is plugged or cases when the membrane is broken and no deflection is monitored by the CTPE sensor but the electrolytic reaction is active.
In order to sensorize the membrane two approaches have been considered and details are given in the next paragraphs.

6.7.5 Membrane sensorization

As shown, the membrane is sensorized with a custom made strain sensor made of a conductive thermoplastic nanocomposite elastomer. It has been chosen as the optimal candidate for constant monitoring of the membrane deformations since it shows a better behavior for low speed deformations, such as those involved in electrolytic reactions (10 ÷ 20 μm/s), in comparison to other viscoelastic materials and nanocomposites (e.g. PDMS).
In fact, the first approach considered has been to load the PDMS membrane with microparticles of graphite but tests on the membrane have shown detrimental properties for this application.
In the next paragraph experiments and results of the microfabrication of the conductive PDMS are illustrated and limits discussed. Then the CTPE solution, introduced to overcome PDMS limitations, is presented.

6.7.5.1 *Conductive PDMS*

The use of conductive PDMS is largely testified in the literature [23].
PDMS has been frequently used because it can be easily prepared and mixed with conductive particles and it is diffused in medical devices development.
PDMS can be made conductive loading the elastomer with conductive particles. Most used conductive particles are graphite powder or flakes, and carbon black.
We decided to use graphite power because of its low-cost and large availability.
The doping of the polymer involves a series of parameters such as dimensions of the graphite particles, percolation, quantity of solvents, time of polymerization of the polymer and cross linking formation. All these parameters have been considered in order to define the optimal fabrication process.

Firstly, two types of power were tested. The first one was lubricant graphite powder by Pressol and the second was the graphite powder < 20µm (282863, by Sigma-Aldrich).

As the first one was difficult to mix with PDMS because of particles size, so micro particles were selected. Microparticles have been also preferred to nanoparticles because they have lower costs.

In order to obtain a conductive polymer, it is very important to identify the percentage of conductive particles in the polymer that is around the percolation threshold (fig. 27).

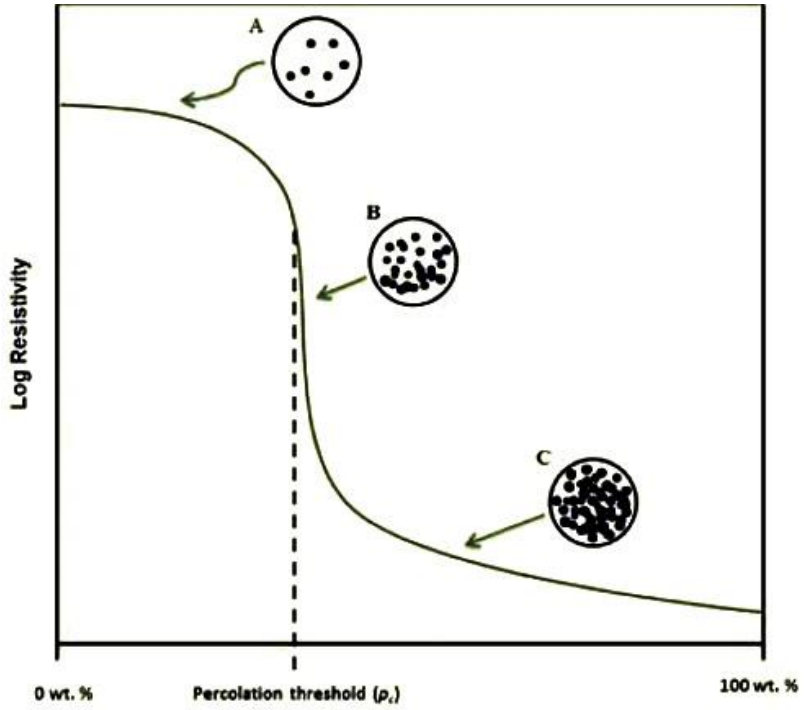

Figure 27 *Logarithmic percolation curve in the conductive polymer vs. the percentage in weight of particles in the polymeric matrix [24].*

The percolation threshold is the value that allows the formation of long-range connectivity in random systems. Below the threshold a giant connected component does not exist; while above it, particles dispersed in the polymeric matrix form a conductive net.

Another non trivial aspect of preparing conductive compounds is the mixing.

In fact, for the blending of graphite microparticles and PDMS it is necessary to use solvents such as toluene or hexane. These solvents increase the miscibility and an

homogenous distribution of the graphite particles in PDMS. Furthermore, the resulting viscosity of the blending mixed with the solvent is very similar to an ink, so it can easily be dispensed with a pipette or spun on the substrate. But an excess of solvent would avoid the crosslinking of the polymer.

Mechanical steering and sonification are used to provide an homogeneous dispersion of conductive particles in in the polymer and a timely evaporation of the solvent and cross-linking of the polymer.

6.7.5.1.2 *Conductive PDMS preparation and characterization*

The PDMS (Sylgard 184, Dow Corning, Midland, MI) matrix was prepared in a class 1000 clear room mixing the elastomer with the curing in 10:1 ratio.

The mixture was then degassed for 30 minutes.

According to data from the literature, the percolation threshold occurs between 12% and 25% of the graphite volume fraction, higher percentages produce higher resistivity [25].

For the preparation of an appropriate quantity of blending, 0.42 g of graphite where used. In order to prepare a mix at 35 wt.% of graphite, 0.7 ml of PDMS (corresponding to 0.749 g) were used.

Some microliters of solvent (toluene) were poured into the beaker and then PDMS and graphite alternately, in order to mix them homogenously. Then the blend undergoes sonication for 15 minutes. Finally, it was degassed in vacuum chamber for 15 minutes, poured on the substrate and cured.

Conductive PDMS (C-PDMS) was then dispensed on Petri dishes and cut in smaller stripes (fig. 28).

Figure 28 *C-PDMS samples.*

Once the fabrication process had been determined, it has been necessary to obtain repeatable characteristics in terms of conductivity, dimensions and thicknesses in order to produce sensorized membranes.

To obtain repeatable properties C-PDMS has been spun coated. The C-PDMS has been spun on a silicon wafer substrate at different speeds to obtain different thicknesses of the membrane.

Table 2 reports data from the trials.

Trial	**Initial speed - duration of the trial**	**Final speed - duration of the trial**
1	500 [rpm] – 15 s	2500 [rpm]- 60 [s]
2	500 [rpm] – 15 s	2000 [rpm]- 60 [s]
3	500 [rpm] – 15 s	1000 [rpm]- 60 [s]

Table 2 *C-PDMS spinning parameters*

2000 and 2500 rpm are too high spinning velocities and prevent the percolation and homogeneous distribution of the graphite microparticles in the PDMS on the substrate (fig. 29).

Figure 29 *C-PDMS at 2000 and 2500 rpm*

A conductive membrane was obtained at a maximum speed of 1000 rpm. (fig. 30).

Figure 30 *C-PDMS at 1000 rpm*

Once the conductive composite was spun, the wafer was cured in the oven at 70°C for 10 minutes and the membrane peeled off and applied on the electrolytic reservoir. In order to facilitate the peeling of the membrane on the wafer a substrate of photo resist was deposited.

The C-PDMS membrane was then cut and fixed to the electrolytic reservoir.

In order to measure resistance of the membrane on the electrolytic reservoir electrical connections were provided and resistance measured with a multimeter. Values of resistance measured were about 500kΩ.

