State-of-the-Art and Future Perspectives in Ingestible Remotely Controlled Smart Capsules for Drug Delivery: A GENEGUT Review

Sophia V. Hoffmann , Joseph P. O'Shea , Paul Galvin , Vincent Jannin , Brendan T. Griffin

PII: S0928-0987(24)00224-0
DOI: https://doi.org/10.1016/j.ejps.2024.106911
Reference: PHASCI 106911

To appear in: *European Journal of Pharmaceutical Sciences*

Received date: 5 July 2024
Revised date: 6 September 2024
Accepted date: 14 September 2024

Please cite this article as: Sophia V. Hoffmann , Joseph P. O'Shea , Paul Galvin , Vincent Jannin , Brendan T. Griffin , State-of-the-Art and Future Perspectives in Ingestible Remotely Controlled Smart Capsules for Drug Delivery: A GENEGUT Review, *European Journal of Pharmaceutical Sciences* (2024), doi: https://doi.org/10.1016/j.ejps.2024.106911

State-of-the-Art and Future Perspectives in Ingestible Remotely Controlled Smart Capsules for Drug Delivery: A GENEGUT Review

Authors: Sophia V. Hoffmann [a], Joseph P. O'Shea [a], Paul Galvin [b], Vincent Jannin [c], Brendan T. Griffin [a,*]

[a] School of Pharmacy, University College Cork, College Road, Cork, Ireland

[b] Tyndall National Institute, University College Cork, T12R5CP Cork, Ireland

[c] Capsugel France SAS, 68000 Colmar, France

[*] Correspondence: brendan.griffin@ucc.ie

Abstract

An emerging concern globally, particularly in developed countries, is the rising prevalence of Inflammatory Bowel Diseases (IBDs), such as Crohn's disease. Oral delivery technologies that can release the active therapeutic cargo specifically at selected sites of inflammation offer great promise to maximise treatment outcomes and minimise off-target effects. Therapeutic strategies for IBD have expanded in recent years, with an increasing focus on biologic and nucleic acid-based therapies. Reliable site-specific delivery in the gastrointestinal (GI) tract is particularly crucial for these therapeutics to ensure sufficient concentrations in the targeted cells. Ingestible smart capsules hold great potential for precise drug delivery. Despite previous unsuccessful endeavours to commercialise drug delivery smart capsules, the current rise in demand and recent advancements in component development, manufacturing, and miniaturisation have reignited interest in ingestible devices. Consequently, this review analyses the advancements in various mechanical and electrical components associated with ingestible smart drug delivery capsules. These components include modules for device localisation, actuation and retention within the GI tract, signal transmission, drug release, power supply, and payload storage. Challenges and constraints associated with previous capsule design functionality are presented, followed by a critical outlook on future design considerations to ensure efficient and reliable site-specific delivery for the local treatment of GI disorders.

Contents

1. Introduction 2

2. State-of-the-Art Smart Capsules 4

3. Design Considerations Smart Drug Delivery Capsules 5

3.1. Consideration for Localisation 6

3.1.1. Mechanical Rotation 6

3.1.2. Sensing of GI Parameters 6

3.1.3. Imaging Methods 7

3.2. Technology for Locomotion 8

3.2.1 Built-In Locomotion Mechanisms 8

3.2.2 Magnetically Controlled Locomotion Mechanisms 9

3.3. Technology for Capsule Retention in a Specific GI Compartment 10

3.4. Strategies for Signal Transmission for Remote Control 11

3.5. Considerations for Drug Release Mechanisms 12
3.5.1. Passive Release Devices 12
3.5.2. Active Release Devices 13
3.6. Considerations for the Power Supply 15
3.7. Considerations for the Drug Reservoir 16
3.8. Balancing Design Criteria with Capsule Size 16
4. Conclusion and Future Directions 17

Abbreviations: GI, gastrointestinal; PEDOT:PSS, poly(3,4-ethylenedioxythiophene) polystyrene sulphonate; RF, radiofrequency; EPM, external permanent magnet; EEM, external electromagnet; IPM, internal permanent magnet; CMOS, complementary metal-oxide semiconductor; HF, high frequency; IPMC, ionic polymer-metal composite; SMA, shape memory alloy; PRM, planetary reducer motor; PDMS, polydimethylsiloxane; mHBC, magnetically-coupled human body communications; PU, polyurethane; GRAS, generally recognized as safe; N/A, not applicable; N.I., no information; anti-TNF, anti-tumour necrosis factor

Keywords: site-specific, drug delivery, remote, smart capsule, inflammatory bowel disease

1. Introduction

Inflammatory Bowel Diseases (IBDs) are chronic inflammatory conditions of the gastrointestinal (GI) tract that occur in a recurring and remitting pattern (Baldan-Martin et al., 2023). It is estimated that approximately 2.5–3 million individuals in Europe were affected by IBDs in 2022 (Kumar et al., 2023). More specifically, Crohn's disease has an incidence rate in Western Europe, estimated to be between 1.85 and 10.5 cases per 100,000 person-years (Kumar et al., 2023; Ng et al., 2017). Hence, IBDs impose a substantial financial burden on the healthcare system, with an average cost of 2'609€ per patient-year (Burisch et al., 2020; Kumar et al., 2023). Current IBD therapeutics can be classified into two main categories: non-biologic and biologic. The initial treatment phase typically involves an induction therapy with oral or systemic corticosteroids, such as budesonide, or biologics to achieve remission of the inflammatory process (Roda et al., 2020). Corticosteroids are not recommended for maintenance therapy due to the potential for adverse effects, such as hypertension, associated with prolonged exposure (Torres et al., 2017). The subsequent maintenance phase may employ a range of immunosuppressant therapies, including non-biologic agents like methotrexate or azathioprine, or biologics such as anti-tumour necrosis factor (anti-TNF) therapies (infliximab, adalimumab, and certolizumab pegol) or ustekinumab, or a combination of these (Roda et al., 2020). Moreover, it is anticipated that therapies based on orally administered nucleic acids will offer a promising avenue for the treatment of IBD in the future.

Anti-TNF therapies are the primary treatment option for high-risk patients due to their high potency, substantial clinical experience, and low incidence of adverse events (Roda et al., 2020; Torres et al., 2017). However, it has been observed that approximately one-third of Crohn's disease patients treated with TNF-α inhibitors demonstrate non-adherence (Fidder et al., 2013), which may be associated with the invasive method of administration. Despite the availability of these therapeutic options, IBD has a significant impact on a patient's social, educational, professional and familial life. This is due to a number of factors, including the symptoms of the disease itself, such as abdominal discomfort, diarrhoea and weight loss, as well as the frequently associated immunosuppressive therapy, hospitalisation and surgery (Roda et al., 2020). Up to 50% of patients with Crohn's disease require bowel resection within 10 years of diagnosis due to complications associated with the disease (Roda et al., 2020).

In IBD, inflammation may occur in different regions of the GI tract, with the terminal ileum and colon being the most commonly affected areas (Torres et al., 2017). A key approach to improve IBD therapy is therefore the implementation of site-specific drug release at disease locations in the GI tract. The overall exposure of the drug to the systemic circulation can be decreased, while concurrently enhancing its concentration at the desired target site. Thereby, therapeutic efficacy of the treatment can be optimised, while mitigating any potential negative effects. The renewed scientific interest in RNA therapy in recent years (Kim, 2022) has contributed to the demand for site-specific delivery. Particularly for orally administered nucleic acid-based therapies achieving a substantial concentration at the intended site of action is crucial, as the accessibility to the afflicted cells is limited (Hua, 2020; O'Driscoll et al., 2019). Consequently, site-specific drug delivery in the GI tract has become a major objective for the treatment of intestinal diseases. Numerous methodologies have been previously explored in the field of site-specific administration, encompassing prodrugs as well as conventional coatings that rely on factors such as pH alterations, transit time, microbiota, and various combinations thereof (see Tab. 1) (Varum et al., 2020a, 2020b; Yadav et al., 2022). One significant concern of these traditional approaches pertains to the intra- and inter-individual variations in terms of physiological parameters which have resulted in insufficient release from drug delivery systems in previous studies (Ibekwe et al., 2006; Yu et al., 2017). Moreover, it is important to acknowledge that particularly IBD patients, may exhibit deviations from the composition and properties of GI fluids when compared to those of healthy individuals that have the potential to influence the efficacy of drug delivery systems. The potential modifications encompass changes in the pH of the chyme, the size of the accessible bile acid pool, and the composition of the microbiome. These changes are largely dependent on the severity of inflammation (Chikina and Matic Vignjevic, 2021; Effinger et al., 2020; Guo et al., 2022; Roda et al., 2020).

Ingestible smart drug delivery capsules are specialised devices designed to release drugs at precise areas throughout the GI tract in response to some form of localisation, using an interactive controller and a wireless signal transmission. Smart drug delivery capsules provide a convincing alternative to traditional coating-based techniques with regard to site-specific drug delivery as they enable the user to have precise control over the point of drug release, thereby offering a potential avenue for the advancement of localised IBD precision therapy. These devices comprise, at a fundamental level, a drug reservoir, a mechanism for the release of the payload and a system for triggering this release from a position external to the body. Additionally, they may require the incorporation of a power source, most frequently a battery. Further possibilities exist with regard to mechanisms for precise capsule localisation in the GI tract or for device retention in a specific region. Moreover, strategies have been developed for the active actuation of devices within the GI tract, targeting specific regions through the use of magnetic or protrusion techniques. Since the introduction of the first smart capsule with a drug delivery function in 1961 (Eriksen et al., 1961), advancements in technology have greatly expanded the

possibilities in this field. Previously developed smart capsules were mostly constrained by physical size (Wilding et al., 2000). Moreover, the delivery of particulate formulations and the release in the colon has been challenging (Wilding et al., 2000). Despite decades of technological advances in smart drug delivery capsules, with limited commercial success, the current rise in demand for site-specific delivery and recent progress in manufacturing and miniaturisation of electrical and mechanical components make smart drug delivery capsules more relevant than ever. The increasing quantity of literature on smart capsules in the past ten years demonstrates their considerable potential (Litvinova et al., 2023). This review, therefore, aims to provide a brief overview of the current advancements in technology for smart diagnostic capsules as well as a comprehensive analysis of various design approaches for the electrical and mechanical components that could be integrated in novel smart drug delivery capsules.

2. State-of-the-Art Smart Capsules

Smart capsules are ingestible monolithic devices that pass through the GI tract for diagnostic or therapeutic purposes and allow interaction with the user (Cummins, 2021). Depending on the application, smart capsules can be equipped with different functionalities such as sensing, imaging, sampling or drug delivery (see Fig. 1). In contrast to drug delivery devices, smart capsules for sampling, sensing and imaging were developed primarily for diagnostic purposes. Although previous reviews on diagnostic smart capsules give a good overview of smart capsules (Cummins, 2021; Rehan et al., 2023; Weitschies et al., 2021), some recent developments need to be discussed.

Sampling is a diagnostic function of smart capsules that has received a lot of attention recently. After being described in 1963, GI sampling devices were mainly used for the diagnosis of various diseases or to gain information on chyme and microbiota composition (Azehaf et al., 2023; Nejati et al., 2022a; Shiner, 1963; Spanogiannopoulos et al., 2016; Weitschies et al., 2021; Yadav et al., 2022). The sampling of GI content is particularly important in the context of IBD, as IBD pathogenesis has been shown to be linked to microbiota alterations (de Alencar Junior et al., 2020; Guo et al., 2022; Lee and Chang, 2021; Lopez et al., 2014; Tojo et al., 2014). Recently a novel smart capsule measuring 26 mm in length and 11 mm in diameter was created to extract 45 µL of GI fluid into three chambers (Park et al., 2022). The capsule body could be rotated by an external magnetic field acting on the built-in magnet. As a result, the input aperture of one of the three microchannels was exposed to intestinal fluid. The movement of an impeller facilitated the creation of a pressure gradient between the interior and exterior of the capsule, therefore enabling the aspiration of intestinal fluid. Shalon et al. introduced sampling capsules with dimensions of 23 mm in length and 6.5 mm in diameter (Shalon et al., 2023). These capsules featured a deflated collection bladder that were securely sealed using a one-way valve and were protected by different enteric coatings based on pH and time. After the disintegration of the coating, the bladder experienced a process of unfolding and expansion, leading to the aspiration of up to 400 µL of intestinal fluid through the one-way valve. A similar technique involved a variety of pH-sensitive enteric polymer coatings and a superabsorbent hydrogel to facilitate the collection of intestinal fluid samples (Nejati et al., 2022a, 2022b).

