Advanced Drug Delivery Reviews 71 (2014) 77–85

Contents lists available at ScienceDirect

Advanced Drug Delivery Reviews

journal homepage: www.elsevier.com/locate/addr

A review of drug delivery systems for capsule endoscopy ☆

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ARTICLE INFO

Available online 30 December 2013

Keywords:
Robotic drug delivery systems
Wireless capsule endoscope
Anchoring mechanism
Release mechanism

ABSTRACT

The development of a highly controllable drug delivery system (DDS) for capsule endoscopy has become an important field of research due to its promising applications in therapeutic treatment of diseases in the gastrointestinal (GI) tract and drug absorption studies. Several factors need to be considered to establish the minimum requirements for a functional DDS. Environmental factors of the GI tract and also pharmaceutical factors can help determine the requirements to be met by a DDS in an endoscopic capsule. In order to minimize the influence of such factors on the performance of an effective DDS, at least two mechanisms should be incorporated into a capsule endoscope: an anchoring mechanism to control the capsule position and a drug release mechanism to control variables such as the drug release rate, number of doses and amount of drug released. The implementation of such remotely actuated mechanisms is challenging due to several constraints, including the limited space available in a swallowable capsule endoscope and the delicate and complex environment within the GI tract. This paper presents a comprehensive overview of existing DDS. A comparison of such DDS for capsule endoscopy based on the minimum DDS requirements is presented and future work is also discussed.

Contents

1. Introduction

In recent years, the development of a highly controllable drug delivery system (DDS) that would allow clinicians to release an appropriate amount of a drug at specific sections of the gastrointestinal (GI) tract has become an important field of research. These systems can be used in different applications, including the therapeutic treatment of diseases in the GI tract [1,5], and drug absorption studies, which represent a cost of millions of dollars per year to the pharmaceutical industry [2].

Of the various prototypes of a DDS for capsule endoscopy, which have been designed and fabricated to release drugs at different sections of the GI tract in a controlled fashion, a great number of these studies have used microelectromechanical systems (MEMS) to perform the tasks involved in the drug releasing process, while other studies have focused more on non-mechanical systems to achieve the same goal [3]. An example of a MEMS system to target and treat pathologies in

☆ This review is part of the Advanced Drug Delivery Reviews theme issue on "Editor's Choice 2014".

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http://dx.doi.org/10.1016/j.addr.2013.12.007

the GI tract has recently been proposed in [19,56]. This system aims to anchor the capsule and release a liquid drug through a needle.

Despite the efforts that have been made in this area, difficulties still arise when an attempt is made to establish a reliable and accurate DDS in a capsule endoscope. Two main challenges are (i) the development of an effective anchoring mechanism, which would enhance the controllability of the capsule position; and (ii) the remote actuation of a drug releasing mechanism [4], which aims to control the amount of drug to be released, the flow rate and the number of doses.

The purpose of this paper is to review recent research into the development of a DDS for capsule endoscopy and provide a comprehensive comparison among all the different approaches, highlighting their advantages, disadvantages and future research directions.

The remainder of this paper is divided into four sections. Section 2 provides a brief overview of the problem of the development of an accurate DDS. Section 3 describes the environment in which the capsule endoscope operates and defines the requirements for a DDS. Section 4 presents a detailed analysis and comparison of different approaches found in the most recent literature. Finally, conclusions and future work are underlined in Section 5.

2. The capsule endoscope

Existing capsule endoscopes are used to diagnose diseases in the GI tract, but they are not yet developed to the point where they are able to perform an accurate therapeutic treatment. A typical capsule endoscope possesses a camera, a battery and electronic circuits that allow physicians to collect pictures of the GI tract while the capsule endoscope moves through it. These pictures are analysed by experts who determine the medical condition of the GI tract [6].

The first commercial capsule endoscope was introduced in 2001 and several improvements have since been achieved in terms of its image resolution and external communication capabilities [8]. The US FDA has approved three small bowel capsules (PillCam SB, EndoCapsule, and MiRo capsule) and one esophageal capsule (PillCam ESO). PillCam Colon is a colonic capsule available in Europe and Japan but not in the USA [57]. All these commercial capsules are imaging devices used for diagnostic purposes and a comparison of the capsules is presented in [58].

However, as the capsule is being driven by the natural peristaltic movements of the GI tract, known as passive locomotion, capsule endoscopes still miss abnormalities and lesions in the GI tract due to the lack of position, orientation and speed control over the capsule camera. This lack of control over the camera has significant implications for their effectiveness given that non-inspected areas may lead to incorrect diagnoses [1,24].

In order to overcome this problem, several systems have been proposed to actively actuate and control the capsule position and orientation in different sections of the GI tract. An important number of these proposed systems consist of legged-like mechanisms that can be deployed by an endoscopic capsule to resist peristaltic forces in narrowed sections of the GI tract, such as the intestine [19]. In other studies, endoscopic capsules have been covered with magnetic shields of different shapes that can interact with external magnetic fields. These mechanisms have shown promising results in sections of the GI tract where the capsule must inspect large areas and move over steep surfaces such as the stomach [11,17]. These proposed systems have been implemented in prototypes and tested in vitro, but will not be available in the market until further in vivo tests are conducted.