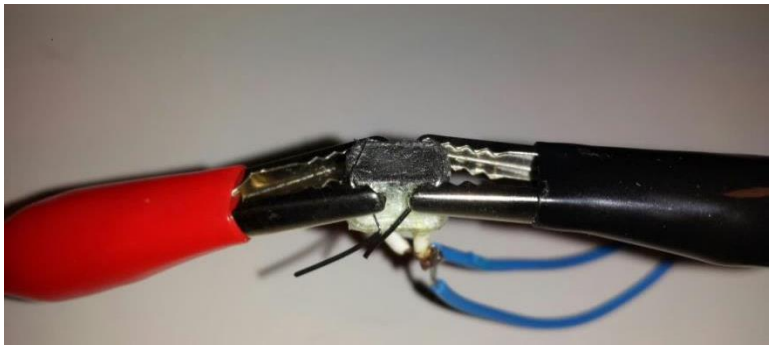

Figure 31 *Conductive PDMS membrane mounted on the electrolytic solution reservoir*

By the way, before measuring resistance variations due to electrolytic gases production, the conductive membrane properties were tested for linear traction, with a material testing machine, in order to investigate the sensor response to mechanical deformations.

Linear traction tests were conducted on a specimen 50 mm long and 0.6 mm wide. The traction test showed undesired properties of the material.

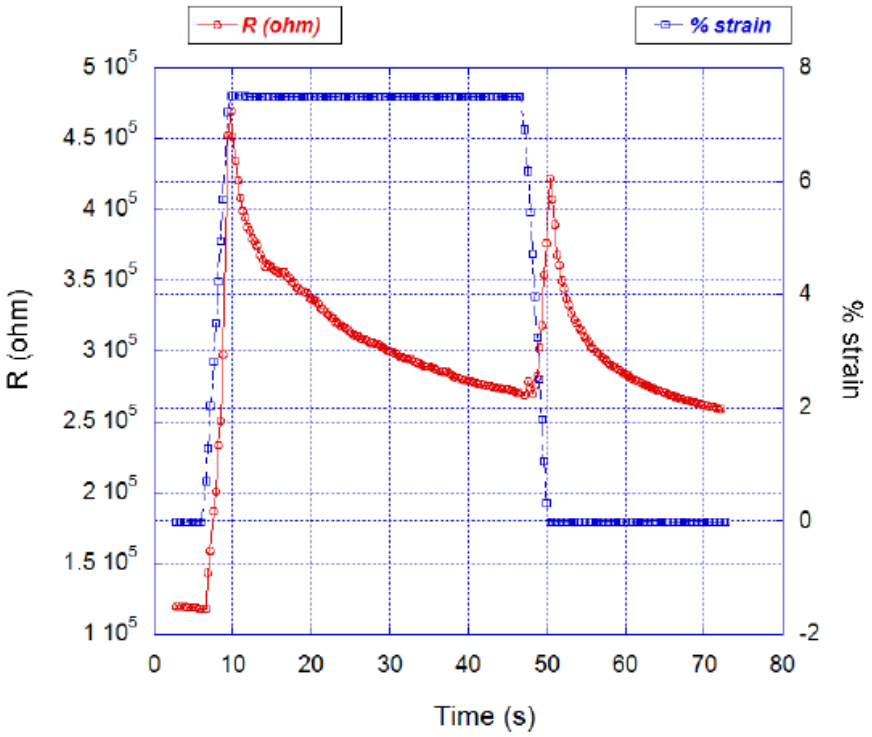

Figure 32 *CPDMS test at 8% of strain*

Firstly, it showed a large drift: the sensor was cyclically stretched at an applied strain of 8%. The strain was maintained for 40 seconds but the sensor resistance dropped down while the strain was maintained constant. Then, when the deformation load was removed the sensor still measured a variation in the resistance value (Fig. 32). The same behavior was shown by tests conducted at 5% and 30% of strain (fig. 33 & 34). An high drift in the value of the resistance and an inverted trend in sensor response in respect to the mechanical deformation were detected.

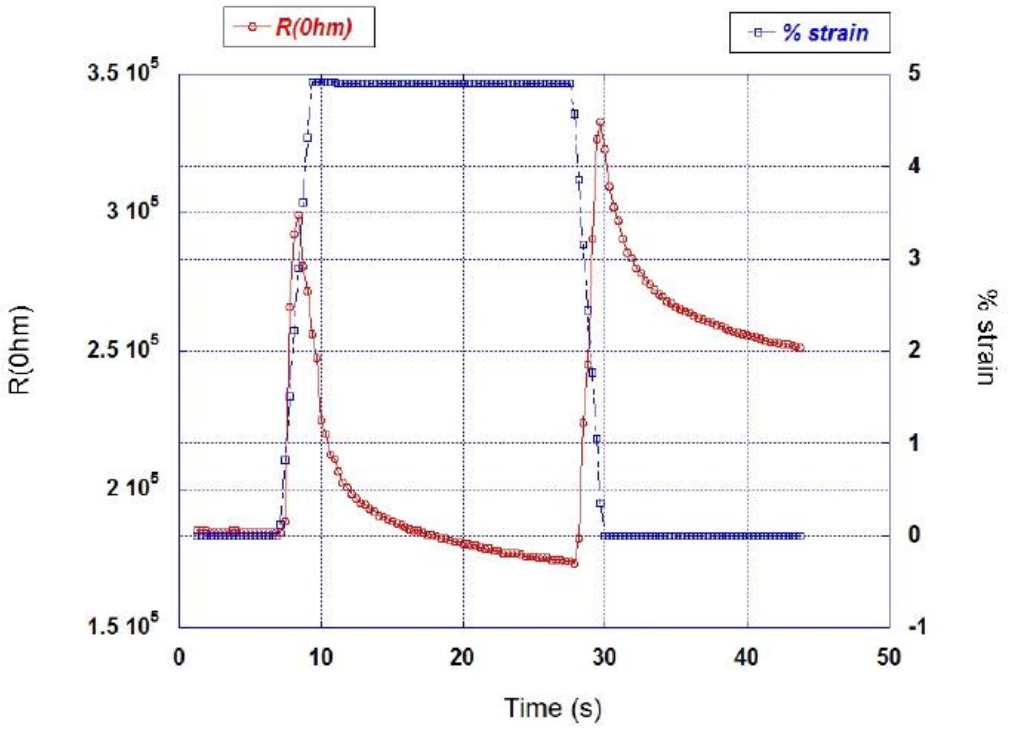

Figure 33 *CPDMS test at 5% of strain*

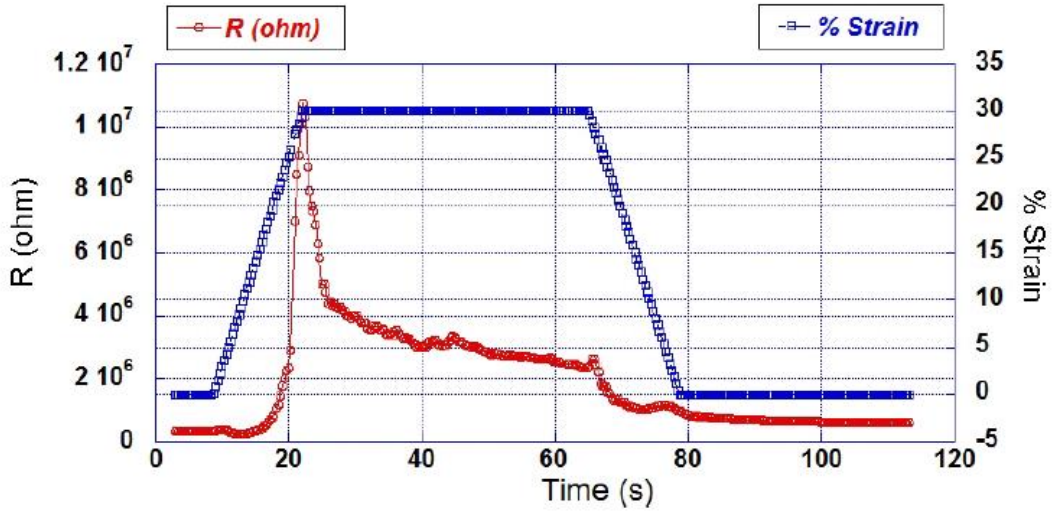

Figure 34 *CPDMS test at 30% of strain*

So, it was deducted that the C-PDMS is not a good candidate to be employed for the measure of small deformations and slow variations as those involved in the electrolytic gas production.