Diagnostic smart capsules with sensing functionalities can be mainly categorised into pH, temperature, pressure and enzyme activity sensors. Capsules dedicated to pH sensing were originally developed for GI motility assessment and pH monitoring (Cummins, 2021; Kwiatek and Pandolfino, 2008; "Medtronic - SmartPill® motility capsule," n.d.; Saad and Hasler, 2011; Tran et al., 2012). These capsules may be employed to investigate disease-dependent alterations in GI pH. For instance, changes in gastric pH levels have been previously described in IBD patients (Effinger et al., 2019). Important examples of this group of diagnostic smart

capsules are the Heidelberg, SmartPill® and Bravo™ capsule (Cummins, 2021; Dressmann and Amidon, 1984; Farmer et al., 2013; Henze et al., 2021; Koziolek et al., 2019; Kwiatek and Pandolfino, 2008; Lui et al., 1986; "Medtronic - SmartPill® motility capsule," n.d.; Mojaverian, 1996; Mojaverian et al., 1991, 1985; Steinberg et al., 1965). These devices have been extensively reviewed before (Cummins, 2021; "Medtronic - SmartPill® motility capsule," n.d.). A recent achievement within this field was the introduction of a novel pH sensor capsule with dimensions of 29 mm in length and 8.5 mm in diameter, designed specifically for monitoring pH levels in both the small and large intestine using a cost-effective ion-sensitive polyaniline-based thread (Asci et al., 2022). The capsule design was aimed at minimising the difficulties associated with the manufacturing process. The sensitivity obtained in the study was -40.0 mV/pH within the pH range of 4-8. Smart capsules that comprise temperature sensors were originally developed to determine anomalies in body temperature, e.g. during physical activity ("BodyCAP, E-Celsius® medical," n.d.; "BodyCAP, E-Celsius® performance," n.d.). However, several biopharmaceutical studies have also used a drop in temperature after ingestion of cold water to detect gastric emptying (Koziolek et al., 2015a; Söderlind et al., 2015). Examples of previously reviewed temperature sensing smart capsules are the SmartPill®, CorTemp®, or e-Celsius® (Bogerd et al., 2018; Bongers et al., 2018; "HQ inc., CorTemp® capsule," n.d.; "Medtronic - SmartPill® motility capsule," n.d.; Koziolek et al., 2015b; Saad and Hasler, 2011; Travers et al., 2016). A relevant advancement in temperature sensors is the development of an ultra-small (0.88 mm x 0.88 mm) sensor (Zhang et al., 2017). The resulting ingestible capsule demonstrated a high level of accuracy, with a temperature measurement precision of 0.05 °C within the range of 20 to 42 °C. Diagnostic smart capsules including a pressure sensing functionality, like the SmartPill®, have previously been reviewed and have been employed for motility studies (Cummins, 2021; "Medtronic - SmartPill® motility capsule," n.d.; Rehan et al., 2023; Saad and Hasler, 2011; Tran et al., 2012). Recently, a novel approach to achieve autonomous navigation for smart capsules was proposed based on pressure sensing (Alsunaydih et al., 2020). The method involved the integration of sensors placed in a spherical configuration, which enabled the measurement of pressure between the device and GI structures. A novel type of smart diagnostic capsule was described by Banis et al. with a device designed to assess pancreatic lipase activity in the small intestine (Banis et al., 2019a). The capsule, with dimensions of 35.0 mm in length and 12.5 mm in diameter, was equipped with an enteric coating that underwent pH-dependent dissolution in the duodenum. Electrodes coated with triglycerides were utilised for capacitance-based measurement of fluid dielectric properties. These triglycerides experienced disintegration upon interaction with pancreatic lipase, as a result of the hydrolysis of ester bonds within the triglyceride molecules.

Smart capsules for imaging have recently been thoroughly reviewed (Cummins, 2021; Weitschies et al., 2021). Tab. 2 presents an overview of currently available endoscopic capsules including different PillCam™ and MiroCam® models, ENDOCAPSULE 10, OMOM® HD, and CapsoCam Plus®. These endoscopy capsules are primarily utilized for diagnostic purposes, such as the assessment of GI inflammation in IBD (Hanscom et al., 2022).

3. Design Considerations Smart Drug Delivery Capsules

Smart drug delivery capsules are ingestible monolithic drug delivery systems that allow the user to interact with the device and can thus be activated remotely by electromechanical, magnetic, or thermal means (Cummins, 2021). The device is activated once the capsule has reached the intended site in the GI tract, which is determined through various techniques such as sensing and external imaging. Previous reviews have examined smart drug delivery capsules such as the IntelliCap® or InteliSite® capsules (Cummins, 2021; Vllasaliu and Thanou, 2022). However, recent advancements in miniaturisation, technology, and features have greatly

expanded design possibilities for smart drug delivery capsules. To thoroughly explore the future potential of these devices, this review presents a schematic overview of the main components and provides a critical summary of the design considerations. The majority of smart capsules designed for drug delivery include a drug reservoir that can be emptied by an associated mechanism, electrical circuits, a transceiver, a module for locating the capsule within the GI tract, a power supply, and possibly a module for active locomotion as schematically depicted in Fig. 2.

3.1. Consideration for Localisation

The targeted delivery of drug payloads to specific sites poses a significant obstacle. In order to enable targeted delivery to specific sites, it is important to ascertain the location of the smart capsule within the GI tract can be precisely determined at any given time. In general there are four approaches for localisation: mechanical rotation, sensing, or indirect or direct imaging. The advantages, limitations, and prior applications of various techniques to smart capsule localisation in the GI tract are summarised in Tab. 3.

3.1.1. Mechanical Strategies

A cost-effective strategy for capsule localisation was employed in the Smith Kline French Cylinder. Eriksen at al. administered a segment of Dacron sewing thread to canines, measuring the length of the thread to ascertain the distance between the capsule and the oral cavity (Eriksen et al., 1961). Similarly, in the Bioperm® device, which allows for local administration of drug solutions or suspensions in the intestinal tract, an ingested radio-opaque plastic capsule (length 30 mm, diameter 10 mm) is affixed to a nasal tube, thereby facilitating precise localisation (Dahlgren et al., 2016; Hofmann et al., 2019).

Lambert et al. developed a capsule that employed a plastic cogwheel (10 mm x 1 mm) as a location detector (Lambert et al., 1991). Each rotation of the wheel caused a corresponding change in the gauge resistance on a flexible lamella with an increase observed during clockwise and a decrease observed during anti-clockwise rotation. These changes in movement on transition through the intestine were transmitted to a receiver via a radio transmitter. This approach displayed numerous limitations due to its doubtful accuracy and restricted applicability to the narrow diameter of the small intestine. Furthermore, the significant size of the device of 39 mm x 11 mm caused it to be retained in the stomach.

3.1.2. Sensing of GI Parameters

A number of studies have used pH and temperature sensors to determine the location of smart drug delivery capsules as the GI fluid changes during transit through the pylorus and ileocecal valve (Maurer et al., 2015; Söderlind et al., 2015; Van Der Schaar et al., 2013; Van der Schaar et al., 2011). Maurer et al. defined ingestion as a quick and persistent rise in temperature to body temperature as well as prompt decline in pH by more than three units, indicative of the capsule's entry into the stomach (Maurer et al., 2015). According to Van der Schaar et al., esophagogastric passage is characterised as a rapid and prolonged drop in pH quickly after oral delivery (Van Der Schaar et al., 2013). Other researchers characterised the pyloric passage as a rapid increase to pH 6 lasting more than 6 minutes, whereas Maurer et al. classified it as a prolonged increase in pH of more than 3 pH units (Maurer et al., 2015; Söderlind et al., 2015; Van Der Schaar et al., 2013). Furthermore, in some trials, a little amount of water was administered, and the absence of a change in temperature was considered to demonstrate capsule transit into the intestine (Maurer et al., 2015; Söderlind et al., 2015). Van der Schaar et al. defined ileocecal valve passage as a sustained decrease in pH of > 0.5 to 2 units within 2 to 5 minutes and at least 30 minutes after pyloric passage, whereas Maurer et al. defined it as a rapid and sustained

drop in pH of > 0.8 pH units at least 1 hour after entry into the intestine to a pH of 6.5 (Maurer et al., 2015; Van Der Schaar et al., 2013). A quick and persistent drop in temperature from body to room temperature verified capsule excretion (Maurer et al., 2015; Van Der Schaar et al., 2013). Identifying the capsule's location based solely on pH can be deceptive because pH values in the human digestive tract are highly dynamic, influenced by the consumption of liquids and meals, and can be altered by various diseases, including IBD (Effinger et al., 2019; Koziolek et al., 2015c; Weitschies et al., 2021). The pH in the large intestine is variable, due to colonisation with various microbes (Koziolek et al., 2015b; Weitschies et al., 2021). Although the decrease in pH in the ileocecal region generally occurs in the first section of the colon in healthy people, the precise site of the pH drop varies among individuals (Zarate et al., 2010). Furthermore, the orientation of the capsule with respect to the mucosa or luminal contents can affect the observed pH (Weitschies et al., 2021).

Despite the potential of pressure sensing to determine the localisation of smart drug delivery capsules, there is currently no known example of this technology being exploited. However, it has been employed in the context of motility studies in diagnostic smart capsules (Cummins, 2021; Saad and Hasler, 2011; Tran et al., 2012). The SmartPill® (Medtronic plc, Minneapolis, USA) was the first U.S. Food and Drug Administration-approved smart capsule with a pressure sensor. The device was based on high-resolution manometry and was able to measure intraluminal pressure. The pressure measurement was accurate to ± 5 mmHg below 100 mmHg. Measurements between 0 and 350 mmHg were feasible with a resolution of 10 mmHg (Cummins, 2021; Farmer et al., 2013; Saad and Hasler, 2011; Tran et al., 2012). Li et al. developed a capsule were able to measure both intraluminal and contractile pressure in vivo in pigs using two orthogonally aligned pressure sensors with a resolution of 0.027 mmHg (Li et al., 2017, 2015). The device by Benken and Gianchandani demonstrated a pressure response of -0.6 kHz/mmHg, an interrogation distance of up to 6 cm, and a resolution of up to 0.8 mmHg (Benken and Gianchandani, 2019). Liao et al. introduced a capsule designed for the detection and monitoring of intraabdominal hypertension that demonstrated the capacity to measure pressure within a range of -100 to 100 mmHg (at 1 atm) with an accuracy of ± 0.75 mmHg. The collected data was transmitted via Bluetooth Low Energy (BLE) 5.1 protocol at a frequency of 10 seconds (Liao et al., 2021). Overall, while there is potential for pressure-sensing functionality to provide insights into the mechanistic processes experienced by devices within the GI tract, the intra- and inter-individual variability in pressure patterns limits this approach and makes it challenging to precisely localise a smart drug delivery capsule. The use of a combination of different sensing strategies may help to mitigate the risk of misinterpretation of individual parameters and improve the localisation accuracy of the smart capsule.