Similar to the fabrication of capsule endoscopes for diagnostic purposes, there has recently been considerable interest in the development of mechanisms that can be incorporated into endoscopic capsules in order to perform additional procedures including biopsy [24,25,46] and therapeutic treatments such as drug delivery [6] and surgical interventions [47]. The addition of these features to current capsule endoscopy will allow clinicians to wirelessly treat diseases of the GI tract, and minimise the discomfort to the patient through this alternative non-invasive procedure [23].

The fabrication of a remotely actuated DDS is challenging since the capsule endoscope must operate in a constrained and delicate environment made of live tissue. The DDS has to be embedded in a swallowable capsule whose dimensions impose a restriction on the size of the DDS. The IntelliCap, the InteliSite and the Enterion capsule can release drugs (up to 1 mL) [56]. The latter one is the most commonly used remotely-controlled device to investigate regional drug absorption since it is capable of delivering a wide range of dosage forms including solutions, suspensions, particulates, and mini tablets [13]. Despite the progress in DDS for capsule endoscopy, these capsules lack an anchoring mechanism and the drug release is not fully controllable yet.

In order to overcome these limitations, a variety of mechanisms to release drugs at specific regions in the GI tract have been proposed and incorporated in prototypes of capsule endoscopes recently. An important number of studies have reported results of remote actuation of release mechanisms built with MEMS technology [3] while other studies have focused more on non-mechanical approaches to develop such untethered mechanisms [7,29].

Most of the MEMS-based systems for DDS in capsule endoscopy incorporate small batteries that are placed inside the capsules to power and actuate the drug releasing mechanism. Similarly, a small number of studies have also included anchoring systems to allow endoscopic capsule prototypes to firmly attach to the walls of the GI tract before releasing the drug [19]. However, all these mechanisms require power that is not easily available from existing batteries. Consequently, other researchers have investigated wirelessly powering and actuating the MEMS-based systems [26–28].

In other studies, researchers have developed and tested non-mechanical approaches to release drug loads remotely. These proposed systems differ greatly from the MEMS-based systems that they do not need batteries or wireless power transmission to operate since their actuation relies mostly on chemical interactions that are triggered in response to certain conditions of the environment, such as the temperature and pH [7]. Despite the advantage of low power consumption offered by these non-mechanical systems, it remains difficult with these systems to control variables, such as the release rate, target location, number of doses and exact amount of drug released, which play an important role in on-demand drug delivery systems [21,22].

Although significant efforts have been made to add features to capsule endoscopes that would enable physicians to perform diagnostic routines and therapeutic treatments, a range of technical problems still remain unsolved. Specifically, in the development of a highly controllable DDS, two main problems have to be addressed. The first is the implementation of an anchoring mechanism that allows further control over capsule position. The second challenge is to implement a reliable and accurate DDS whose performance can be fully controlled. Its performance could be measured in terms of the ability to control variables such as release rate, number of doses and amount of drug released [10,21].

Endowing capsule endoscopes with such mechanisms will facilitate the treatment of diseases in the GI tract that are currently not possible with existing tethered endoscopy. These mechanisms can also be implemented and adapted in different procedures such as biopsy and therapeutic treatments. Furthermore, a DDS for capsule endoscopy will offer great benefits in pharmaceutical studies where drug absorption evaluation is a fundamental part in the creation of new medicaments [5,13,14,21]. In order to better understand the restrictions and requirements for DDS in capsule endoscopy, a detailed description of the environment under which the DDS would operate along with technical requirements is set out in the following section.

3. Operational environment and requirements for DDS

The GI tract can be divided into four main different sections, the oesophagus, stomach, small intestine and large intestine or colon [12] as

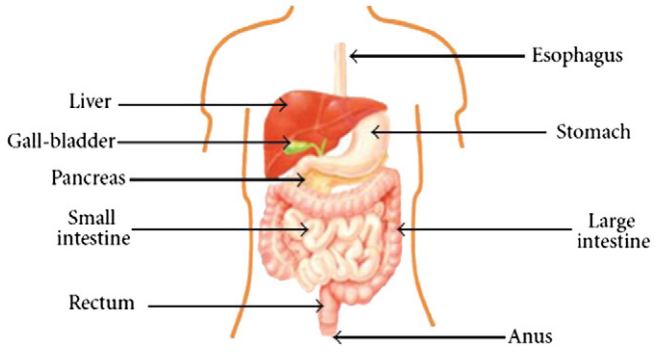

Fig. 1. Architecture of the GI tract [12].

shown in Fig. 1. The small intestine possesses three main sub-compartments, that is, the duodenum, jejunum and ileum [13]. Similarly, the large intestine consists of four sections, the ascending colon, transverse colon, descending colon, sigmoid colon and the rectum [14].

The small intestine is about 6 m long, its diameter is 2.5 to 3 cm and the transit time through it is typically 3 h [13,18]. The duodenum has a C shape, and is 30 cm long. Due to its direct connection with the stomach, it is physically more stable than the jejunum and ileum, which are sections that can freely move.

The jejunum is 2.4 m in length and the ileum is 3.6 m in length and their surface areas are 180 m^2 and 280 m^2 respectively [13,19]. On the other hand, the large intestine is 1.5 m long, its diameter is between 6.3 and 6.5 cm, the transit time though this section is 20 h and has a reduced surface area of approximately 150 m^2 [12–14].