By the way, it has been successfully proposed in literature for applications such as cardiac beats monitoring, where rapid and short variations are involved [26].

The causes of drift in the C-PDMS can be retraced in the mechanical properties of the PDMS. The elastomer's Poisson ratio is in fact about 0.5 that is to say that PDMS is quite incompressible so no volume changes occur when stretched.

This property influences the determination of percolation paths.

When the PDMS is stretched, longitudinal percolation paths decrease forming some cracks in the material and the measured resistance increases.

Increasing the strain, orthogonal percolation paths appear and consequently, there is an inspected decrease of resistance.

When the strain is no longer applied, some movements of the graphite particles are still present in the matrix and the measured value of resistance can vary depending on the percolation paths that are formed (longitudinal or orthogonal).

When the equilibrium of the material is modified, increasing or subtracting the strain in the matrix, also the equilibrium in percolation path is interrupted and the resistance measured increases again [27].

Once identified the problems linked to the use of the conductive PDMS to sensorize the membrane, conductive thermoplastic nanocomposite elastomer (C-TPE), was considered as an alternative.

6.7.5.2 The *Thermoplastic elastomer (TPE) and the Conductive TPE properties*

Thermoplastic elastomers (TPEs) combine processing properties of plastics with those of elastomers. Table 3 summarizes properties of the TPE.

TPE Properties
- **Easy thermoplastic processing**
- **Short cycle times**
- **Low energy consumption**
- **Thermal stability, providing large processing window**
- **Multi-component processing and thus reduced assembly costs**
- **Combination of two materials (hard-soft composite)**
- **100% recyclable**

Table 3 *Thermoplastic elastomer properties*

TPE is made of blocks of a thermoplastic (Styrene) alternated by the elastic Isoprene or butadiene (Fig. 35).

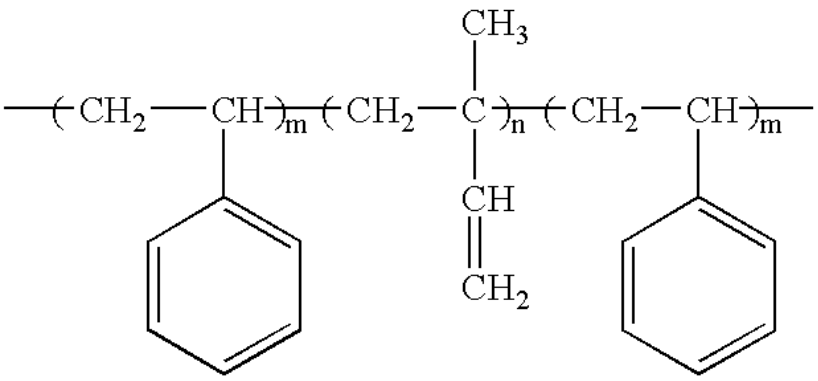

Figure 35 *TPE Chemical formula*

At room temperature, central parts of the molecule give the elastomeric properties to the material.

When a copolymer as TPE undergoes linear strain it acts like shown in figure 36.

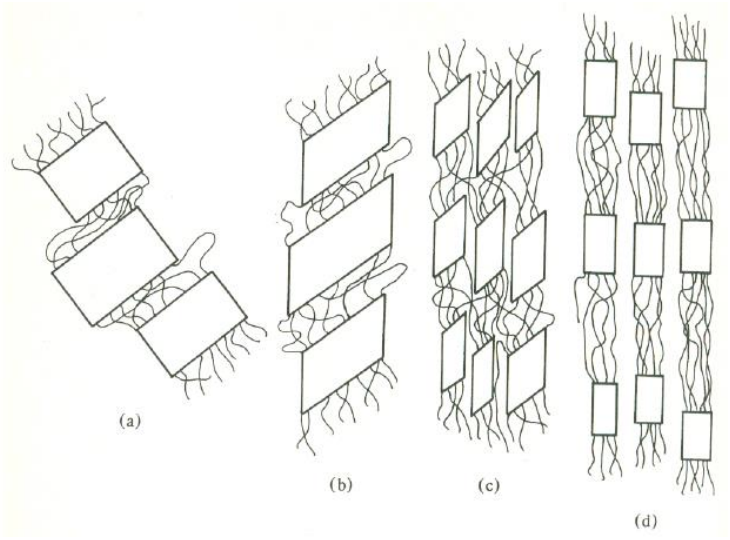

Figure 36 *TPE behavior under linear strain [28]*

Starting from an unloaded condition (a), when the material is stretched, crystalline lamellae slide (b) until they fragment in crystalline blocks (c). When the rubbery part of the polymer are completely stretched, lamellae are aligned (d). In this condition the behavior of the material is completely elastic.

TPE discloses the Mullins effect [29]: under cyclic loading conditions the stress-strain curve at each cycle depends on the previous deformation. The same is valid for TPE loaded with conductive particles, but, under small deformations, the effect is named Payne effect [30].

The Young modulus of TPE is variable, in particular it decreases when rubbery blocks increase.

Conductive TPE (CTPE) is realized loading the TPE with a mixture of graphite nanoparticles.

Taking into account the material properties, conductive TPE was considered in place of C-PDMS to sensorize the membrane of the electrolytic pump. The CPTE used was provided by Kraiburg TPE GmbH & Co. properties of the CTPE used are reported in table 4:

Property	***Value***
Density	1.07 g/cm^3
Hardness	84 shA
Resistance to traction	10.9 N/mm^2
Working temperature range	(-40 ÷110)°C

Table 4 *Conductive thermoplastic elastomer properties*

6.8 Strain sensor fabrication and characterization

The CTPE was provided in the form of squared plate 10x10 cm^2 (fig. 37).

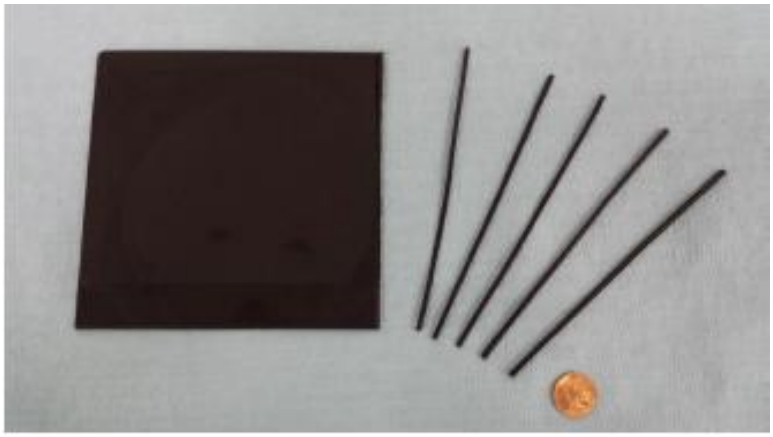

Figure 37 *CTPE in form of squared plate and some sensors cut before the pre-treatment.*

The strain sensor was cut, to fit on the PDMS membrane, from the CTPE material in a stripe (30 x 1 x 0.2 mm) with a value of resistance $R_{tpe} \sim 15\ k\Omega$.