3.1.3. Imaging Methods

Numerous studies employed indirect imaging techniques, such as X-ray and gamma scintigraphy, to determine the precise location of smart drug delivery capsules (Clear et al., 2001; Eriksen et al., 1961; Harder et al., 1990; Mc Caffrey et al., 2008; McGirr et al., 2009; Parasrampuria et al., 2015; Parr et al., 1999; Pithavala et al., 1998; Staib et al., 1989, 1986; Wilding et al., 2000). In the context of gamma scintigraphy, the tested formulation was supplemented with radioactive markers, either technetium-99m or indium-111, either directly incorporated into the formulation or placed in a specifically designed compartment within the smart capsule (Clear et al., 2001; Mc Caffrey et al., 2008; McGirr et al., 2009; Parasrampuria et al., 2015; Parr et al., 1999; Pithavala et al., 1998; Wilding et al., 2000). Currently, there are unexplored possibilities for reducing radiation exposure in smart drug delivery capsules, such as the utilisation of magnetic marker monitoring or magnetic resonance imaging (Senekowitsch et al., 2022). The advantages and disadvantages are presented in Tab. 3. Another approach that can be considered is the utilisation of direct imaging techniques, such as conventional push endoscopy or

capsule endoscopes. In the conventional technique of endoscopy, a long and flexible tube equipped with a video camera is introduced into the patient's mouth or rectum (Mehedi et al., 2023). Capsule endoscopes represent a minimally invasive option, offering a wide range of imaging capsules readily available nowadays (Ciuti et al., 2011; Hanscom et al., 2022; Kim and Chun, 2021; Mehedi et al., 2023; Nam et al., 2018; Park et al., 2018; Senekowitsch et al., 2022). When comparing to conventional endoscopy, this approach provides many benefits such as enhanced patient comfort, elimination of sedation requirements, and reduced interference with biopharmaceutical processes (Ciuti et al., 2011). In a study conducted by Blaabjerg et al., it was demonstrated that beagle dogs had a high level of tolerance towards capsule endoscopes, which proved to be an effective instrument for monitoring the process of tablet dissolution (Blaabjerg et al., 2020). Additionally, the study provided evidence that the introduction of the endoscopic capsule did not result in any significant changes to the pharmacokinetic characteristics.

3.2. Technology for Locomotion

To date, the majority of previously developed smart drug delivery capsules are dependent on natural peristalsis for passive transport through the GI tract. However, with the increasing development of actively agitated wireless capsules, particularly in the field of capsule endoscopy, active control of a device's movement merits consideration. Active locomotion technology would substantially expand smart capsule applications by allowing the capsule to be quickly manoeuvred to the desired part of the digestive tract and retained there if necessary.

3.2.1 Built-In Locomotion Mechanisms

Several methodologies have been previously described for integration of locomotion mechanisms into smart capsules, encompassing diverse techniques such as shape memory alloy components, clampers, or propellers. To date, drug delivery capsules have not integrated any of the aforementioned elements. However, the inclusion of these mechanisms would significantly broaden the scope of potential applications.

Karagozler et al. introduced a methodology utilising shape memory alloy, wherein a device equipped with a six-legged module anchoring to the intestinal wall to achieve controlled movement within the small intestine was designed (Ciuti et al., 2011; Karagozler et al., 2006). The anchoring module applied polydimethylsiloxane micropatterned adhesives integrated at the base of each leg. In order to facilitate movement, a pair of casings were joined together by means of a piston that contained a spring. Coil-shaped wires made of shape memory alloy were attached to the ends of both casings. The shape memory alloy wire and the spring sequentially opened and closed the legs and actuated the piston which facilitated the movement of the device in a way comparable to an inchworm. Several studies have introduced comparable methodologies employing shape memory alloy systems achieving inchworm-like locomotion (Ciuti et al., 2011; Kim et al., 2005b, 2005a; Steiner et al., 2022; Wang et al., 2020; Zhao et al., 2023). Li et al. devised a spring-based mechanism to replicate the motion of cilia expansion (Ciuti et al., 2011; Li et al., 2006). This system employed two-way shape memory alloy actuators that were made up of two sets of parallel-connected shape memory alloy springs, enabling bidirectional movement capabilities. Park et al. developed an alternate device that also utilised shape memory alloy materials (Ciuti et al., 2011; Park et al., 2006). The device employed a paddling-based technique, whereby a set of legs were placed in a radial pattern and performed a sequential folding and unfolding motion.

Alternative methodologies were based upon the utilisation of electrical currents. Wu and Lu developed a remotely controlled locomotion device involving the application of three cylindrical integrated permanent

magnets and an electromagnetic coil (Wu and Lu, 2022). The precise linear motion was obtained through the pulsed presence and absence of attractive or repulsive forces between the permanent magnets and the electromagnetic coil controlled by the regulation of current amplitude or frequency. The capsule's propulsion was subsequently achieved through the force generated by the collision between the internal mass and the capsule. One benefit of this method is in the removal of cumbersome external appendages such as legs or pedals. Guo et al. designed a robotic system that mimicked the shape of a fish, utilising ionic polymer-metal composite actuators to control the movement of a body and tail fin (Ciuti et al., 2011; Guo et al., 2006). The application of an input voltage to the metal induced a significant rate of bending, resulting in the displacement of the device. Woo et al. constructed an innovative smart capsule that achieved locomotion through the application of electrical stimulation to smooth muscle, facilitated by a pair of surface-mounted electrodes (Woo et al., 2009). The contraction of the muscle cells achieved an accelerated movement of the capsule beyond the pace of natural peristalsis, thereby enabling the adjustment of the capsule's direction inside the intestinal system.

As an alternative to shape memory alloy materials, Gao et al. developed a smart imaging capsule that included both a fixed and an adjustable clamper to facilitate active navigation with a horizontal speed of 6.32 cm/min in both directions, as well as a vertical speed of 2.69 cm/min (Gao et al., 2021). Tortora et al. employed an alternate design involving four integrated propellers, which exhibited velocities of up to 7 cm/s (Carta et al., 2009; Ciuti et al., 2011; Tortora et al., 2009). Fig. 3 displays smart capsules with active internal locomotion features that have been previously described.

3.2.2 Magnetically Controlled Locomotion Mechanisms

A potential alternative strategy for achieving controlled locomotion of smart capsules with reduced spatial requirements involves the utilisation of magnetism. This approach entails the integration of a permanent magnet within the device, while an external magnetic source is positioned outside the targeted body. The key limitation of this approach is that the magnitude of the electric field produced by the permanent magnet(s) diminishes significantly as the distance from the source increases (Martel, 2015). As outlined by Lucarini et al., for the in vivo application in the colon, it is essential to consider the friction coefficient and diameter of the colon, which can range from 0.1 to 0.7 and from 30 to 60 mm, respectively (Lucarini et al., 2015). These parameters depend on the operational conditions and the distance from the abdominal wall, which is typically between 70 and 100 mm (Lucarini et al., 2015). Ciuti et al. developed an endoscopic capsule propelled by four magnetic cylinders evenly distributed at 90° intervals on the outer surface of the capsule (Ciuti et al., 2010). An optimal magnetic force of 335 mN over a distance of 150 mm was achieved. As a result, the capsule demonstrated an average spatial resolution of 3 cm, measured from its central point. Munoz et al. introduced a method for enhancing the performance of external permanent magnets in order to further mitigate the magnetic connection loss resulting from extended working distances and the downsizing of components in endoscopy capsules (Munoz et al., 2014). An increase in the maximum operating distance from 150 mm to 180 mm (with two magnets) or 240 mm (with four magnets) was achieved by employing integrated cylindrical permanent magnets that could be rotated using an array of external cylindrical permanent magnets. In recent years, numerous approaches to magnetic actuation have been presented by different research groups (Greenwood et al., 2022; Xu et al., 2022; Zhou and Alici, 2022). Xu et al. observed indications that increasing the actuating angle on straight passages could enhance actuation efficiency while maintaining the precision of localisation (Xu et al., 2022).

In general, magnetically-controlled locomotion platforms can be performed by either external electromagnets or external permanent magnets (see Fig. 4). Electromagnets possess several advantages, including the ability to rapidly turn on and off, as well as the capability to alter polarity (Kim and Zhao, 2022). Numerous publications have presented studies on the application of electromagnets to regulate the movement of smart capsules throughout the GI tract (Hoang et al., 2021; Lee et al., 2022; Rey et al., 2012; Sadeghi Boroujeni et al., 2023; Yuan et al., 2019). However, permanent magnets have been employed to a greater extent because of superior energy efficiency and ability to generate stronger magnetic fields (Kim and Zhao, 2022). Simi et al. have proposed a device that integrated both built-in remote control and magnetically-driven locomotion. The prototype capsule (44 x 14 mm, weight 13.5 g), was equipped with a three-legged actuation mechanism and a set of compact integrated permanent magnets, which could be manipulated by an external cylindrical permanent magnet. One benefit of employing a hybrid mechanism is the ability to activate the leg mechanism in instances where the capsule becomes lodged within constricted regions of the GI tract. Interference between both mechanisms may possibly occur, leading to a reduction in the motor torque required for leg locomotion. However, the finite element analysis undertaken in the study revealed that the presence of an external magnetic field had no effect on the operating efficiency of the motor when positioned at a distance of 10 cm (Simi et al., 2010). Furthermore, the use of magnetic strategies for locomotion is constrained by safety concerns in certain patient populations, such as patients with metal implants.

3.3. Technology for Capsule Retention in a Specific GI Compartment

The capacity of smart drug delivery systems to hold the capsules in a particular region of the GI tract, allowing for a longer release of the payload, could considerably expand potential applications. In the context of IBD, the retention of a drug delivery system within the inflamed GI region may facilitate prolonged drug exposure. Initial techniques for smart drug delivery capsule retention involved the utilisation of a thread to position and anchor the device at a specific distance along the intestine (Eriksen et al., 1961). However due to the intrinsic anatomical variances across individuals, this method's accuracy is restricted, making it inappropriate for frequent use in medical treatment. One potential option involves using suitable materials that exhibit mechanical or elastic deployment or shape memory effect.

The term 'mechanical or elastic deployment' refers to mechanisms that experience expansion following the removal of the mechanical constraint that initially compressed the material (Uboldi et al., 2022). Several drug delivery systems resembling films have been successfully designed as retentive devices. The mechanical strength of these objects was found to diminish during a period of 48 hours while inside the stomach due to erosion and breakdown, resulting in simple excretion (Kagan et al., 2006; Eytan A. Klausner et al., 2003a; Eytan A Klausner et al., 2003; Eytan A. Klausner et al., 2003b; Rimawi et al., 2019; Sivaneswari et al., 2017; Uboldi et al., 2022; Verma et al., 2014). In addition to expandable films, several devices employing mechanical or elastic unfolding mechanisms of diverse forms, sizes, and flexibility have been developed for the purpose of retention inside the gastric environment (Babaee et al., 2019; Bellinger et al., 2016; Cargill et al., 1988; Fix et al., 1993; Hayward et al., 2018; Kanasty et al., 2019; Kirtane et al., 2019, 2018; Kong et al., 2019; Uboldi et al., 2022; Zhang et al., 2015). Recently, Berg et al. developed a novel retentive intestinal delivery device for oral delivery of glucagon-like peptide-1 (GLP-1) receptor agonist peptide drug co-delivered with the permeation enhancer sodium caprate into the lumen of the small intestine (Berg et al., 2023). The device, which was surgically implanted in the intestine, subsequently expanded, limiting its mobility within the digestive tract and allowing the release of both the drug and permeation enhancer at a specific location in the gut. The device was loaded with immediate-release mini tablets that were placed in contact with the intestinal epithelium to

achieve unidirectional drug release. The findings from the tests conducted on Göttingen minipigs indicated that dosage forms that restrict the dilution in the intestines may be effective in reducing the variability in absorption of peptides when co-delivered with permeation enhancers. However, no substantial advantages in terms of enhancing bioavailability have been shown.

Shape memory materials offer an alternative to conventional mechanical or elastic employment systems. The alteration of the form is a result of external stimuli that are non-mechanical in nature, such as the application of heat to the material (Uboldi et al., 2022). These materials, e.g. nitinol or cross-linked polycaprolactone-based polyurethan, have been subject to investigation on the ability to remain within the gastric cavity (Inverardi et al., 2021; Kong et al., 2019; Melocchi et al., 2019; Uboldi et al., 2022).