The higher surface area of the small intestine enhances its capacity for drug absorption. Thus, this section of the GI tract is of great interest in regional drug absorption studies that aim to understand the pharmacological behaviours of the majority of molecules administered orally [13]. However, the complex geometry of this section of the GI tract makes it more difficult for conventional endoscopes to pass through the small intestine [12]. On the contrary, the large intestine possesses a reduced surface area and lower motility that enhance the mucoadhesion which is a desirable feature to be considered in the development of anchoring systems in capsule endoscopy [9].

Due to the disparities between the sections of the GI tract, different capsule endoscopes have been implemented to target individual sections of the GI tract. Specifically, there are commercial endoscopic capsules that aim to target the oesophagus, the small intestine and the colon for medical diagnoses [12]. Since the physical dimensions of the GI tract such as length, diameter and shape, vary throughout the digestive system, capsule endoscopes are restricted in size. This constraint is mainly imposed by the smallest diameter in the GI tract. Existing capsule endoscopes are 11 mm in diameter, 26 mm long, with a volume of 3.0 cm^3 and any device with similar dimensions can be considered swallowable [15,19].

In addition to the size constraints, the transit times in the GI tract vary greatly from one section to another. In order to actively control the transit time of a capsule endoscope, an anchoring or stopping system must be developed and incorporated to wireless capsule endoscopy. Different efforts have been made to allow clinicians to control the position of a capsule endoscope and explore areas of interest in more detail for a prolonged time. These anchoring systems have been developed to meet environmental conditions of each section of the GI tract. For instance, an anchoring system was proposed in [16] for oesophageal inspection, in [17] authors developed the stopping mechanism for stomach inspection, and other studies have focused more on the intestine sections [1,19].

In order to design and develop an accurate drug delivery system for capsule endoscopy, several pharmaceutical conditions of the administered drug and physiological factors of the GI tract must be considered. Pharmaceutical factors such as dosage form (e.g., liquid or powder compounds) and physiological factors such as gastric emptying rate, fluid, and motility are common factors that affect drug absorption [20].

Changes in the GI tract such as the diameter of the intestine, the pH level, the motility, peristalsis and transit time can occur for several reasons including disease conditions and the ageing factor. For instance, gastroesophageal reflux disease is characterized by diminished peristalsis and chronic primary constipation may be associated with reduced intestinal transit rates in the large intestine. In addition to disease conditions, there are also normal changes in the GI tract as the age advances [50]. When establishing a DDS system, the resulting system should allow changes in operation parameters or conditions in a non-invasive, easy and quick way before it is deployed—it should be adaptable to various physiological changes in the GI tract and patient's conditions.

For instance, a DDS with a passive release mechanism is highly dependent on the fluid availability of the region where the drug is administered. This can be problematic for regions with low fluid such as the colon [9]. Thus, a full control over parameters such as timing, duration, release rate, volume of the drug reservoir, number of doses, dosage form and targeted location in a DDS is highly desirable to minimize the dependency on both pharmaceutical and physiological factors [10,21,22].

The physiological, mechanical and chemical characteristics of each specific section of the GI tract along with pharmaceutical factors determine the requirements to be met by a DDS in capsule endoscopy. Since different DDSs have been developed to allow endoscopic capsules to deliver drugs at targeted sections of the GI tract, their technical features differ from one to another. In order to compare these proposed DDS in capsule endoscopy, the following variables can be used to measure their performance: release rate, release amount, number of doses, and dosage form if the drug is released in a specific position or over a section. The controllability of all these variables will offer great advantages in DDS of capsule endoscopes and are discussed in the following section.

4. Comparison of existing DDS

The development of an effective DDS for capsule endoscopy should include at least an anchoring mechanism and a release mechanism. The first mechanism would enhance the capsule's capability to resist peristaltic forces, thus allowing the clinician to fully control the capsule position and orientation at any time. This is a requirement to minimize or eliminate the transit time variable which is an environmental factor that varies across the GI tract. The second mechanism would allow the clinician to deliver specific amounts of drug at a target location, thus improving therapeutic effectiveness while minimizing side effects.

Since a number of researchers have focused on the development of anchoring systems and others on the release mechanism, only few have been able to implement prototypes of both mechanisms in a capsule endoscope. By using the frame suggested in [29] for micropump classification, all these systems could be classified into two categories: mechanical and non-mechanical systems. Mechanical systems usually consist of moving parts that include a physical actuator. On the other hand, non-mechanical systems refer to mechanisms that do not require of such a physical actuator to accomplish its design purpose. The following sub-sections will review these categories in more detail for each mechanism.

4.1. Mechanical systems for anchoring mechanisms

In [30], the authors proposed a capsule with two legs in the front and two legs in the rear of the capsule body to enhance its steerability. These sets of legs could be deployed to actively control the position of the capsule at any section of the GI tract. A detailed analysis of the leg shapes was included in this study to determine the best possible configuration of the legs around the capsule body. This analysis aimed to develop the less invasive system that would produce minimal discomfort to the patient. It was found that a leg with a C shaped tip would be the most appropriate strategy to actively control the position of the capsule. The

legged mechanism was designed to reach 40 mm when the legs were completely expanded.

Despite the promising results achieved in this study, several challenging issues were reported. For example, these legs were powered by an on-board battery that actuated a micromotor. Therefore, power consumption limitation and space available within the capsule to house all the electronic components are the main technical drawbacks. In addition, a failure in the synchronization of the legs may cause injury to the GI tract wall since the legs could fold the tissue if they are not controlled correctly. Although this legged mechanism would be adequate to propel a capsule endoscope through any section of the GI tract, due to the legs' length limitation, it would not be suitable as an anchoring mechanism for sections of the GI tract where the average diameter is larger than 40 mm such as the stomach (Fig. 2).