As CTPE can work in four different regimes (fig. 38) according to the pre-treatment to which the material is subjected, the stripe underwent a pre-strain procedure: it was stretched to break the bonds inside the polymer and stabilize the resistance to a percentage of the desired strain, thus obtaining a length on average three times higher than the starting one and a resistance $R_0 \sim 80k\Omega$. The treatment is performed to force the device to work in the recoverable damage regime (regime III). The effect of the pre-treatment is a consequence of the Payne effect.

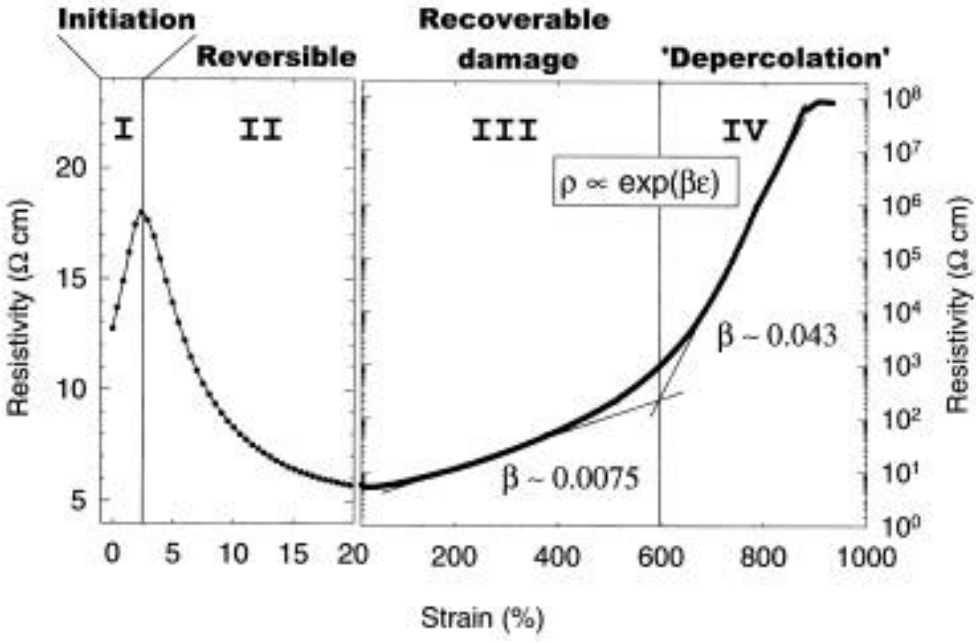

Figure 38 *Different response of a conductive thermoplastic material after the pre-treatment (Flandin curve) [31]*

This regime was selected to obtain a sensor with repeatable characteristics and a customized value of resistance that can guarantee low power consumption, necessary for the application of the device in a DDS.

Electrical connections are provided at the edge of the stripe in order to read its resistance. The variation of resistance of the CTPE sensor is measured with a multimeter (Hp1444a) and plotted in a Matlab Inc. interface.

Furthermore, the CTPE sensor can track deformations from 0.07% to 20%, while maintaining a good sensitivity to small movements, as those produced by the pump membrane and acceptable hysteresis [32].

Preliminary strain tests on this conductive thermoplastic nanocomposite have been carried out by cyclically stretching (5 cycles) the device in a single direction with a materials testing machine (Instron 3365) at a speed of 100µm/sec at different applied strain (5%, 10% and 20%). The smallest hysteresis is shown in fig.39 for 5% strain.

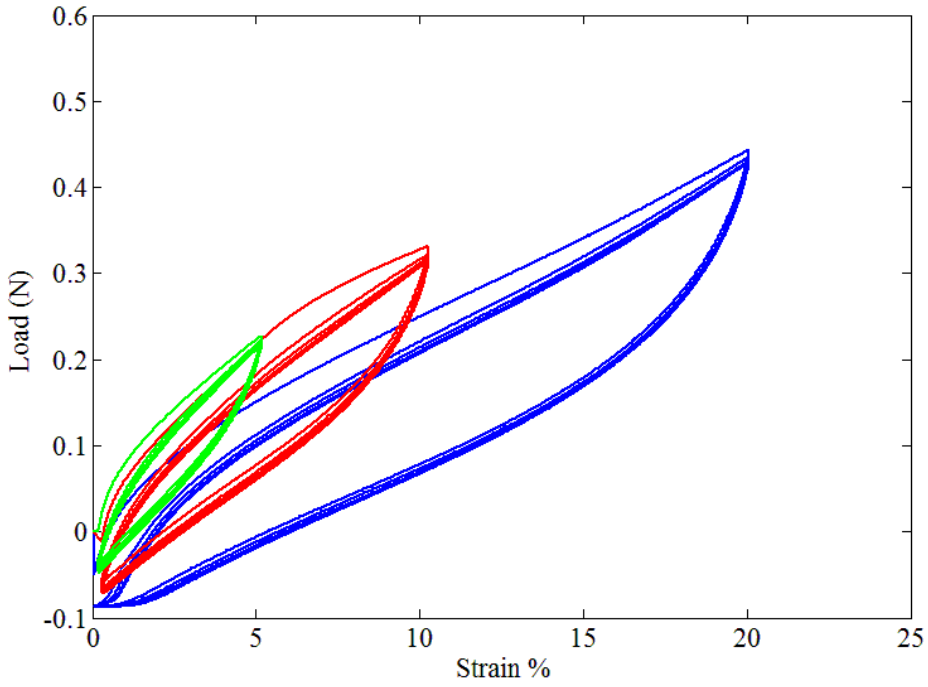

Figure 39 *Hysteresis for the CTPE sensor obtained at different strain % (5%, 10%, 20%) at a speed of 100 µm/s*

Since the amplitude of the hysteresis cycle is proportional to strain-rate, hysteresis can be neglected at sufficiently low deformation speed as those involved in the electrolytic reaction.

Fig. 40 shows the sensor response during a cyclic traction trial at 5% strain. The values of the resistances reported are normalized in respect to the value R_0 at rest.

The sensor response curve tracks the deformation curve. Small deviations depend on the speed of deformation (12µm/s) and on the overall amount of strain.

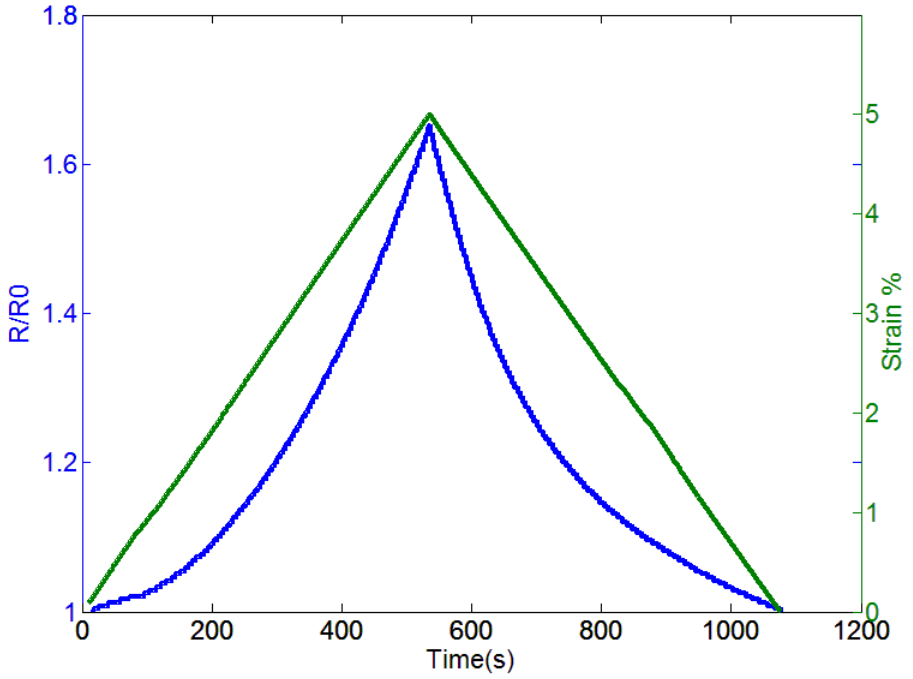

Figure 40 *Behavior of the sensor (blue curve) for a one cycle traction (green curve)*

The increase of resistance is due to increasing spacing of the conductive nanoparticles inside the polymeric matrix.