The 'SOMA' (self-orienting millimetre-scale applicator) device, developed by MIT and Novo Nordisk was used to deliver insulin through the stomach mucosa (Abramson et al., 2019; Brayden et al., 2020). The design concept, derived from leopard tortoises, aims to accomplish rapid self-orientation in a stable upright position, while also being able to withstand external forces such as fluid flow and peristaltic motion.

3.4. Strategies for Signal Transmission for Remote Control

A key limitation of the vast majority of smart capsules developed to date is the variability in the site of release and hence the development of a dependable mechanism for remote-controlled activation is of utmost significance to advance this technology. The methods employed in previous research predominantly rely on radiofrequency or magnetism. Several techniques were employed to regulate smart capsules externally by the use of a radiofrequency pulse emitted by a high-frequency generator outside the body. These pulses were transmitted at frequencies ranging from 6.78 to 433 MHz, with the intention of activating and modulating drug delivery by inducing heat buildup, for instance in a wire (D'Andrea and Schentag, 1994; Eriksen et al., 1961; Gröning, 1997; Guo et al., 2019; McGirr et al., 2009; Pithavala et al., 1998; Staib et al., 1989). The efficacy of signal transmission in this technique is heavily contingent on the localisation of the capsule inside the GI tract, as the radiofrequency pulse is incapable of penetrating into deep parts of the intestine due to path loss with increasing distance and absorption of energy by body tissue (Lopez et al., 2014). Furthermore, significant durations of transmission are required for the thermal accumulation to take place (Wilding et al., 2000). In order to ensure the safe clinical use, it is of the utmost importance that the energy is focused on the respective material and that the application is brief to avoid hyperthermic injury of surrounding tissues (Zhu et al., 2024). This is a particular risk for patients with metal implants, which are subjected to greater heat build-up, leading to increased temperatures and possible implant failure.

The communication technique employed by the INSERM U61 Telemetric Capsule differed from conventional methods, as it utilised a permanent magnet to activate a magnetic switch from outside the body (Lambert et al., 1991; Wilding et al., 2000). Several smart capsules subsequently proposed by other groups were similarly remotely activated using a signal transmission systems based on external permanent magnets (Munoz et al., 2018, 2016; Yim et al., 2013). In the case of Munoz et al., numerous arc-shaped electromagnetic actuation systems were employed to enhance the force applied to the drug delivery mechanism (Munoz et al., 2018, 2016; Yim et al., 2013). The activation of various other smart capsules was effectively controlled by an external electromagnetic field, as opposed to the permanent magnet mechanisms (Lee et al., 2022; Mc Caffrey et al., 2008).

The IntelliCap® Capsule incorporated a wireless two-way transceiver as a modern alternative for signal transmission (Van Der Schaar et al., 2013). Prior research in several domains has established the practicability of utilising alternate wireless communication techniques, such as Bluetooth. Chu et al. presented an innovative

antenna design for facilitating wireless communication between a Bluetooth-enabled smartphone and a wireless capsule (Chu et al., 2019). The sampling and sensing smart gadget, developed by Banis et al., utilised Bluetooth technology to establish contact with an external Android phone (Banis et al., 2019b). Kong et al. introduced an innovative system specifically developed for the stomach, which integrated a wireless 2.4 GHz Bluetooth circuit board (Kong et al., 2019). These technologies have significant promise to enable remote drug delivery. Healthcare providers and researchers may have the ability to regulate drug delivery through the use of a smartphone application in future drug delivery devices.

Ultrasound is an alternative that has not yet been implemented in smart drug delivery capsules, but has been investigated for implanted medical devices (Amar et al., 2015). It has been shown to be a viable alternative to conventional transmission strategies such as radiofrequency due to the simplicity with which different operating wavelengths can be selected as well as the low attenuation in the body and the small dimensions of the receivers (Kawasaki et al., 2021; Saccher et al., 2021). So far, mainly transducers made of lead zirconate titanate have been used to convert acoustic energy into electrical energy (Amar et al., 2015; Saccher et al., 2021). However, because of toxicity, they would have to be hermetically sealed in the body, obstructing the ultrasound signal (Amar et al., 2015). Recently, pre-charged capacitive micromachined ultrasonic transducer elements have been proposed as a potential alternative to common ultrasonic receivers (Kawasaki et al., 2021). Ultrasound can be employed for both signal transmission and to power devices. The implant described by Kawasaki et al. featured a high power transfer efficiency over a wide bandwidth and was biocompatible due to its passivation with a thick Si_3N_4 layer (Kawasaki et al., 2021; Saccher et al., 2021).

3.5. Considerations for Drug Release Mechanisms

The payload release mechanism is regarded as an essential component of smart drug delivery capsules. An explicit distinction can be made between active and passive delivery mechanisms. Passive devices release the payload upon remote opening of a drug reservoir, allowing GI fluid to ingress, followed by diffusion of the payload (Cummins, 2021). Therefore, passive drug release is considered to rely on passive diffusion as the mechanism of release from the drug reservoir, whereas active delivery requires additional technology, such as pumps, to ensure that the payload is expelled from the capsule body.

3.5.1. Passive Release Devices

Various smart drug delivery capsules have been designed that implemented a passive payload release mechanism by harnessing a thermomechanical process that takes advantage of the heat generated by a radiofrequency current. The spring and plunger mechanism of the device developed by Hugemann and Schuster, commonly known as the high frequency (HF)- capsule, was activated by the melting of a nylon filament resulting in the displacement of a needle (Harder et al., 1990; Staib et al., 1989, 1986). The needle punctured a latex balloon, which served as a drug reservoir. This led to the passive release of the contents through holes in the capsule wall. In the case of the InteliSite® capsule created by Innovative Devices, a comparable mechanism was employed, comprising of an inner and outer capsule sleeve, each equipped with six apertures (Clear et al., 2001; Parr et al., 1999; Pithavala et al., 1998; Wilding et al., 2000). Shape memory alloy wires, made of nitinol, underwent a process of straightening at a temperature of 40 °C, which was achieved through the use of a radiofrequency current. The torque generated allowed the inner wall of the capsule to rotate with respect to the outer wall, thereby aligning the openings and facilitating the entry of intestinal fluid into the capsule. The passive mechanisms of both the HF- and InteliSite® capsules displayed some limitations with incomplete release in vivo, especially with particulate formulations and in the colon due to the lower fluid

volume (Wilding et al., 2000). The subsequent InteliSite® Companion Device demonstrated a significant augmentation in the exposed surface area to around 70%, while in its open form (McGirr et al., 2009). This enhancement enabled a more effective dispersion of its payload. The apparatus consisted of a pair of clips made from shape memory alloy wire, which were designed to maintain the compression of a spring. The wire clips were subjected to a radiofrequency pulse, resulting in a temperature rise to 40 °C. This increase in temperature led to the deformation of the wire clips, thus causing the release of the spring, Thereby, a reservoir compartment located within the capsule body was ejected, exposing the payload to intestinal fluid. The InteliSite® Companion Device did not demonstrate the aforementioned challenges, which may likely be ascribed to its larger exposed surface area when in an open condition which promoted the entry of digestive fluids and subsequent diffusion of the payload (McGirr et al., 2009).

3.5.2. Active Release Devices

Compared to passive smart capsules, active devices allow for remote ejection of the drug payload rather than relying on diffusion. Numerous techniques, including thermomechanical, electrochemical, electromechanical, and magnetic release, have been previously devised for the purpose of smart drug delivery capsules. Active release devices, as compared to other mechanisms, often require the incorporation of components like pistons, which take up a considerable amount of space.

3.5.2.1. Thermomechanical Mechanisms

Eriksen et al. employed a thermomechanical activation mechanism in a smart drug delivery capsule, also known as the Smith Kline French Cylinder, which exhibited an active payload release mechanism (Eriksen et al., 1961). The metal tube within the capsule was subjected to thermal energy from the radiofrequency signal, resulting in the gradual loosening of the front wax plug and subsequent opening of the capsule. The radiofrequency signal was employed concurrently to induce thermal energy in an iron pusher, subsequently causing the activation of a spring within the temperature range of 50 - 52 °C. This spring, upon being triggered, exerted force on the frame, resulting in the displacement of the drug contents towards the front wax plug, thereby facilitating active ejection. In addition, the plunger, with its progressive motion, created an aperture in the posterior wax seal. This facilitated an additional passive discharge of the drug payload. A micro-furnace was employed in the INSERM U61 device to produce heat, which led to the breakdown of a plastic strip (Wilding et al., 2000) The following ejection of a compressed spring resulted in the opening of an aperture, leading to the emptying of the drug reservoir that had been maintained under a vacuum. Gastrotarget has developed a smart capsule that exhibited thermal activation, resulting in the release of a membrane (D'Andrea and Schentag, 1994; Wilding et al., 2000). The membrane was thereby perforated by an integrated needle, resulting in the mixing of reagents and the generation of carbon dioxide through a chemical reaction. The gas production caused the movement of a piston through an increase in pressure, subsequently expelling a stopper and discharging the payload. Quotient Clinical has created a device known as the Enterion™ capsule, which incorporated a compact heating element (Mc Caffrey et al., 2008; Parasrampuria et al., 2015; Wilding et al., 2000). This element produced heat to induce softening of a high-strength polymer filament, ultimately leading to its fracture. As a result, a previously compressed spring was released. The force exerted by the spring propelled a piston into the drug compartment, generating sufficient pressure to dislodge the O-ring sealing cap. Consequently, the contents of the capsule were quickly expelled. Although thermomechanical processes have been extensively studied and proven to be functional, it is worth noting that radiofrequency-dependent devices are also subject

to the constraints mentioned previously, such as the possible increase in temperature in the surrounding tissue (Amar et al., 2015).

3.5.2.2. Electrochemical and Electromechanical Mechanisms

Gröning et al. developed a smart drug delivery capsule that applied an electrochemical actuation method (Gröning, 1997; Gröning et al., 2008, 2007; Gröning and Bensmann, 2009). Following the remote activation of the capsule, the process of hydrolysis of acidified water within a gas generating cell resulted in the production of hydrogen gas. The gas-induced pressure was harnessed to facilitate the displacement of a piston, thereby effectively expelling the contents of the drug reservoir via a small aperture. The IntelliCap® capsule utilised an electromechanical mechanism, where a built-in stepper motor was responsible for moving an actuator (Koziolek et al., 2015; Maurer et al., 2015; Söderlind et al., 2015; Van Der Schaar et al., 2013; Van der Schaar et al., 2011). This actuator propelled a piston driven by a screw rod into the drug compartment. Consequently, the contents of the capsule were expelled through the orifices located in the wall of the capsule. Söderlind et al. validated the drug release pattern of the IntelliCap® capsule in vivo within human GI tract. The study determined that the IntelliCap® system is highly suitable for efficiently and accurately generating in vivo pharmacokinetic data for extended release drug profiles (Söderlind et al., 2015). However, it showed limitations in pulsed delivery of drugs to the lower GI tract as the second pulse was not properly discharged. Another constraint associated with most electromechanical release mechanisms is the relatively higher power requirement to operate components such as pistons. Plano et al. recently developed a novel piezoelectric silicon micropump (5 x 5 x 0.6 mm^3) with a power consumption of < 23 mW, that could be incorporated into a smart drug delivery capsule (Plano et al., 2024). The pump was suitable for the delivery of drug solutions with individualizable release profiles, including pulsatile release, with high precision and reproducibility over a range of 0.05 to 50 µL/min. The delivery of suspensions was also successful, but was limited by the consistency of release to low concentrations and up to 1 µm particle size.