In order to reduce the possible damage that legs could produce to the GI tract tissue, it was proposed in [15] to increase the number of legs in the capsule endoscope. A twelve legged mechanism was designed, implemented and tested and it was found that this mechanism not only improves the propulsion but also reduces the negative impact that one single leg can cause to the GI tract tissue. This study also suggests that when legs are opened to a diameter of approximately 30–35 mm, the capsule is able to engage the colon wall without damaging it. The improvement of minimal damage to the tissue is obtained through an increase in the number of legs. This strategy decision implied the incorporation of two micro motors that were able to actuate the sets of legs independently. Consequently, the power supply and miniaturization to embed all these electronic parts in the capsule still remain among the major challenges. Furthermore, the possible damage that those legs could cause to the tissue and the legs' length constraints need to be considered in future studies.

In another attempt to eliminate or at least minimize the legs' length limitation present in previous studies, [19] developed a mechanical anchoring system that consisted of a two legged round-shaped mechanism that could be opened as far as 71.25 mm. These legs when fully deployed possess six points of contact with the intestine wall. The rounded ends of the legs aim to minimize damage to the GI tract tissue. This approach is similar to the anchoring system proposed in [24] where the capsule deploys a four legged-like mechanism but each leg possesses a wider contact area to treat the tissue more softly. Although increasing the legs' length to 71.25 mm seems to be useful as an anchoring mechanism for more sections of the GI tract, its applicability in the stomach whose average diameter is larger than 71.25 mm would not be possible. Since these legs are powered by a battery and actuated by a micromotor, the miniaturization and power supply are still challenging and the focus of further investigation.

As can be seen, the mechanical anchoring systems, whose working principle consists of deploying legs to allow the capsule to firmly attach to the wall of the GI tract, are powered by an on-board battery that powers micromotors embedded in the capsule. From the technical perspective, it is challenging to incorporate all these electronic components in a capsule volume. In order to overcome this issue, [33] presents an analysis and optimization of the electronics required to drive the micromotor. This study reported an area reduction of about 90% for a battery and micromotors so that more actuators and mechanisms can be embedded in the endoscopic capsule to enhance its capabilities.

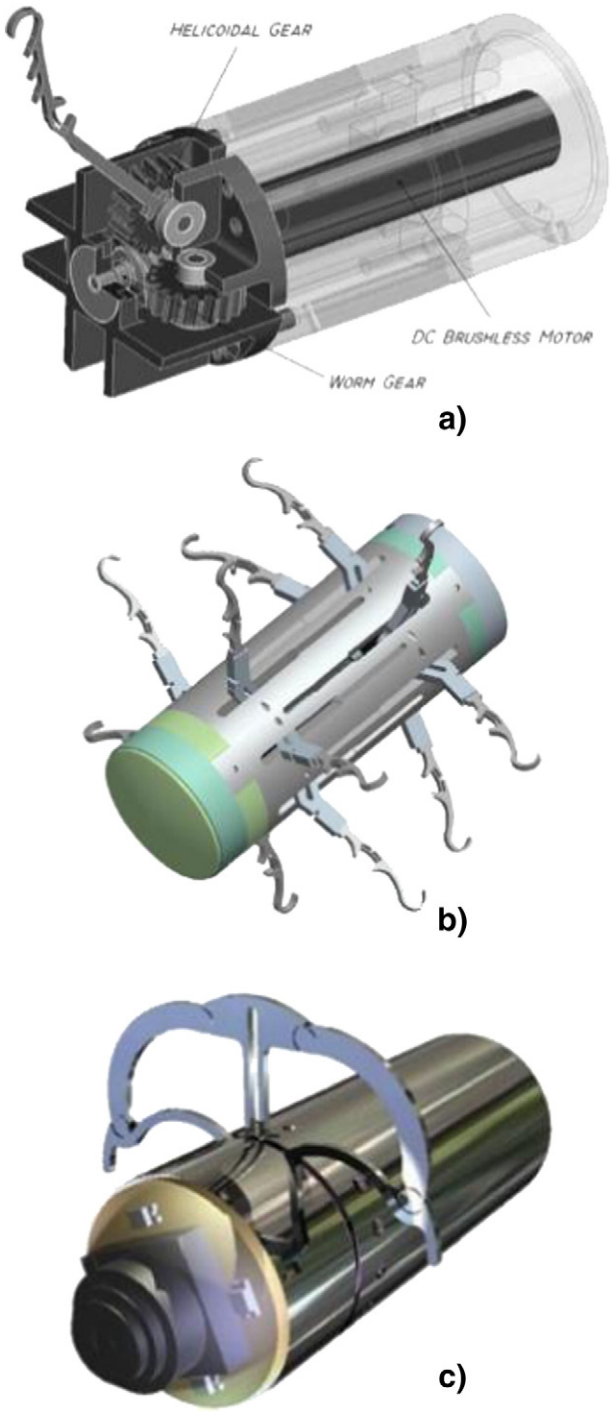

Fig. 2. Legged mechanisms, a) four legged design [30], b) twelve legged design [15] and c) two legged rounded shaped mechanism [19].