As tests on the CTPE showed a proper behavior of the material for the application of interest, the membrane was sensorized: the sensor is fixed to the abovementioned PDMS membrane (fig. 41) which is then glued to the electrolytic solution reservoir prefilled with the saline solution.

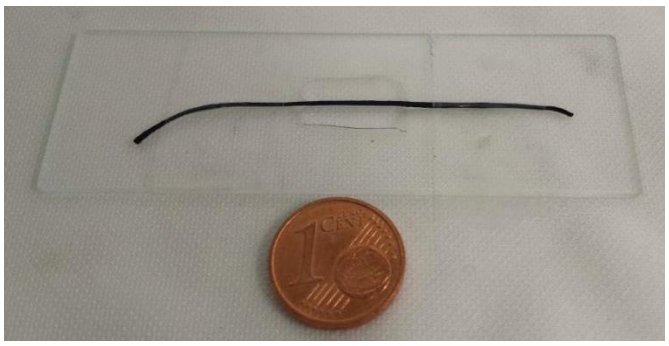

Figure 41 *CTPE sensor fixed on the PDMS membrane*

In order to verify that the sensor can properly detect deformations due to the electrolytic reaction, the sensor response was collected while gas was electrolytically

produced until the maximum deformation of the membrane was reached and after the membrane breaking, thus coming back to the initial position.

Figure 42 shows the resistance registered during the electrolytic reaction. Resistance increases until the maximum deformation is reached, and rapidly falls down when the membrane deflates.

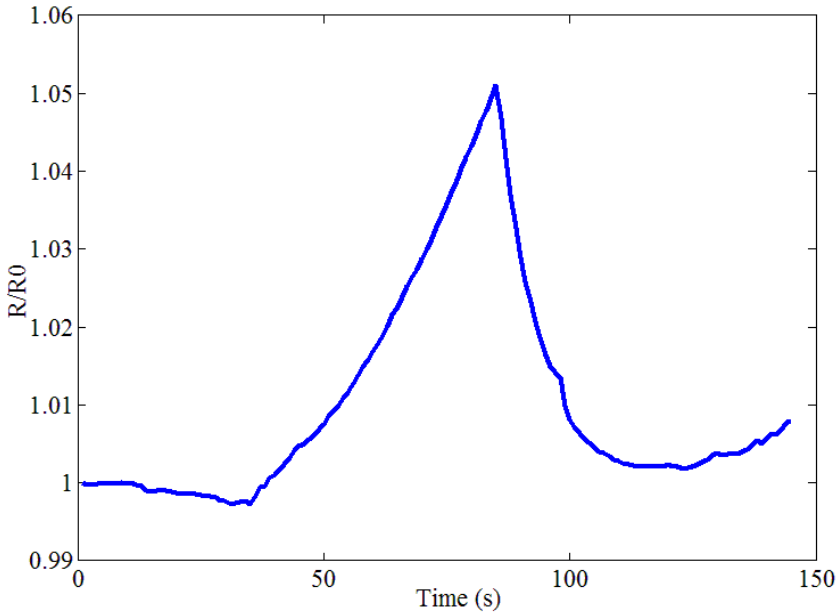

Figure 42 *Resistance measured when the membrane is deformed by inflation/deflation*

Comparing fig. 42 and fig. 40 (blue curve), it can be seen that resistance measured during the standard linear traction test (speed of deformation 12 µm/s) with the traction machine and while the membrane is deformed by the electrolytic reaction (speed of deformation 11 µm/s), have a similar trend, with numerical differences in R/R_0 due to the different values of maximum strain reached.

Finally, as CTPE resistance can be significantly influenced by changes in temperature, this value was monitored with a thermocouple J during the electrolytic reaction. No appreciable changes in temperature were measured so alteration of the CTPE performances are excluded during the system activation on the capsule.

6.9 Sensorized membrane experimental setup

As illustrated so far, firstly, the membrane was fabricated, then its performances, an in particular volumetric deformations, were simulated exploiting the pressure-load model and the finite elements analysis.

Secondly, the performances expected from simulations were compared with experimental results of electrolytic gases production.

Finally, the CPTE strain sensor was prepared and fixed on the membrane to monitor the membrane deformation, thus providing an indirect measure of the pressure inside the chamber and so a control over the volume of the drug delivered.

In order to compare simulation results with real membrane deflections and the corresponding displaced volumes a setup was fabricated. The dedicated setup (fig. 43) was 3D printed in order to have a stable structure for repeated tests.

This setup has permitted to collect data about the displacement and the sensor response at the different pressure till the maximum value supposed to be produced by the V_{gas} measured during the electrolytic reaction. The values of resistance measured were correlated to volumetric displacement. Those data can be used to implement the control and have been verified on the drug delivery system during the electrolytic reaction.

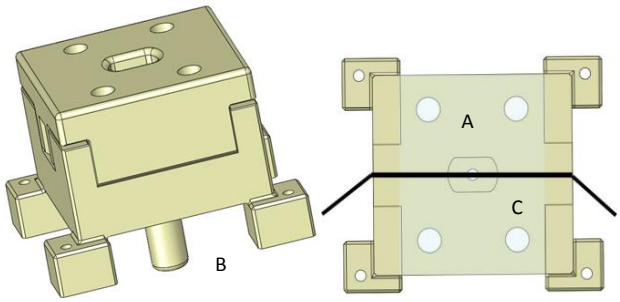

Figure 43 *Setup 3D CAD: it presents a central cavity (A) of the same shape of the electrolytic solution reservoir with a hole in the bottom to allow the connection to a tube for air insufflation (B). On the surface of the setup the PDMS membrane is laid and the CTPE fixed (C)*

The setup presents a central cavity of the same shape of the electrolytic solution reservoir with a hole in the bottom to allow the connection to a tube for air insufflation.

On the surface of the setup the PDMS membrane is laid and the CTPE fixed on it with electrical connections at the edges in order to monitor resistance variations with a multimeter (Hp 1444A).

The membrane is squeezed by the upper part of the setup to ensure the chamber is leak tight. A hole on this part in correspondence of the chamber in the bottom side allows monitoring of the membrane deformation with a miscoscope (Superyes 3.5). The initial membrane deflection was retrieved from the frame recorded with the microscope.

6.10 Experimental results

The membrane was pressurized incrementally, from 0.02 bar to 0.34 bar. Air was inflated from the bottom inlet with a fluid dispenser (Techcon Systems TS255) (fig 44).