3.5.2.3. Magnetical Mechanisms

Yim and Sitti proposed a device that consisted of a drug chamber equipped with a permanent magnet positioned at each end (Yim et al., 2013). Through the application of an external magnetic field, the reservoir was effectively compressed, resulting in the active expulsion of the loaded medication from four distinct orifices. By manipulating the frequency of the magnetic pulse, it was feasible to alter the release. The prototype smart drug delivery capsule developed by Munoz et al. was based on a slider-crank mechanism that was coupled to an embedded permanent magnet (Munoz et al., 2018, 2016). The rotational movement of the crank mechanism facilitated the active expulsion of the drug substance by means of a pusher, which exerted force to expel the drug through an opening. By manipulating the relative location and orientation of the external permanent magnets in relation to the device, it was possible to modify the release profile, quantity of payload released, and number of doses. Guo et al. created an alternative system comprising a unidirectional valve that facilitated the active expulsion of cargo (Guo et al., 2019). This discharge was achieved by employing a multi-layered electromagnet coil functioning as a piston. The activation of the coil was facilitated by the presence of two magnets positioned on opposite sides of the drug chamber, each with a distinct orientation. The modification of parameters, including time, dose, and mean flow of release could be facilitated by a central control unit by adjustments in the intensity and duration of the electrical current. The magnetically actuated smart drug delivery capsule developed by Lee et al. was operated using a six-coil electromagnetic field and an embedded permanent magnet (Lee et al., 2022). The state of the capsule could be adjusted to either open or

closed by manipulating the lid through the utilisation of a hitching pin. During the open condition, the incorporated mucoadhesive patch was exposed and could be applied to the intended lesion using magnetic force.

3.6. Considerations for the Power Supply

While certain devices operate without the need for a battery and are triggered by external magnetic fields or radiofrequency, there are other smart capsules that necessitate an internal power supply. The implementation of electromechanical mechanisms would likely necessitate the incorporation of a sizable battery, capacitor, and/or power management unit to achieve the requisite voltages and current levels to effectively expel the payload. The absence of realistic and practical energy solutions has resulted in the use of primary batteries, which present significant obstacles regarding sustainability as well as space limitations. These issues arise from the hazardous nature, bulky dimensions, restricted battery lifespan, and concerns on sustainability (Rezaie et al., 2023). In addition, the necessity for hermetic sealing within the capsule in order to protect the battery may result in a significant increase in the overall cost. Efforts have been undertaken to explore the development of "bio-batteries" as potential alternatives to conventional batteries. The potential integration into smart drug delivery capsules, particularly with regard to patient safety, warrants future consideration. The development of bio-batteries poses challenges due to the absence of viable energy sources within the intestinal environment. The extraction methods of mechanical and thermal energy from the GI tract exhibit irregularities, localised effects, and inefficiencies in terms of energy conversion (Rezaie et al., 2023).

An instance of a bio-battery-powered smart device was designed by Gröning, who successfully created an insulin pump featuring glucose-controlled release (Gröning, 1997). The membrane capsule included an amount of 10 mg of freeze-dried yeast, which exhibited the ability to generate carbon dioxide upon exposure to glucose. The gas was introduced into the gas chamber, situated behind the insulin reservoir piston, by means of an injection needle piercing a septum. The displacement of the piston was induced by the pressure exerted by carbon dioxide, ultimately resulting in glucose-dependent discharge of around 400 µL of insulin.

Han et al. proposed the concept of utilising microbiome as a power source, which is commonly referred to as a microbial fuel cell (Han et al., 2010). Bacterial cells have more resilience in comparison to other catalysts, such as enzymes and inorganic substances, owing to the innate abilities for self-sustenance, self-repair, and self-assembly. However, the dimensions of the device were deemed too large for ingestion and the resulting power generation capabilities were limited (Han et al., 2010). Rezaie et al. developed a capsule that incorporates *B. subtillis* to function efficiently in the hypoxic environment of the small intestine (Rezaie et al., 2023). The main component of the microbial fuel cell consisted of a carbon-based anode that was subjected to modifications using poly(3,4-ethylenedioxythiophene) polystyrene sulphonate (PEDOT:PSS) and dimethyl sulfoxide, in addition to an oxygenated cathode. Endospores were utilised due to their resilience, which allows them to endure unfavourable environmental circumstances for prolonged durations. The revival of endospores by means of exposure to nutrient-rich intestinal fluid led to the production of bioelectricity as a result of bacterial metabolism. In order to enhance the efficiency of the present germination process, a nutritional layer was implemented in the anodic channel resulting in a substantial decrease in the lag time, as seen by the near entirety of cellular activity being detected within a timeframe of 60 minutes. The capsule exhibited the ability to produce a current density of 470 µA/cm^2, a power density of 98 µW/cm^2, and an open circuit voltage of 0.6 V when tested in simulated intestinal fluids.

De la Paz et al. developed a self-powered biofuel cell, with the purpose of measuring glucose levels within the intestine (De la Paz et al., 2022). Although the device was not designed as a drug delivery capsule, it

has relevance due to its biofuel cell technology which was employed to supply power to the integrated circuit, as well as to operate a magnetically-coupled human body communications antenna. The process of energy generation involved the reduction of oxygen at the cathode and the oxidation of glucose at the anode. The device that was constructed showed a notable level of stability and reversibility. Various biobattery solutions are illustrated in Fig 5.

While recent advances in materials and nanotechnology have enabled the advancement of more compact and less energy consuming components, the increasing need for communication and interaction with other devices requires a significantly higher power output to operate future devices (Amar et al., 2015). The significant limitation of bio-batteries is the low power output, making conventional batteries currently better suited as a source of energy as long as safety is ensured through hermetic sealing.

3.7. Considerations for the Drug Reservoir

Smart capsules that have been established in previous years (see Fig. 6) have had pharmaceutical payloads with volumes ranging from 0.3 mL to 1 mL (Becker et al., 2014; Harder et al., 1990; Koziolek et al., 2015; Maurer et al., 2015; Mc Caffrey et al., 2008; McGirr et al., 2009; Parasrampuria et al., 2015; Söderlind et al., 2015; Staib et al., 1989, 1986; Van der Schaar et al., 2011; Wilding et al., 2000). The dimensions of the drug reservoir are significantly influenced by the size of the capsule and constrained by the spatial requirements of the accompanying electrical and mechanical components. The possible payloads of smart drug delivery devices are comparable to those of conventional capsules, but may not be sufficient for compounds with low bioavailability. Hence, there is still a need for continuous advancement in the miniaturisation of electrical and mechanical components.

3.8. Balancing Design Criteria with Capsule Size

The physical dimensions constitute a significant constraint in the advancement of smart capsules. The devices should possess proportions that enable easy ingestion by both humans and big preclinical models, while also facilitating passage through the GI tract without encountering any undesired retention issues associated with size. The dimensions of smart drug delivery capsules described in previous studies varied from 16 x 8 mm to 40 x 15 mm (for details see Tab. 4) (Eriksen et al., 1961; Yim and Sitti, 2012). Hence, many smart capsules exhibited dimensions that were similar to commercially available capsule sizes (size 00: 23.3 x 8.58 mm), while others surpassed these dimensions. The substantial dimensions of these smart capsules may give rise to difficulties associated with the act of swallowing and the unintended retention of the devices within the GI tract. Consequently, issues may arise regarding the feasibility of employing these capsules for in vivo purposes. Previous literature has documented issues pertaining to the retention of smart capsules, particularly among patients with pre-existing conditions such as nonsteroidal anti-inflammatory drugs enteropathy (Li et al., 2008). In most cases, patients remained asymptomatic despite capsule retention. The severity of the situation presented the need for intervention through surgical removal, with its inherent risks (Li et al., 2008). Given that IBD is associated with bowel obstruction, it is possible that undesired retention of smart capsules may be exacerbated (Torres et al., 2017). Moreover, the aforementioned strategies for active actuation, which encompass various protrusions, may contribute to the issue. The shape and dimensions of the smart drug delivery capsules should therefore be regarded as a fundamental aspect of the design, and should be evaluated during any clinical assessment. The process of miniaturising individual components has made significant progress in comparison to the early smart capsules (Gao et al., 2020; Hasan et al., 2018; Neebha et al., 2020). However, it is crucial to continue reducing the size of the components in order to facilitate the integration of

diverse functionalities including localisation, actuation, retention, as well as additional diagnostic capabilities such as imaging, sensing, or sampling. A range of materials, including plastics like polyurethane, polyethylene, polypropylene, as well as resin, have been employed for the production of the capsule shells (Eriksen et al., 1961; Gröning and Bensmann, 2009; Harder et al., 1990; Lambert et al., 1991; Lee et al., 2022; Yim and Sitti, 2012). The use of 3D printing for the production of capsule shells has previously been demonstrated and could allow for simplified manufacturing in the future (Lee et al., 2022; Yim and Sitti, 2012).

4. Conclusion and Future Directions

The use of smart drug delivery capsules offers significant potential for the site specific delivery of therapeutics for the treatment of GI diseases such as IBD. While the advantages of site-specific delivery are significant, there are still some obstacles to overcome to facilitate effective IBD treatment, e.g. nucleic acid delivery into the target cells (O'Driscoll et al., 2019). However, the design possibilities for smart drug delivery capsules are vast and surpass the strategies delineated in this the paper, encompassing piercing devices furnished with (micro)needles (Cummins, 2021; Zhou and Alici, 2022) or capsules that stimulate the secretion of hormones via electrical stimuli (Ramadi et al., 2023). A key concern related to smart capsules is the considerable physical dimensions, which can result in retention within the GI tract (Li et al., 2008). Despite significant advancements in the miniaturisation of electrical and mechanical components, the current state of research has not yet reached a stage where a substantial number of features may be integrated into a readily ingestible capsule. Therefore, employing multiple capsules with specific features rather than a solitary, extensive system may be considered a more favourable approach. It is imperative that future advancements focus on the reduction in size of the individual components, subsequently leading to a decrease in the overall dimensions of smart capsules. This is essential to facilitate easy administration and mitigate the potential for GI retention. Furthermore, the integration of advanced communication techniques, such as Bluetooth, between the user and the smart device is desirable to enhance functionality and ensure an uninterrupted user interaction. It is also critical to establish the validity of emerging approaches that enable accurate localisation of the capsule within the GI tract, while minimising the reliance on costly and bulky equipment as well as the potential risks associated with radiation exposure. The potentially high unit cost associated with using these medical devices to deliver IBD therapies is another limiting factor. As a result, the therapeutic strategy for a smart drug delivery capsule may only be considered for specific patient populations, for example, patients who exhibit an insufficient response to first-line therapy, which is observed in approximately 10 to 30% of patients undergoing initial treatment with TNFα antagonists (Roda et al., 2016). Although current platforms are single-use, the potential high unit cost of therapies using smart drug delivery capsules, along with the increasing drive for the sustainability of materials, may give rise to the idea of reusable devices. However, this would entail the establishment of a more complex infrastructure in relation to device use, particularly with regard to retrieval, handling and sterilisation. In a practical setting, concerns may arise regarding the appropriate safe disposal of single-use devices and the potential for either reuse or recycling components following retrieval. While more research is needed to advance the development of smart drug delivery systems and overcome the limitations listed above, they already have a wide range of applications in research and diagnostics (Henze et al., 2021; Koziolek et al., 2015; Liao et al., 2016; Maurer et al., 2015). Overall, given the new concepts being developed for treatment of IBD, demand for smart capsules is anticipated to increase to provide new avenues for localised precision therapy of these debilitating diseases.

Funding

Funding for this publication is provided under the GENEGUT (https://genegut.eu/) project funded by the European Commission as a Horizon Europe Research and Innovation Action (RIA) under the call tools and technologies for a healthy society (2021) (HORIZON-HLTH-2021-TOOL-06, GA 101057491).

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

References

Abramson, A., Caffarel-Salvador, E., Khang, M., Dellal, D., Silverstein, D., Gao, Y., Frederiksen, M.R., Vegge, A., Hubálek, F., Water, J.J., Friderichsen, A. V, Fels, J., Kirk, R.K., Cleveland, C., Collins, J., Tamang, S., Hayward, A., Landh, T., Buckley, S.T., Roxhed, N., Rahbek, U., Langer, R., Traverso, G., 2019. An ingestible self-orienting system for oral delivery of macromolecules. Science (1979) 363, 611–615.