4.2. Non-mechanical systems for anchoring mechanisms

These types of anchoring mechanisms usually exploit magnetic interactions between a permanent magnet located inside the capsule and an external magnetic field that could be generated by either an electromagnet or a permanent magnet [34]. For example, in [11] a permanent magnet, 10 mm in diameter and 6 mm long, was placed in a capsule prototype. An attractive magnetic force was exerted on this magnet by an external permanent magnet that was located as far as 100 mm. It was reported that the capsule successfully can anchor on a stomach surface prototype. This proposed anchoring system could be used in practice at any section of the GI tract since the robot capsule shape is reconfigurable [48].

An attempt to use less volume of the capsule and increase the operation distance was reported in [17] with a capsule that incorporated a ring-shaped permanent magnet. This hollow magnet gives more space for additional elements to be incorporated in the capsule. The operation distance between the external permanent magnet and the magnet placed in the capsule was 120 mm. This capsule prototype demonstrated the feasibility of an effective anchoring system in the stomach but could also work at any other section of the GI tract.

The evident advantage of these non-mechanical anchoring mechanisms is the simplicity of their implementation since they do not require moving parts to be embedded in the capsule. Consequently, these systems are less susceptible to faults and use less volume in the capsule. On the other hand, its disadvantages may include the need of an adequate alignment between magnets and the dependency of the operation distance since the magnetic force is drastically affected by the separation between the magnets [40,44,45].

Finally, other studies have proposed anchoring mechanisms consisting of a combination of mechanical and non-mechanical systems. For example, [1] and [35] presented prototypes of endoscopic capsules with legs that were covered with micropillar adhesives coated with silicone oil layer. The addition of such adhesives to the legs will improve the ability of the capsule to resist peristaltic forces in the intestine. A similar concept was used in [49] to release a bioadhesive patch to enhance the anchoring capability of the robot capsule.

4.3. Mechanical systems for drug release mechanisms

In regard to the release mechanism, the following sub-categories are the most commonly implemented: passive and active drug delivery systems. A passive drug delivery system refers to a mechanism that only exposes the drug to the opened environment and relies on the fluid availability, or environmental conditions present at the target location to void the drug reservoir. On the other hand, an active delivery system refers to the ability of the capsule to expel the drug out of the reservoir once its release mechanism is remotely activated. This eliminates the dependency of the diffusion rate of the drug in the environment.

4.3.1. Passive mechanical release mechanism

In [36], it was reported that a DDS consisted of two slotted sleeves, the inner and the outer sleeves. A RF signal, generated from a distance of 10 cm, activated a resistor that heated a mechanism that allowed the rotation of the inner sleeve when a temperature of 40 °C was reached. When the inner sleeve rotated, its slots aligned with those of the outer sleeve, exposing to the GI fluid the drug contained in the inner sleeve (approx. 0.8 mL) as shown in Fig. 3.

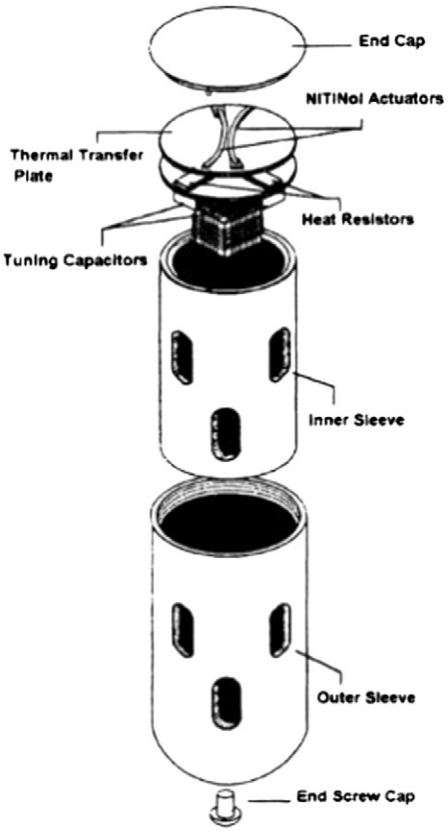

Fig. 3. DDS for capsule endoscopy [36].

The total volume of this capsule is approximately 2.75 mL since the capsule is 10 mm wide and 35 mm long. Therefore, the ratio Rdc of the volume of the drug reservoir to the total volume of the capsule is 0.29. This means that almost 71% of the total capsule volume is used to incorporate the battery, antenna, and electronic components while only 29% is used to load the drug. Some difficulties observed in this study were leakages before the DDS were activated and a slower diffusion rate in the colon probably due to the lack of fluidity and the diminished intestine motility in this segment of the GI tract.

An improved DDS was fabricated in [9] to eliminate leakages. This device consists of two main parts; the outer sleeve which has a hollow plastic cylindrical body and a removable inner cage that fits in the outer sleeve. Almost 70% of the inner cage surface is opened and liquid or powder diffusion can occur through these slots. The inner cage is spring loaded and held in compression with two shape memory alloy wire clips. Activation of the DDS is initiated by placing the capsule onto the remote antenna for 2 min. This signal deforms the wire clips and activates the spring which propels the inner cage out and away from the capsule body and the drug can be dispersed from the opened sides and bottom of the cage, as shown in Fig. 4.

The released volume was 1 mL in a capsule with total volume of 2.75 mL and the operating distance was 19 cm. The Rdc for this device is 0.36, which represents an improvement with respect to the previous device. However, one of the major drawbacks found in this system was the retention of a powder drug in the inner cage.