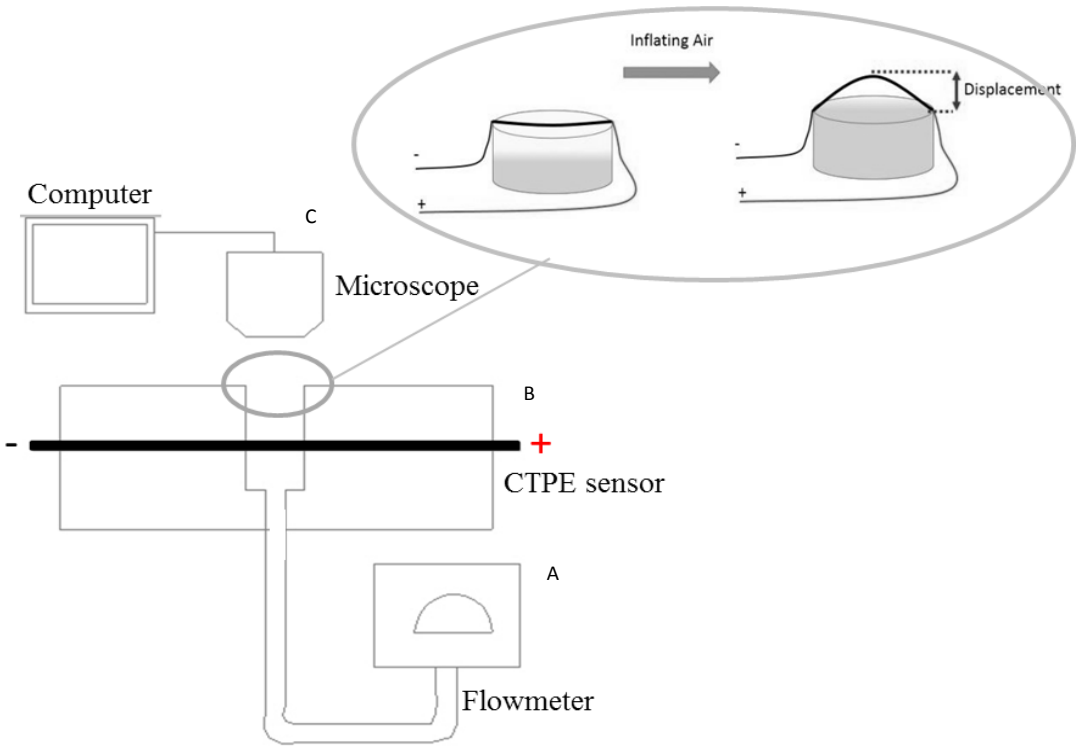

Figure44 *Experimental test: the sensorized membrane is inflated from a bottom inlet (A), the sensor response is read by a multimeter (B). Membrane deformation is monitored from the top with a microscope (C).*

Load-deflection data are plotted in figure 45.

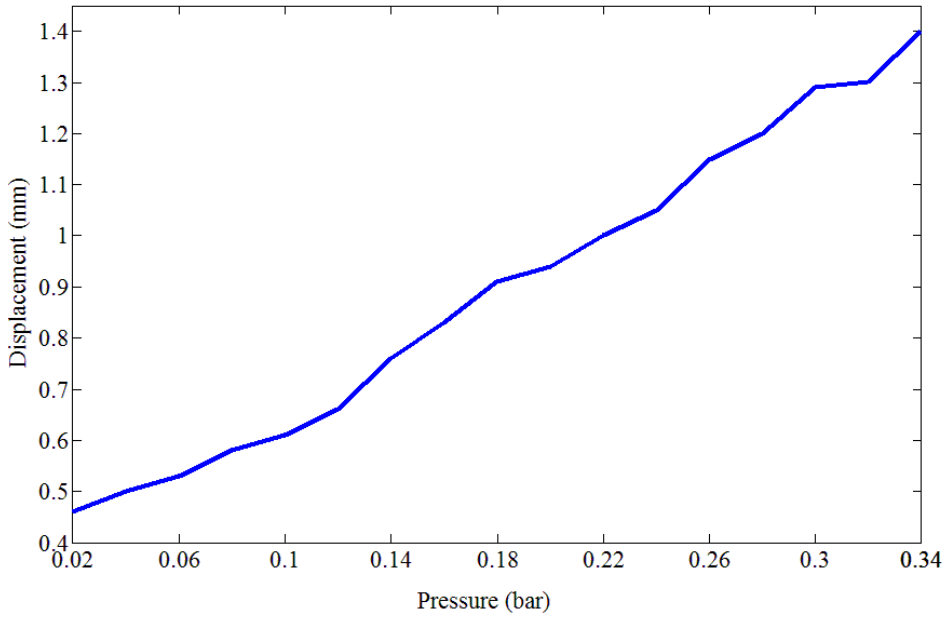

Fig. 45 *Load-deflection behavior*

As the displacement increased with pressure also the resistance of the strain sensor increased.

Figure 46 shows the sensor response at increasing pressure applied.

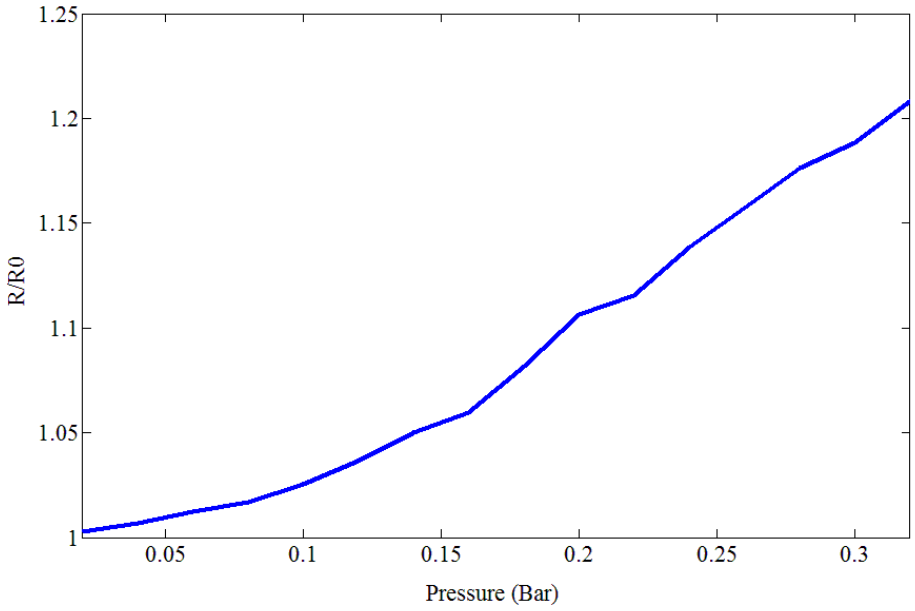

Figure 46 *Resistance Vs. applied load*

Once the displacement of the center of the membrane is retrieved from the frames acquired by the microscope, the volumetric deflection can be calculated. The sensor response at increasing displaced volume corresponding to the measured membrane displacement is shown in fig. 47.