Alsunaydih, F.N., Arefin, M.S., Redoute, J.M., Yuce, M.R., 2020. A navigation and pressure monitoring system toward autonomous wireless capsule endoscopy. IEEE Sens J 20, 8098–8107. https://doi.org/10.1109/JSEN.2020.2979513

Amar, A. Ben, Kouki, A.B., Cao, H., 2015. Power approaches for implantable medical devices. Sensors (Switzerland) 15, 28889–28914. https://doi.org/10.3390/s151128889

Asci, C., Del-Rio-Ruiz, R., Sharma, A., Sonkusale, S., 2022. Ingestible pH sensing capsule with thread-based electrochemical sensors, in: Proceedings of IEEE Sensors. Institute of Electrical and Electronics Engineers Inc. https://doi.org/10.1109/SENSORS52175.2022.9967347

Azehaf, H., Benzine, Y., Tagzirt, M., Skiba, M., Karrout, Y., 2023. Microbiota-sensitive drug delivery systems based on natural polysaccharides for colon targeting. Drug Discov Today 28. https://doi.org/10.1016/j.drudis.2023.103606

Babaee, S., Pajovic, S., Kirtane, A.R., Shi, J., Caffarel-Salvador, E., Hess, K., Collins, J.E., Tamang, S., Wahane, A. V, Hayward, A.M., Mazdiyasni, H., Langer, R., Traverso, G., 2019. Temperature-responsive biometamaterials for gastrointestinal applications. Sci Transl Med 11, eaau8581.

Baldan-Martin, M., Rubín de Célix, C., Orejudo, M., Ortega Moreno, L., Fernández-Tomé, S., Soleto, I., Ramirez, C., Arroyo, R., Fernández, P., Santander, C., Moreno-Monteagudo, J.A., Casanova, M.J., Casals, F., Casabona, S., Becerro, I., Lozano, J.J., Aransay, A.M., Chaparro, M., Gisbert, J.P., 2023. Long Non-Coding RNA Signatures in the Ileum and Colon of Crohn's Disease Patients and Effect of Anti-TNF-α Treatment on Their Modulation. Int J Mol Sci 24. https://doi.org/10.3390/ijms242115691

Banis, G.E., Beardslee, L.A., Stine, J.M., Sathyam, R.M., Ghodssi, R., 2019a. Integrated capsule system for gastrointestinal pH triggered sampling and sensing, in: 2019 20th International Conference on Solid-State Sensors, Actuators and Microsystems & Eurosensors XXXIII (TRANSDUCERS & EUROSENSORS XXXIII). IEEE, pp. 314–317.

Banis, G.E., Beardslee, L.A., Stine, J.M., Sathyam, R.M., Ghodssi, R., 2019b. Gastrointestinal targeted sampling and sensing via embedded packaging of integrated capsule system. Journal of Microelectromechanical Systems 28, 219–225. https://doi.org/10.1109/JMEMS.2019.2897246

Becker, D., Zhang, J., Heimbach, T., Penland, R.C., Wanke, C., Shimizu, J., Kulmatycki, K., 2014. Novel orally swallowable IntelliCap® device to quantify regional drug absorption in human GI tract using diltiazem as model drug. Ageing Int 15, 1490–1497. https://doi.org/10.1208/s12249-014-0172-1

Bellinger, A.M., Jafari, M., Grant, T.M., Zhang, S., Hannah, †, Slater, C., Wenger, E.A., Mo, S., Lee, Y.-A.L., Mazdiyasni, H., Kogan, L., Barman, R., Cleveland, C., Booth, L., Bensel, T., Minahan, D., Hurowitz, H.M., Tai, T., Daily, J., Nikolic, B., Wood, L., Eckhoff, P.A., Langer, R., Traverso, ‡ Giovanni, 2016. Oral, ultra-long-lasting drug delivery: Application toward malaria elimination goals. Sci Transl Med 8, 365ra157-365ra157.

Benken, A., Gianchandani, Y., 2019. Passive wireless pressure sensing for gastric manometry. Micromachines (Basel) 10. https://doi.org/10.3390/mi10120868

Berg, S., Uggla, T., Antonsson, M., Nunes, S.F., Englund, M., Rosengren, L., Fahraj, M., Wu, X., Govender, R., Söderberg, M., Janzén, D., Van Zuydam, N., Hugerth, A., Larsson, A., Abrahmsén-Alami, S., Abrahamsson, B., Davies, N., Bergström, C.A.S., 2023. Evaluation in pig of an intestinal administration device for oral peptide delivery. Journal of Controlled Release 353, 792–801. https://doi.org/10.1016/j.jconrel.2022.12.011

Blaabjerg, L.I., Fan, L., Chen, X., Sassene, P.J., 2020. The use of capsule endoscopy to determine tablet disintegration in vivo. Pharmaceutics 12. https://doi.org/10.3390/pharmaceutics12060498

BodyCAP, E-Celsius® medical [WWW Document], n.d. . BodyCAP Website. URL https://www.bodycap-medical.com/ecelsius-medical-medical-device-for-a-continuous-core-temperature-monitoring-telemetric-pills/ (accessed 1.23.24).

BodyCAP, E-Celsius® performance [WWW Document], n.d. . BodyCAP Website. URL https://www.bodycap-medical.com/e-celsius-performance-body-temperature-monitoring-telemetric-pill/ (accessed 6.23.23).

Bogerd, C.P., Velt, K.B., Annaheim, S., Bongers, C.C.W.G., Eijsvogels, T.M.H., Daanen, H.A.M., 2018. Comparison of two telemetric intestinal temperature devices with rectal temperature during exercise. Physiol Meas 39. https://doi.org/10.1088/1361-6579/aaad52

Bongers, C.C.W.G., Daanen, H.A.M., Bogerd, C.P., Hopman, M.T.E., Eijsvogels, T.M.H., 2018. Validity, reliability, and inertia of four different temperature capsule systems. Med Sci Sports Exerc 50, 169–175. https://doi.org/10.1249/MSS.0000000000001403

Brayden, D.J., Hill, T.A., Fairlie, D.P., Maher, S., Mrsny, R.J., 2020. Systemic delivery of peptides by the oral route: Formulation and medicinal chemistry approaches. Adv Drug Deliv Rev 157, 2–36. https://doi.org/10.1016/j.addr.2020.05.007

Burisch, J., Vardi, H., Schwartz, D., Friger, M., Kiudelis, G., Kupčinskas, J., Fumery, M., Gower-Rousseau, C., Lakatos, L., Lakatos, P.L., D'Incà, R., Sartini, A., Valpiani, D., Giannotta, M., Arebi, N., Duricova, D., Bortlik, M., Chetcuti Zammit, S., Ellul, P., Pedersen, N., Kjeldsen, J., Midjord, J.M.M., Nielsen, K.R., Winther Andersen, K., Andersen, V., Katsanos, K.H., Christodoulou, D.K., Domislovic, V., Krznaric, Z., Sebastian, S., Oksanen, P.,

Collin, P., Barros, L., Magro, F., Salupere, R., Kievit, H.A.L., Goldis, A., Kaimakliotis, I.P., Dahlerup, J.F., Eriksson, C., Halfvarson, J., Fernandez, A., Hernandez, V., Turcan, S., Belousova, E., Langholz, E., Munkholm, P., Odes, S., Turk, N., Cukovic-Cavka, S., Nicolaou, A., Lukas, M., Shonová, O., Blichfeldt, B., Marker, D., Carlsen, K., Weimers, P., Aalykke, C., Kudsk, K., Vind, I., Thorsgaard, N., Skamnelos, A., Politis, D., Vegh, Z., Demenyi, P., Nemethne Kramli, S., Dal Piaz, G., Santini, A., Girardin, G., Kupcinskas, L., Jonaitis, L., Valantiene, I., Zykus, R., Kucinskiene, R., Lazar, D., Nikulina, I., de Castro, L., Pineda, J.R., Pereira, S., Martinez-Cadilla, J., Sanroman, L., Figueira, M., Ares, D.M., Rodriguez-Prada, J.I., Carmona, A., Gonzalez-Portela, C., Widen, U.B., Myers, S., Ashton, K., Whitehead, E., 2020. Health-care costs of inflammatory bowel disease in a pan-European, community-based, inception cohort during 5 years of follow-up: a population-based study. Lancet Gastroenterol Hepatol 5, 454–464. https://doi.org/10.1016/S2468-1253(20)30012-1

Cargill, R., Caldwell, L.J., Engle, K., Fix, J.A., Porter, P.A., Gardner, C.R., 1988. Controlled gastric emptying. 1. Effects of physical properties on gastric residence times of nondisintegrating geometric shapes in beagle dogs. Pharm Res 5, 533–526.

Carta, R., Tortora, G., Thoné, J., Lenaerts, B., Valdastri, P., Menciassi, A., Dario, P., Puers, R., 2009. Wireless powering for a self-propelled and steerable endoscopic capsule for stomach inspection. Biosens Bioelectron 25, 845–851. https://doi.org/10.1016/j.bios.2009.08.049

Chikina, A., Matic Vignjevic, D., 2021. At the right time in the right place: How do luminal gradients position the microbiota along the gut? Cells and Development 168. https://doi.org/10.1016/j.cdev.2021.203712

Chu, H., Wang, P.J., Zhu, X.H., Hong, H., 2019. Antenna-in-package design and robust test for the link between wireless ingestible capsule and smart phone. IEEE Access 7, 35231–35241. https://doi.org/10.1109/ACCESS.2019.2891880

Ciuti, G., Menciassi, A., Dario, P., 2011. Capsule endoscopy: From current achievements to open challenges. IEEE Rev Biomed Eng 4, 59–72. https://doi.org/10.1109/RBME.2011.2171182

Ciuti, G., Valdastri, P., Menciassi, A., Dario, P., 2010. Robotic magnetic steering and locomotion of capsule endoscope for diagnostic and surgical endoluminal procedures. Robotica 28, 199–207. https://doi.org/10.1017/S0263574709990361

Clear, N.J., Milton, A., Humphrey, M., Henry, B.T., Wulff, M., Nichols, D.J., Anziano, R.J., Wilding, I., 2001. Evaluation of the Intelisite capsule to deliver theophylline and frusemide tablets to the small intestine and colon. European Journal of Pharmaceutical Sciences 13, 375–384.

Cummins, G., 2021. Smart pills for gastrointestinal diagnostics and therapy. Adv Drug Deliv Rev 177, 113931. https://doi.org/10.1016/j.addr.2021.113931

Dahlgren, D., Roos, C., Lundqvist, A., Abrahamsson, B., Tannergren, C., Hellström, P.M., Sjögren, E., Lennernäs, H., 2016. Regional intestinal permeability of three model drugs in human. Mol Pharm 13, 3013–3021. https://doi.org/10.1021/acs.molpharmaceut.6b00514

D'Andrea, D.T., Schentag, J.J., 1994. United States patent 5,270,607: Telemetry capsule and process.

de Alencar Junior, H., Paiotti, A.P.R., de Araújo Filho, H.B., Oshima, C.T.F., Miszputen, S.J., Ambrogini-Júnior, O., 2020. The relationship between the commensal microbiota levels and Crohn's disease activity. JGH Open 4, 784–789. https://doi.org/10.1002/jgh3.12338

De la Paz, E., Maganti, N.H., Trifonov, A., Jeerapan, I., Mahato, K., Yin, L., Sonsa-ard, T., Ma, N., Jung, W., Burns, R., Zarrinpar, A., Wang, J., Mercier, P.P., 2022. A self-powered ingestible wireless biosensing system for real-time in situ monitoring of gastrointestinal tract metabolites. Nat Commun 13, 7405. https://doi.org/10.1038/s41467-022-35074-y

Dressmann, J.B., Amidon, G.L., 1984. Radiotelemetric method for evaluating enteric coatings in vivo. J Pharm Sci 73, 935–938.