In the previous two passive release mechanisms, the capsules possessed on-board batteries and electronics systems to remotely actuate the DDS. However, to minimize possible faults due to all the components integrated in the capsule, [2] proposed a capsule with a total volume of approximately 0.847 mL that was made of two magnetic parts. These two parts were magnetically attracted to each other with enough magnetic force to keep the capsule closed during its travel through the GI tract. Once the capsule reached the target position, an external magnetic field was used to open the capsule and release 0.34 mL of content as presented in Fig. 5. Since magnets are part of the capsule body, this device offers more volume for the drug chamber, and its Rdc is 0.4.

Fig. 4. Spring loaded capsule releasing drug reservoir [9].

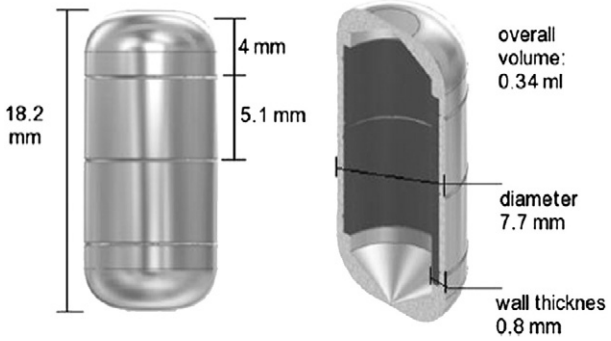

Fig. 5. Capsule made of two magnets [2].

However, one of the major drawbacks found in this system was the retention of certain forms of drug that could not be completely released at the target.

4.3.2. Active mechanical release mechanism

The aim of an active release mechanism is to have a higher control over the drug release rate, thus making the DDS less dependent on the fluid availability in the area of interest.

For this purpose, several studies have focused on different techniques to propel a piston that would push the drug out of its reservoir [32,42]. For instance, it was reported in [5] a mechanism that allowed a drug release chamber of 0.51 mL in a capsule whose maximal size is 10.2 mm in diameter and 30.0 mm in length. The release mechanism consisted of a stretchable component that was released when a signal triggered a calorific element in the capsule. This signal was generated from a maximum distance of 1 m and allowed the stretchable component to push the piston that expelled the drug out of the reservoir as shown in Fig. 6.

The total volume of the capsule is approximately 2.45 mL. Therefore, the ratio Rdc of volume of drug reservoir to total volume of capsule is 0.208. This means that almost 80% of the total volume is used to incorporate the battery, antenna, electronic components and the piston while only 20% is used to load the drug. A few disadvantages of this device include its poor reproducible release of the drug due to the usage of the stretchable component and the fact that only one dose can be released at a time.

In order to overcome these two drawbacks, [22] proposed the propulsion of the piston by the pressure of hydrogen gas generated by a small gas producing cell as shown in Fig. 7. In this study, a high frequency signal induced current in an oscillating circuit embedded in the capsule. This electrical current activated the gas producing cell that consequently moved the piston forward and emptied the drug reservoir. The results suggest that it is possible to activate the capsule on demand after intervals of some hours and get a reproducible release of the drug. The prototype

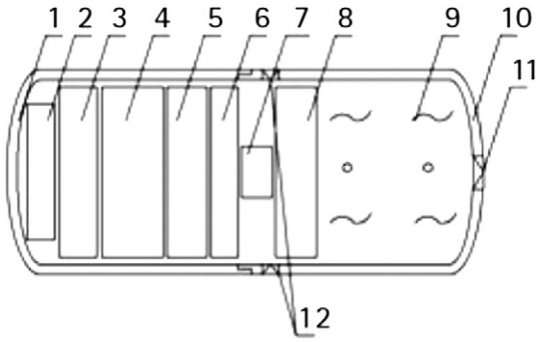

Fig. 6. Schematic diagram of the remote-controlled capsule. (1) Front crust; (2) microscale localizer; (3) energy source; (4) receiver circuit unit; (5) microelectromechanical systems driving device; (6) sealed layer; (7) driving linker; (8) piston; (9) reservoir; (10) back crust;(11) outward diffuse switch; and (12) inside diffuse switch [5].

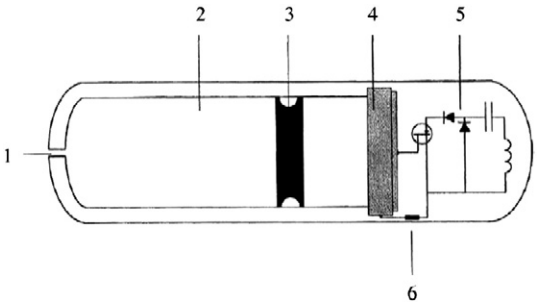

Fig. 7. Schematic diagram of a remote-controlled capsule with a gas producing cell and a high frequency receiver to control drug release. (1) Feed opening, (2) drug reservoir, (3) piston, (4) gas producing cell, (5) high frequency receiver with integrated transistor, and (6) resistor [22].

capsule has a length of about 25 mm and a diameter of 8 mm. Its total volume is 1.25 mL and the drug reservoir volume is 0.17 mL. Therefore, the Rdc is approximately 0.14. Although this device offers the advantage of multiple doses, the lack of control over its activation time makes it less attractive for scenarios where an interval of time of several hours between doses is unacceptable. Another disadvantage is that only 16% of the total volume is used to load the drug.