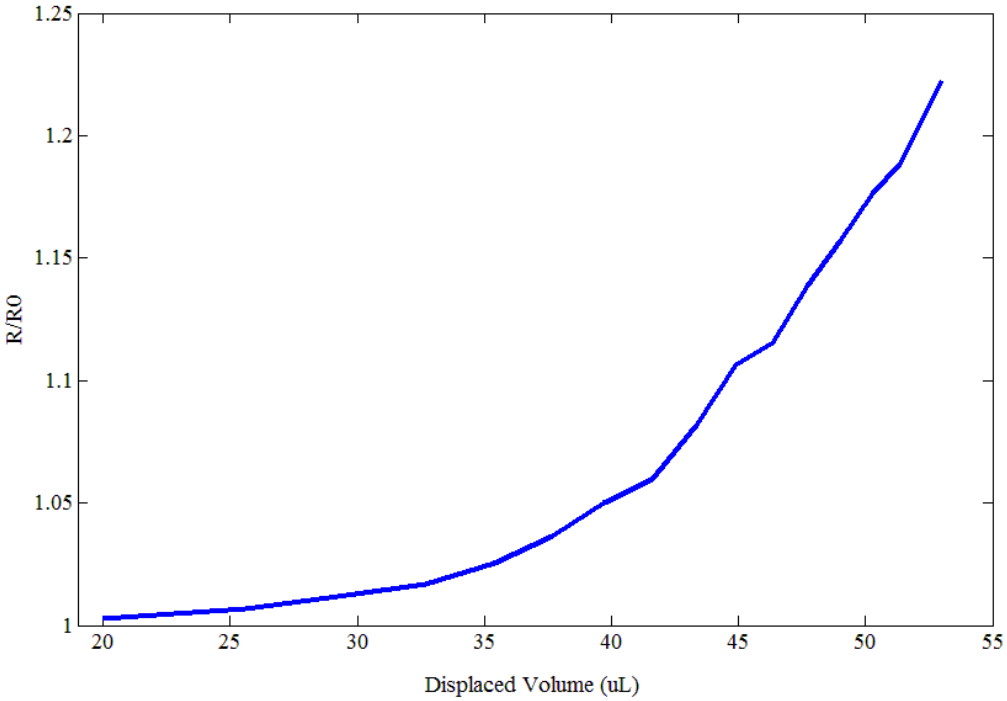

Figure 47 *Resistance Vs. displaced volume*

Data of CTPE normalized resistance R_0 corresponding to increasing volume of gas production and so to drug delivered are reported in table 5. Such values can be used in the control system.

Pressure (bar)	***Normalized resistance R/R_0***	***Volume (µl)***
0.02	1.0029	19.98
0.04	1.0068	25.60
0.06	1.0121	29.60
0.08	1.0169	32.70
0.10	1.0256	35.40
0.12	1.0363	37.70
0.14	1.0498	39.70
0.16	1.0595	41.60
0.18	1.0818	43.33
0.20	1.1064	44.90
0.22	1.1156	46.36
0.24	1.1388	47.70
0.26	1.1572	49.00
0.28	1.1761	50.27
0.30	1.1882	51.34
0.32	1.2080	52.33
0.34	1,2225	53.13

Table 5 *Sensor response at different volumetric displacements*

The capability of the CTPE sensor to monitor small deformations and to detect rapid variations is confirmed by the experimental tests.

Figure 48 shows the sensor response to a continuous increase of pressure from 0.02 bar to 0.34 bar until the membrane is deflated. The CTPE sensor maintains a good sensitivity to small displacement due to small pressure increases.

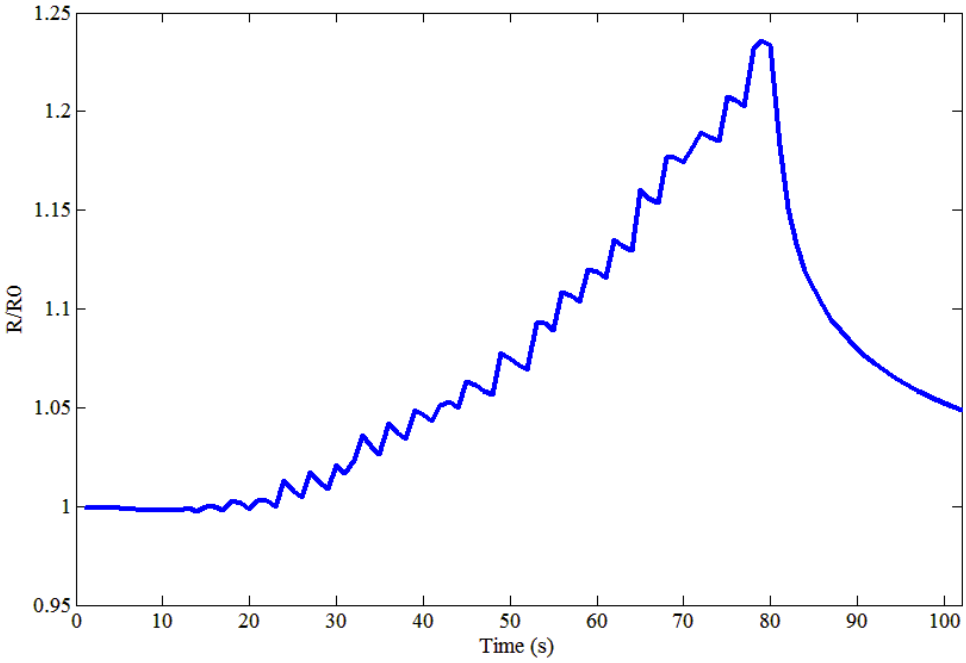

Figure 48 *Sensor response during pressure increase (0.02- 0.34 bar) and deflation*

Deflections of the membrane and sensor response have also been measured on the pump during the electrolytic reaction and the volume of drug delivered controlled (Fig. 49).

The pump was powered at 3V for about 50s. At the beginning of the reaction, the

Figure 49 *Membrane deformation during the electrolytic reaction*

increase of the resistance is lower because initial deformation is small, then, there is a rapid increase of resistance. The maximum value of the resistance measured at the sensor was R/R_0 = 1.1. A V_d of 45 µl can be delivered in correspondence of the measured resistance (Fig. 50).

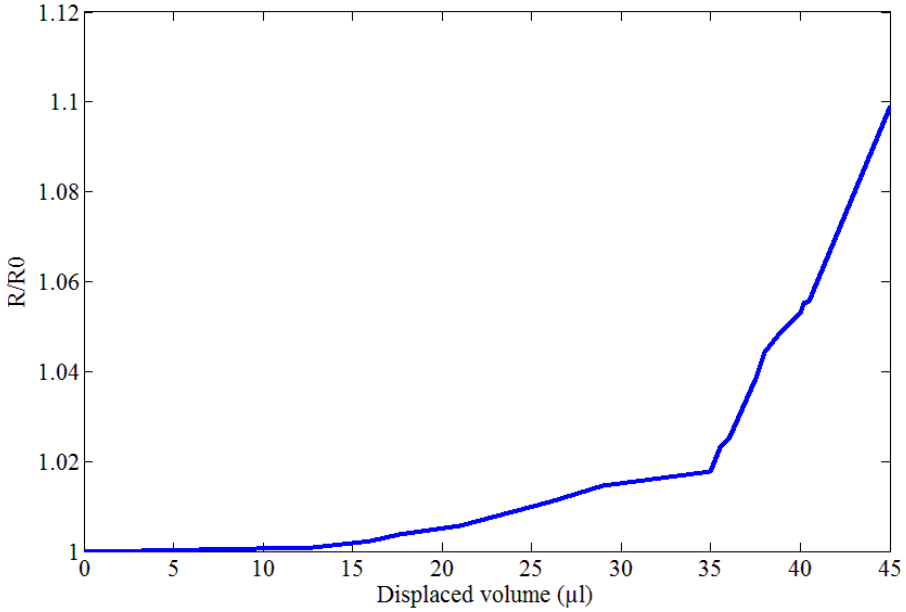

Figure 50 *Resistance vs. displaced volume during the electrolytic reaction*

To prove the accuracy of the measure, the deflection was monitored with the microscope. A displacement of 1.8 mm is reached, that corresponds to the expected volume. So the gas produced by the electrolytic reaction generates a pressure on the membrane that can be estimated to be of about 0.2 bar comparing displacement results with those obtained from simulation.