Effinger, A., O'Driscoll, C.M., McAllister, M., Fotaki, N., 2020. Gastrointestinal diseases and their impact on drug solubility: Crohn's Disease. European Journal of Pharmaceutical Sciences 152. https://doi.org/10.1016/j.ejps.2020.105459

Effinger, A., O'Driscoll, C.M., McAllister, M., Fotaki, N., 2019. Impact of gastrointestinal disease states on oral drug absorption – implications for formulation design – a PEARRL review. Journal of Pharmacy and Pharmacology 71, 674–698. https://doi.org/10.1111/jphp.12928

Eriksen, S.P., Swintosky, J. V., Serfass, E.J., Lin, T.H., Abrams, J., Sturtevant, F.M., 1961. Equipment and methodology for relating gastrointestinal absorption to site of drug release. J Pharm Sci 50, 151–156.

Farmer, A.D., Scott, S.M., Hobson, A.R., 2013. Gastrointestinal motility revisited: The wireless motility capsule. United European Gastroenterol J 1, 413–421. https://doi.org/10.1177/2050640613510161

Fidder, H.H., Singendonk, M.M.J., van der Have, M., Oldenburg, B., van Oijen, M.G.H., 2013. Low rates of adherence for tumor necrosis factor-α inhibitors in Crohn's disease and rheumatoid arthritis: Results of a systematic review. World J Gastroenterol 19, 4344–4350. https://doi.org/10.3748/wjg.v19.i27.4344

Fix, J.A., Cargill, R., Engle, K., 1993. Controlled gastric emptying. III. Gastric residence time of a nondisintegrating geometric shape in human volunteers. Pharm Res 10, 1087–1089.

Gao, C., Bai, C., Gao, J., Xiao, Y., Han, Y., Shaista, A., Zhao, Y., Qu, L., 2020. A directly swallowable and ingestible micro-supercapacitor. J Mater Chem A Mater 8, 4055–4061. https://doi.org/10.1039/c9ta12880h

Gao, J., Zhang, Z., Yan, G., 2021. Locomotion analysis of a clamper-based capsule robot in a compliant tube. IEEE/ASME Transactions on Mechatronics 26, 55–65. https://doi.org/10.1109/TMECH.2020.2999959

Greenwood, T.E., Cagle, H., Pulver, B., Pak, O.S., Kong, Y.L., 2022. Ingestible functional magnetic Robot with localized flexibility (MR-LF). Advanced Intelligent Systems 4, 2200166. https://doi.org/10.1002/aisy.202200166

Gröning, R., 1997. Computer-controlled drug release from small-sized dosage forms. Journal of Controlled Release 48, 185–193.

Gröning, R., Bensmann, H., 2009. High frequency controlled capsules with integrated gas producing cells. European Journal of Pharmaceutics and Biopharmaceutics 72, 282–284. https://doi.org/10.1016/j.ejpb.2009.01.003

Gröning, R., Bensmann, H., Müller, R.S., 2008. Control of drug release from capsules using high frequency energy transmission systems. Int J Pharm 364, 9–13. https://doi.org/10.1016/j.ijpharm.2008.07.007

Gröning, R., Danco, I., Müller, R.S., 2007. Development of sensor elements to control drug release from capsular drug delivery systems. Int J Pharm 340, 61–64. https://doi.org/10.1016/j.ijpharm.2007.03.024

Guo, S., Ge, Y., Li, L., Liu, A., 2006. Underwater swimming micro robot using IPMC actuator, in: 2006 IEEE International Conference on Mechatronics and Automation. pp. 249–254.

Guo, X., Huang, C., Xu, J., Xu, H., Liu, L., Zhao, H., Wang, J., Huang, W., Peng, W., Chen, Y., Nie, Y., Zhou, Yongjian, Zhou, Youlian, 2022. Gut microbiota is a potential biomarker in inflammatory bowel disease. Front Nutr 8. https://doi.org/10.3389/fnut.2021.818902

Guo, X., Luo, Z., Cui, H., Wang, J., Jiang, Q., 2019. A novel and reproducible release mechanism for a drug-delivery system in the gastrointestinal tract. Biomed Microdevices 21. https://doi.org/10.1007/s10544-019-0383-z

Han, Y., Yu, C., Liu, H., 2010. A microbial fuel cell as power supply for implantable medical devices. Biosens Bioelectron 25, 2156–2160. https://doi.org/10.1016/j.bios.2010.02.014

Hanscom, M., Stead, C., Feldman, H., Marya, N.B., Cave, D., 2022. Video capsule endoscopy and device-assisted enteroscopy. Dig Dis Sci 67, 1539–1552. https://doi.org/10.1007/s10620-021-07085-0

Harder, S., Fuhr, U., Beermann, D., Staib, A.H., 1990. Ciprofloxacin absorption in different regions of the human gastrointestinal tract. Investigations with the HF-capsule. Br J Clin Pharmacol 30, 35–39. https://doi.org/10.1111/j.1365-2125.1990.tb03740.x

Hasan, R.R., Saraff, R., Dutta, P., Roy, S., Mosabbir, A., Nath, S., 2018. Ingestible antenna at inner-wall of capsule for capsule endoscopy, in: 2018 10th International Conference on Electrical and Computer Engineering (ICECE). IEEE, pp. 201–204.

Hayward, A., Bensel, T., Mazdiyasni, H., Rogner, J., Kirtane, A.R., Lee, Y.A.L., Hua, T., Bajpayee, A., Collins, J., McDonnell, S., Cleveland, C., Lopes, A., Wahane, A., Langer, R., Traverso, G., 2018. Scalable gastric resident systems for veterinary application. Sci Rep 8. https://doi.org/10.1038/s41598-018-30212-3

Henze, L.J., Koehl, N.J., Bennett-Lenane, H., Holm, R., Grimm, M., Schneider, F., Weitschies, W., Koziolek, M., Griffin, B.T., 2021. Characterization of gastrointestinal transit and luminal conditions in pigs using a telemetric motility capsule. European Journal of Pharmaceutical Sciences 156, 105627. https://doi.org/10.1016/j.ejps.2020.105627

Hoang, M.C., Nguyen, K.T., Le, V.H., Kim, J., Choi, E., Kang, B., Park, J.O., Kim, C.S., 2021. Independent electromagnetic field control for practical approach to actively locomotive wireless capsule endoscope. IEEE Trans Syst Man Cybern Syst 51, 3040–3052. https://doi.org/10.1109/TSMC.2019.2917298

Hofmann, M., Thieringer, F., Nguyen, M.A., Månsson, W., Galle, P.R., Langguth, P., 2019. A novel technique for intraduodenal administration of drug suspensions/solutions with concurrent pH monitoring applied to ibuprofen formulations. European Journal of Pharmaceutics and Biopharmaceutics 136, 192–202. https://doi.org/10.1016/j.ejpb.2019.01.010

HQ inc., CorTemp® capsule [WWW Document], n.d. . HQ Inc. Website. URL https://www.hqinc.net/cortemp/ (accessed 6.23.23).

Hua, S., 2020. Advances in oral drug delivery for regional targeting in the gastrointestinal tract - Influence of physiological, pathophysiological and pharmaceutical Factors. Front Pharmacol 11. https://doi.org/10.3389/fphar.2020.00524

Ibekwe, V.C., Liu, F., Fadda, H.M., Khela, M.K., Evans, D.F., Parsons, G.E., Basit, A.W., 2006. An investigation into the in vivo performance variability of pH responsive polymers for ileo-colonic drug delivery using gamma scintigraphy in humans. J Pharm Sci 95, 2760–2766. https://doi.org/10.1002/jps.20742

Inverardi, N., Scalet, G., Melocchi, A., Uboldi, M., Maroni, A., Zema, L., Gazzaniga, A., Auricchio, F., Briatico-Vangosa, F., Baldi, F., Pandini, S., 2021. Experimental and computational analysis of a pharmaceutical-grade shape memory polymer applied to the development of gastroretentive drug delivery systems. J Mech Behav Biomed Mater 124. https://doi.org/10.1016/j.jmbbm.2021.104814

Kagan, L., Lapidot, N., Afargan, M., Kirmayer, D., Moor, E., Mardor, Y., Friedman, M., Hoffman, A., 2006. Gastroretentive accordion pill: Enhancement of riboflavin bioavailability in humans. Journal of Controlled Release 113, 208–215. https://doi.org/10.1016/j.jconrel.2006.03.022

Kanasty, R., Low, S., Bhise, N., Yang, J., Peeke, E., Schwarz, M., Wright, J., Carter, B., Moorthy, S., Grant, T., DeBenedictis, B., Bishoff, M., Simses, C., Bellinger, A.M., 2019. A pharmaceutical answer to nonadherence: Once weekly oral memantine for Alzheimer's disease. Journal of Controlled Release 303, 34–41. https://doi.org/10.1016/j.jconrel.2019.03.022

Karagozler, M.E., Cheung, E., Kwon, J., Sitti, M., 2006. Miniature endoscopic capsule robot using biomimetic micro-patterned adhesives, in: The First IEEE/RAS-EMBS International Conference on Biomedical Robotics and Biomechatronics, 2006. pp. 105–111.

Kawasaki, S., Westhoek, Y., Subramaniam, I., Saccher, M., Dekker, R., 2021. Pre-charged collapse-mode capacitive micromachined ultrasonic transducer (CMUT) for broadband ultrasound power transfer, in: 2021 IEEE Wireless Power Transfer Conference, WPTC 2021. Institute of Electrical and Electronics Engineers Inc. https://doi.org/10.1109/WPTC51349.2021.9458104

Kim, B., Lee, S., Park, J.H., Park, J.O., 2005a. Design and fabrication of a locomotive mechanism for capsule-type endoscopes using shape memory alloys (SMAs). IEEE/ASME Transactions on Mechatronics 10, 77–86. https://doi.org/10.1109/TMECH.2004.842222

Kim, B., Park, S., Yeol, C., Seok, J., Yoon, J., 2005b. An earthworm-like locomotive mechanism for capsule endoscopes, in: 2005 IEEE/RSJ International Conference on Intelligent Robots and Systems. pp. 2997–3002.

Kim, S.H., Chun, H.J., 2021. Capsule endoscopy: Pitfalls and approaches to overcome. Diagnostics 11. https://doi.org/10.3390/diagnostics11101765

Kim, Y., Zhao, X., 2022. Magnetic soft materials and robots. Chem Rev 122, 5317–5364. https://doi.org/10.1021/acs.chemrev.1c00481

Kim, Y.K., 2022. RNA therapy: rich history, various applications and unlimited future prospects. Exp Mol Med. https://doi.org/10.1038/s12276-022-00757-5

Kirtane, A.R., Abouzid, O., Minahan, D., Bensel, T., Hill, A.L., Selinger, C., Bershteyn, A., Craig, M., Mo, S.S., Mazdiyasni, H., Cleveland, C., Rogner, J., Lee, Y.A.L., Booth, L., Javid, F., Wu, S.J., Grant, T., Bellinger, A.M., Nikolic, B., Hayward, A., Wood, L., Eckhoff, P.A., Nowak, M.A., Langer, R., Traverso, G., 2018. Development of an oral once-weekly drug delivery system for HIV antiretroviral therapy. Nat Commun 9. https://doi.org/10.1038/s41467-017-02294-6

Kirtane, A.R., Hua, T., Hayward, A., Bajpayee, A., Wahane, A., Lopes, A., Bensel, T., Ma, L., Stanczyk, F.Z., Brooks, S., Gwynne, D., Wainer, J., Collins, J., Tamang, S.M., Langer, R., Traverso, G., 2019. A once-a-month oral contraceptive. Sci Transl Med 11, eaay2602.

Klausner, E.A., Eyal, S., Lavy, E., Friedman, M., Hoffman, A., 2003a. Novel levodopa gastroretentive dosage form: In-vivo evaluation in dogs. Journal of Controlled Release 88, 117–126. https://doi.org/10.1016/S0168-3659(02)00487-X

Klausner, E.A, Lavy, E., Barta, M., Cserepes, E., Friedman, M., Hoffman, A., 2003. Novel gastroretentive dosage forms: Evaluation of gastroretentivity and its effect on levodopa absorption in humans. Pharm Res 20, 1466–1473.