Space limitation within the capsule is a drawback of the previous approaches. To overcome this issue, [37] proposed a micro-thruster to push the piston rapidly. Because it is the build-up gas pressure generated by the micro-thruster and not the spring-like mechanics that acts on the piston, drug reflex is effectively eliminated. Furthermore, the drug reservoir volume is 0.7 mL in a regular capsule of 25 mm long and with 11 mm in diameter (total volume of approx. 2.3 mL). Therefore, the Rdc is 0.30, which allocates 30% of the total volume to the drug reservoir. Fig. 8 shows the internal parts of this device. One of the disadvantages of this proposed system is that only one dose can be released.

The most significant disadvantages of DDS reported in [5,22,37] is that there is no anchoring mechanism. There is no guarantee of holding the capsule at a specific location while activating the release mechanism. The capsule will move forward upon the activation of the drug release mechanism and pose a significant safety problem.

The above studies have reported different techniques to push a piston that releases the drug from the capsule reservoir. Some of these approaches are more efficient in optimizing the volume of the capsule. However, none of them possesses an Rdc higher than 0.40 and only one dose can be released in a short period of time for practical purposes. The controllability of the number of doses and release rate were enhanced in [11,31], through the usage of magnetic interactions between internal on-board permanent magnets (IPM) and an external permanent magnet EPM as shown in Fig. 9.

When the EPM moves closer to the capsule, the drug chamber is squeezed and the drug is released. When the EPM moves away from the capsule, the restoring force Fres allows the capsule to go back to its previous uncompressed state in which no drug is released. This

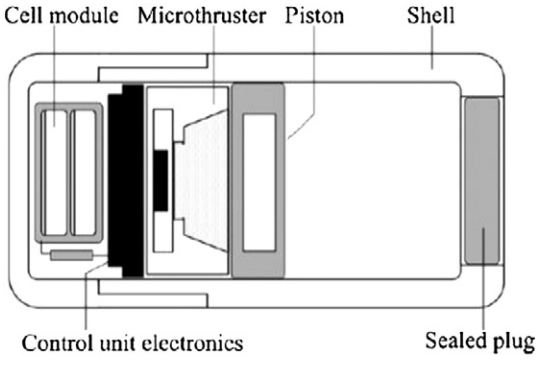

Fig. 8. Micro-thruster release mechanism [37].

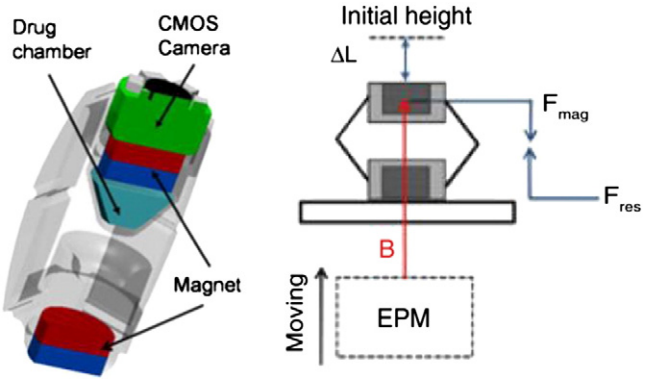

Fig. 9. Capsule with two IPMs and one EPM [11].

process can be repeated until the chamber is fully emptied. This proposed system has a drug chamber volume of 0.17 mL and the total volume of the capsule is 2.3 mL. Therefore, the Rdc is 0.07. The advantage of this system is its ability to release multiple doses and a better control of the drug release rate. Despite the feasibility of this system, further miniaturization is required to increase the volume of the drug chamber. In addition, this DDS operates at a maximum distance of 100 mm between EPM and IPMs. Thus a careful alignment between magnets is required to obtain a repeatable drug release mechanism.

A similar magnetic mechanism was employed in [4] to achieve on-demand concentrations of drugs since controlling the number of doses and release rate would decrease fluctuations in plasma concentration and lower the potential for toxicity. In this study, a thin magnetic membrane was constantly deflected by an external magnetic field. Although this DDS was not designed for capsule endoscopy, its working principle may be applicable to endoscopic capsules.

As it was presented, the development of an active drug release mechanism implied different strategies to supply power to the actuators. When batteries were embedded in the capsule, it reduced the effective volume to be used by the drug reservoir. With the purpose of increasing both the drug reservoir volume and the availability of power in the capsule, a variety of magnetic systems have been proposed [4,11,31], but also wireless power transmission systems have been intensively investigated [38,39]. Despite the advancements in this area, it still remains difficult to effectively transmit the required power to actuate all the mechanisms in a capsule endoscope. One of the major issues to overcome is the safety of the live tissues since the human body may absorb part of the power transmitted.

4.4. Non-mechanical systems for drug release mechanisms

Similar to the sub-classification of mechanical release mechanisms, the non-mechanical drug release mechanisms could be divided into two categories: passive and active drug delivery systems.

Passive release mechanisms consist mainly of chemical interactions that are triggered in response to certain conditions of the environment, such as the temperature and pH [7]. In these systems, the manipulation of physicochemical property of compounds is performed to increase intestinal concentration of drugs. This strategy has shown promising results for colon targeting as reported in [41]. However, it remains difficult with these systems to control variables, such as the release rate, target location, number of doses and exact amount of drug released, since the properties of the GI tract can vary greatly among the patients [43].