6.11 Discussion and conclusions

The drug delivery system integrated on the smart pill consists of a sensorized electrolytic pump and a drug chamber. The integrated electrolytic pump can deliver a useful amount of drug (>50µl) in about 1 min. Furthermore, the electrolytic pump is equipped with a novel strain gauge sensor in order to monitor membrane deformation due to gases production in the electrolytic pump and to correlate it to a measured resistance. The measure of the deformation of the membrane of the electrolytic pump is functional to the control of the drug released. The strain sensor used is made of a conductive thermoplastic nanocomposite elastomer that can be easily integrated on the pump membrane. Results of the experimental tests showed that CTPE can successfully be applied as strain sensor on the electrolytic reservoir because of its

high sensitivity to any, even small (> 0.1 mm), membrane displacement. Consequently, the sensor response has been correlated to the volume of drug delivered.

CTPE has been chosen as an alternative to more diffused CPDMS: it has been shown that Conductive PDMS cannot properly monitor the deformations of the membrane imposed by the electrolytic reaction that is quite slow, in fact large drift phenomena are produced by the reaction in the conductive PDMS mainly because of the nature of the material.

Another advantage provided by the use of CTPE is the possibility of customizing its resistance, in that way, power consumption issues, that are crucial, can be satisfied.

In chapter 5 we investigate the importance of containing power consumption for an autonomous ingestible device such as the smart pill. The possibility to produce a sensor with an high value of resistance at rest (R0 ~1 MΩ) allows to keep power consumption compatible with power source on-board.

Finally, the drug delivery system developed on the smart pill maintains characteristics of simplicity, low-cost and easiness of use but combines these aspects with sophisticated features such as biocompatibility, high integrability and high performances in terms of efficacy with low consumption achieved through the smart solutions described.

The drug delivery system is completely integrated on the capsule, and provides the possibility to achieve personalized treatment.

Also to this respect, an important innovative feature introduced in the drug delivery system developed is the sensor. The choice of the strain sensor for the monitoring of the membrane deformations, allows an exact control of the volume of drug released in fact the measure is not influenced by external factors (i.e. gastric fluids viscosity) as will happen with a control based on pressure measurement inside the capsule. Considering these aspects, the device developed is very versatile because can be used with different types of medication according to specific needs, as asked to achieve personalized treatment.

Furthermore, the strain sensor can be fully integrated with the membrane of the micro-pump developed not requiring extra space. In this way, size, that is another important requirement for the capsule, is not modified.

Finally, the sensor response can be correlated to the volumetric displacement of the membrane and so, together with the measurement of the gases produced by the electrolytic reaction at the electrodes, to the drug delivered. Consequently, the drug delivery system can release a controlled amount of drug for localized therapy up to a maximum of 53µl.

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Chapter 7

Conclusions

Smart pills, which have been originally developed mainly for diagnosis, are being increasingly applied also to therapy, more specifically for drug delivery. In particular, local delivery of drugs reduces side effects often associated to systemic treatments. Focusing on the major application field of such devices, i.e. the treatment of digestive system pathologies, our aim has been to develop a smart pill for local drug delivery.

First of all, the capsule has been designed to fulfill the environmental requirements. Constraints on capsule dimensions are mainly imposed by the smallest diameter in the GI tract, i.e. the esophagus, that has a mean diameter of 20 mm. The capsule developed is 21 mm in length and 14 mm in diameter. The shape is designed to have a major contact area of the surface sensing electrodes with the intestinal walls.

The materials selected for the capsule are all biocompatible; in particular PDMS, platinum and a saline solution have been used.

The capsule has been sensorized with an impedance sensor in order to obtain information about the physiological or pathological state of the tissue. It is known that electrical properties of the tissue are determined by the type of cells and by the physiological structure of the tissue. For this reason, biological tissues have different responses to different frequencies of stimulation. Different types of tissue can be discriminated according to their response. To this respect, the correlation between pathological conditions and alteration of the tissue electrical impedance have been investigated in literature. In particular, it has been shown that cancerous tissue has

different electrical characteristics compared to normal tissue. So, electrical impedance measurement has emerged also as a diagnostic tool. The developed impedance sensor was tested on esophageal tissue because impedance is usually measured in medical practice in combination with pH-metry for esophagus screening, in particular for the diagnosis of esophageal reflux.
It was demonstrated that the developed impedance sensor could successfully measure impedance on the gastrointestinal tract as an extended range of impedance values has been read by the sensor. The alteration of physiological conditions of the tissue are expected to be correlated to an alteration of electrical properties of the tissue. Such monitored alterations can be used to trigger the activation of the drug delivery system.

The drug delivery system is the other functional element of the capsule. It occupies one lobe of the capsule. The drug delivery system exploits a custom made electrolytic micropump that displaces the drug exploiting the deformation of an elastic membrane.

In order to control the amount of drug released, the electrolytic reaction is monitored measuring the current through the electrodes. Also the membrane deformation is monitored in order to have a closed-loop control over the drug flow.
To monitor the membrane deflections a novel strain gauge sensor has been fabricated using a conductive thermoplastic elastomer loaded (CTPE) with graphite particles. The resistance of the material increases as the membrane is inflated and so the sensor is stretched and particles of graphite are moved apart from each other.

The integration of the strain sensor on the membrane of the micropump makes the drug delivery system appropriate for the dispensing of different kinds of liquid drugs. In fact, the measure is not influenced, for example, by the fluid viscosity as it would happen using a control based only on the measurement of the pressure inside the capsule.
The closed-loop control is fundamental for the proper functioning of the smart pill as it is supposed to be able to reject all possible failures during navigation. Possible malfunctions could be caused by the external pressure exerted by gastric fluids on the capsule and in particular on the nozzle. The monitoring of the membrane

deformations could permit to identify any cases of nozzle plugging. The measure of the current at the electrodes allows a double check for cases when the gas is produced in the electrolytic pump but no deformation of the membrane is read because the nozzle is plugged or cases when the membrane breaks and no deflection is detected by the strain sensor while the electrolytic reaction is active.

Conductive thermoplastic nanocomposite elastomer can successfully be applied as strain sensor on the electrolytic reservoir because of its high sensitivity to any, even small (<0.1mm), membrane displacement. Furthermore, a great advantage given by the use of a CTPE sensor for this application is the possibility to achieve low power consumption. In fact, as the sensor resistance can be customized through the pre-treatment, so to choose the regime in which the sensor works, a high value of resistance (~1 MΩ) can be obtained. This is very important considering that the smart pill is powered by on-board batteries. In fact, all the components of the pill have been designed to achieve low power consumption (e.g. choice of the microcontroller, activation time of sensors and microcontroller, electrolytic pump for drug delivery).

The integrated electrolytic pump can deliver a useful amount of drug (>50µl) in about 1 min.

In conclusion, the developed capsule is a novel swallowable tool for local drug delivery with sensing capabilities. The impedance sensor developed is a novel diagnostic tool, used not in combination but as an alternative to the known chemical pH measurement, that is more susceptible to external factors (e.g. food and drink assumption).

The drug delivery system is also innovative because it does not exploit commercial motors or pumps but a custom made pump that constitutes part of the capsule itself.

The smart pill developed is an autonomous capsule for local drug delivery that contributes to tackle the main challenge of implementing therapeutic functions on board of swallowable robotic capsules.

List of publications

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- **R.Goffredo**, D.Accoto, E.Guglielmelli "Swallowable smart pills for local drug delivery: present status and future perspectives", Expert review of Medical Devices, Vol. 12, Issue 5, pp. 585- 599, DOI:10.1586/17434440.2015.1061933.

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