In contrast to a passive release mechanism, the active one is characterized by micropump systems where non-mechanical energy such as magneto-hydrodynamic energy is transformed into kinetic energy. This energy transformation process drives the liquid drug out of the reservoir. The advantage of this approach is that it creates a bigger volume for the drug reservoir but its disadvantage is that the motion of the fluid sample depends on the drug's physicochemical properties [29].

Table 1 compares the different studies reviewed in this work. As shown in Table 1, the dosage form in all the studies varies from liquid to powder compounds. In order to make the DDS less dependent on the dosage form, it would be of great benefit to fabricate a robot capsule platform with the capability of releasing a wide variety of drug compounds (e.g. drugs with different solubility, viscosity, in liquid, solid and/or gas form) by making little or no modifications to such platform. For instance, hemostatic agents in powder form were released in [51,52] to achieve hemostasis in the GI tract, while in [53] the cargo released consisted of micro-grippers to achieve biopsy in the stomach. This latter study slightly modified the MASCE platform proposed in [11] to release the micro-grippers and to determine its location in order to estimate the 3D geometrical model [54]. Furthermore, a capsule endoscope generated gas to provide insufflation to the intestine. The gas was produced when liquids and powders were mixed inside the capsule [55].

It can also be seen, that only one study incorporated the anchoring and the release mechanisms in a capsule prototype and two studies reported higher controllability over the release rate, amount and number

Table 1
A comparison of the key mechanisms for DDS in capsule endoscopy.

Article	Includes anchoring mechanism	Mechanical release mechanism	Controllable release rate	Controllable release amount	Drug reservoir volume	Controllable number of doses	Operating distance	Powered by	Rdc	Sample of drug released
[15,24,30,33]	Yes	NA	NA	NA	NA	NA	NA	Battery	NA	NA
[19]	Yes	Active	–	–	1 mL	–	–	Battery	0.33	Liquid
[11]	Yes	Active	Yes	Yes	0.174 mL	Yes	100 mm	Magnetic field	0.07	Mucoadhesive polymer
[17]	Yes	NA	NA	NA	NA	NA	120 mm	Magnetic field	NA	NA
[1,35]	Yes	NA	NA	NA	NA	NA	NA	Battery	NA	NA
[36]	No	Passive	NA	NA	0.8 mL	No	100 mm	Battery	0.29	Solution of ranitidine hydrochloride
[9]	No	Passive	NA	NA	1 mL	No	190 mm	Battery	0.36	Mucoadhesive polymer
[2]	No	Passive	NA	NA	0.847 mL	No	–	Battery	0.4	Acetylsalicylic powder
[5]	No	Active	No	No	0.51 mL	No	1000 mm	Battery	0.21	Aminophylline
[22]	No	Active	No	No	0.17 mL	No	–	Battery	0.14	Solution of oxprenolol hydrochloride
[37]	No	Active	No	No	0.7 mL	No	–	Battery	0.3	Aminophylline
[42]	No	Active	Yes	Yes	0.3 mL	Yes	–	Battery	0.1	Solution of 99 m technetium-pertechnetate

– indicates that the information is unavailable.

of doses. Most of the studies have focused on either the anchoring system or on the release mechanism. The reported findings meet specific requirements of a particular region of interest in the GI tract.

5. Conclusions and future work

The GI tract represents a challenging environment for the development of an effective anchoring and drug release mechanism. In order to successfully implement a wireless DDS for capsule endoscopy, several factors need to be considered. All these factors were discussed in this work and included an overview of the physiological and mechanical properties of the GI tract, pharmaceutical requirements such as release rate, amount of drug, dosage form, number of doses and also size constraints imposed on the capsule along with the technical requirements.

An important number of studies have attempted to implement capsule prototypes that were able to anchor in tubular sections and in more opened regions such as the stomach. One of the main advantages in legged-like mechanisms is that due to the on-board battery and micro motors housed in the capsule, the anchoring mechanism can be remotely activated at an adequate distance without severely compromising its functionality. On the other hand, the main advantage of a magnetic actuation system is its more straightforward implementation which makes it less susceptible to electronic faults that can be caused by malfunctions of on-board actuators and power exhaustion [48].

Despite the promising results reported in these studies, further investigation needs to be conducted to miniaturize electronic elements and mechanical parts that are incorporated in the capsule body.

The reviewed studies do not provide data regarding the capability of the proposed capsule endoscopes to release different dosage forms. Thus, it is not possible in this paper to complete a more detailed analysis to assess this functionality. Further studies need to be conducted to evaluate the performance of available capsule endoscopes when the dosage form is changed. In addition, materials to fabricate the drug reservoir and the storing modality to preserve the drug effectiveness are not clearly reported in the literature reviewed in this paper, and therefore it is worthy of consideration in future work.

Among all the studies presented in this paper, the results shown in Table 1 suggest that [11] is one of the most complete studies that incorporated both the anchoring and the release mechanism. In addition, it is one of the two studies that report the functionality of releasing multiple doses and allows a higher control over the release rate and amount, which are the parameters that should be controlled in a functional and versatile DDS. Although the study reported in [11] fulfils more closely the requirements for a DDS set in this paper, its lowest Rdc ratio suggests that additional optimization of the space in the capsule is required to increase the volume of the drug reservoir. Furthermore, one of the most challenging issues to overcome with magnetic systems such as the one used in [11] is the complex interaction between an external permanent magnet and the magnets located in the capsule. This is especially relevant when the magnets are not properly aligned or are far away from each other. These are also the research issues to be addressed in future work.

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