Klausner, E.A., Lavy, E., Stepensky, D., Cserepes, E., Barta, M., Friedman, M., Hoffman, A., 2003b. Furosemide pharmacokinetics and pharmacodynamics following gastroretentive dosage form administration to healthy volunteers. J Clin Pharmacol 43, 711–720. https://doi.org/10.1177/0091270003254575

Kong, Y.L., Zou, X., McCandler, C.A., Kirtane, A.R., Ning, S., Zhou, J., Abid, A., Jafari, M., Rogner, J., Minahan, D., Collins, J.E., McDonnell, S., Cleveland, C., Bensel, T., Tamang, S., Arrick, G., Gimbel, A., Hua, T., Ghosh, U., Soares, V., Wang, N., Wahane, A., Hayward, A., Zhang, S., Smith, B.R., Langer, R., Traverso, G., 2019. 3D-printed gastric resident electronics. Advanced Material Technologies 4. https://doi.org/10.1002/admt.201800490

Koziolek, M., Grimm, M., Becker, D., Iordanov, V., Zou, H., Shimizu, J., Wanke, C., Garbacz, G., Weitschies, W., 2015a. Investigation of pH and Temperature Profiles in the GI Tract of Fasted Human Subjects Using the Intellicap® System. J Pharm Sci 104, 2855–2863. https://doi.org/10.1002/jps.24274

Koziolek, M., Grimm, M., Becker, D., Iordanov, V., Zou, H., Shimizu, J., Wanke, C., Garbacz, G., Weitschies, W., 2015b. Investigation of pH and temperature profiles in the GI tract of fasted human subjects using the Intellicap® system. J Pharm Sci 104, 2855–2863. https://doi.org/10.1002/jps.24274

Koziolek, M., Grimm, M., Bollmann, T., Schäfer, K.J., Blattner, S.M., Lotz, R., Boeck, G., Weitschies, W., 2019. Characterization of the GI transit conditions in Beagle dogs with a telemetric motility capsule. European Journal of Pharmaceutics and Biopharmaceutics 136, 221–230. https://doi.org/10.1016/j.ejpb.2019.01.026

Koziolek, M., Schneider, F., Grimm, M., Mode, C., Seekamp, A., Roustom, T., Siegmund, W., Weitschies, W., 2015c. Intragastric pH and pressure profiles after intake of the high-caloric, high-fat meal as used for food effect studies. Journal of Controlled Release 220, 71–78. https://doi.org/10.1016/j.jconrel.2015.10.022

Kumar, A., Yassin, N., Marley, A., Bellato, V., Foppa, C., Pellino, G., Myrelid, P., Millan, M., Gros, B., Avellaneda, N., Catalan-Serra, I., El-Hussuna, A., Cunha Neves, J.A., Roseira, J., Cunha, M.F., Verstockt, B., Bettenworth, D., Mege, D., Brookes, M.J., 2023. Crossing barriers: the burden of inflammatory bowel disease across Western Europe. Therap Adv Gastroenterol 16. https://doi.org/10.1177/17562848231218615

Kwiatek, M.A., Pandolfino, J.E., 2008. The BravoTM pH capsule system. Digestive and Liver Disease 40, 156–160. https://doi.org/10.1016/j.dld.2007.10.025

Lambert, A., Vaxman, F., Crenner, F., Wittmann, T., Grenier, J.F., 1991. Autonomous telemetric capsule to explore the small bowel. Med Biol Eng Comput 29, 191–196.

Lee, J., Kim, D., Bang, S., Park, S., 2022. Drug-loaded mucoadhesive patch with active delivery and controlled releasing ability. Advanced Intelligent Systems 4, 2100203. https://doi.org/10.1002/aisy.202100203

Lee, M., Chang, E.B., 2021. Inflammatory Bowel Diseases (IBD) and the Microbiome—Searching the Crime Scene for Clues. Gastroenterology 160, 524–537. https://doi.org/10.1053/j.gastro.2020.09.056

Li, F., Gurudu, S.R., De Petris, G., Sharma, V.K., Shiff, A.D., Heigh, R.I., Fleischer, D.E., Post, J., Erickson, P., Leighton, J.A., 2008. Retention of the capsule endoscope: a single-center experience of 1000 capsule endoscopy procedures. Gastrointest Endosc 68, 174–180. https://doi.org/10.1016/j.gie.2008.02.037

Li, P., Kothari, V., Terry, B.S., 2015. Design and preliminary experimental investigation of a capsule for measuring the small intestine contraction pressure. IEEE Trans Biomed Eng 62, 2702–2708. https://doi.org/10.1109/TBME.2015.2444406

Li, P., Kreikemeier-Bower, C., Xie, W., Kothari, V., Terry, B.S., 2017. Design of a wireless medical capsule for measuring the contact pressure between a capsule and the small intestine. J Biomech Eng 139. https://doi.org/10.1115/1.4036260

Li, W., Guo, W., Li, M., Zhu, Y., 2006. A novel locomotion principle for endoscopic robot, in: IEEE International Conference on Mechatronics and Automation. Luoyang, China, pp. 1658–1662.

Liao, C.H., Cheng, C.T., Chen, C.C., Jow, U.M., Chen, C.H., Lai, Y.L., Chen, Y.C., Ho, D.R., 2021. An ingestible electronics for continuous and real-time intraabdominal pressure monitoring. J Pers Med 11, 1–10. https://doi.org/10.3390/jpm11010012

Liao, Z., Hou, X., Lin-Hu, E.Q., Sheng, J.-Q., Ge, Z.-Z., Jiang, B., Hou, X.-H., Liu, J.-Y., Li, Z., Huang, Q.-Y., Zhao, X.-J., Li, N., Gao, Y.-J., Zhang, Y., Zhou, J.-Q., Wang, X.-Y., Liu, J., Xie, X.-P., Yang, C.-M., Liu, H.-L., Sun, X.-T., Zou, W.-B., Li, Z.-S., 2016. Accuracy of magnetically controlled capsule endoscopy, compared with conventional gastroscopy, in detection of gastric diseases. Clinical Gastroenterology and Hepatology 14, 1266-1273.e1. https://doi.org/10.1016/j.cgh.2016.05.013

Litvinova, O., Klager, E., Yeung, A.W.K., Tzvetkov, N.T., Kimberger, O., Kletecka-Pulker, M., Willschke, H., Atanasov, A.G., 2023. Bibliometric analysis and evidence of clinical efficacy and safety of digital pills. Front Pharmacol 14. https://doi.org/10.3389/fphar.2023.1023250

Lopez, K., Roman, -Linares, Vermeeren, G., Thielens, A., Joseph, W., Martens, L., 2014. Characterization of path loss and absorption for a wireless radio frequency link between an in-body endoscopy capsule and a receiver outside the body. EURASIP J Wirel Commun Netw 21.

Lucarini, G., Mura, M., Ciuti, G., Rizzo, R., Menciassi, A., 2015. Electromagnetic control system for capsule navigation: Novel concept for magnetic capsule maneuvering and preliminary study. J Med Biol Eng 35, 428–436. https://doi.org/10.1007/s40846-015-0055-2

Lui, C.Y., Amidon, G.L., Berardi, R.R., Fleisher, D., Youngberg, C., Dressman, J.B., 1986. Comparison of gastrointestinal pH in dogs and humans: Implications on the use of the beagle dog as a model for oral absorption in humans. J Pharm Sci 75, 271–274.

Martel, S., 2015. Magnetic nanoparticles in medical nanorobotics. Journal of Nanoparticle Research 17. https://doi.org/10.1007/s11051-014-2734-2

Maurer, J.M., Schellekens, R.C., Van Rieke, H.M., Wanke, C., Iordanov, V., Stellaard, F., Wutzke, K.D., Dijkstra, G., Van Der Zee, M., Woerdenbag, H.J., Frijlink, H.W., Kosterink, J.G.W., 2015. Gastrointestinal pH and transit time profiling in healthy volunteers using the IntelliCap system confirms ileo-colonic release of ColoPulse tablets. PLoS One 10. https://doi.org/10.1371/journal.pone.0129076

Mc Caffrey, C., Chevalerias, O., Twomey, K., 2008. Swallowable-capsule technology. IEEE Pervasive Comput 7, 23–29.

McGirr, M.E.A., McAllister, S.M., Peters, E.E., Vickers, A.W., Parr, A.F., Basit, A.W., 2009. The use of the InteliSite® Companion device to deliver mucoadhesive polymers to the dog colon. European Journal of Pharmaceutical Sciences 36, 386–391. https://doi.org/10.1016/j.ejps.2008.11.007

Medtronic - SmartPill® motility capsule [WWW Document], n.d. . Medtronic - SmartPill Motility Capsule Webpage. URL https://www.medtronic.com/covidien/en-gb/products/motility-testing/smartpill-motility-testing-system.html# (accessed 6.16.23).

Mehedi, I.M., Rao, K.P., Alotaibi, F.M., Alkanfery, H.M., 2023. Intelligent wireless capsule endoscopy for the diagnosis of gastrointestinal diseases. Diagnostics 13. https://doi.org/10.3390/diagnostics13081445

Melocchi, A., Uboldi, M., Inverardi, N., Briatico-Vangosa, F., Baldi, F., Pandini, S., Scalet, G., Auricchio, F., Cerea, M., Foppoli, A., Maroni, A., Zema, L., Gazzaniga, A., 2019. Expandable drug delivery system for gastric retention based on shape memory polymers: Development via 4D printing and extrusion. Int J Pharm 571. https://doi.org/10.1016/j.ijpharm.2019.118700

Mojaverian, P., 1996. Evaluation of gastrointestinal pH and gastric residence time via the Heidelberg Radiotelemetry Capsule: Pharmaceutical application. Drug Dev Res 38, 73–85. https://doi.org/10.1002/(SICI)1098-2299(199606)38:2<73::AID-DDR1>3.0.CO;2-H

Mojaverian, P., Ferguson, R.K., Vlasses, P.H., Rocci, M.L., Oren, A., Fix, J.A., Caldwell, L.J., Gardner, C., 1985. Estimation of gastric residence time of the heidelberg capsule in humans: Effect of varying food composition. Gastroenterology 89, 392–397. https://doi.org/10.1016/0016-5085(85)90342-7

Mojaverian, P., Reynolds, J.C., Ouyang, A., Wirth, F., Kellner, P.E., Vlasses, P.H., 1991. Mechanism of gastric emptying of a nondisintegrating radiotelemetry capsule in man. Pharm Res 8, 97–100.

Munoz, F., Alici, G., Li, W., 2016. A magnetically actuated drug delivery system for robotic endoscopic capsules. Journal of Medical Devices, Transactions of the ASME 10. https://doi.org/10.1115/1.4031811

Munoz, F., Alici, G., Li, W., 2014. Design optimization of a magnetomechanical system for drug delivery in wireless capsule endoscopy, in: 2014 IEEE/ASME International Conference on Advanced Intelligent Mechatronics. IEEE, pp. 1097–1102.

Munoz, F., Alici, G., Zhou, H., Li, W., Sitti, M., 2018. Analysis of Magnetic Interaction in Remotely Controlled Magnetic Devices and its Application to a Capsule Robot for Drug Delivery. IEEE/ASME Transactions on Mechatronics 23, 298–310. https://doi.org/10.1109/TMECH.2017.2764902

Nam, S.J., Lee, H.S., Lim, Y.J., 2018. Evaluation of gastric disease with capsule endoscopy. Clin Endosc 51, 323–328. https://doi.org/10.5946/ce.2018.092

Neebha, T.M., Andrushia, A.D., Durga, S., 2020. A state-of-art review on antenna designs for ingestible application. Electromagn Biol Med 39, 387–402. https://doi.org/10.1080/15368378.2020.1821707

Nejati, S., Wang, J., Heredia-Rivera, U., Sedaghat, S., Woodhouse, I., Johnson, J.S., Verma, M., Rahimi, R., 2022a. Small intestinal sampling capsule for inflammatory bowel disease type detection and management. Lab on a Chip - Miniaturisation for Chemistry and Biology 22, 57–70. https://doi.org/10.1039/d1lc00451d

Nejati, S., Wang, J., Sedaghat, S., Balog, N.K., Long, A.M., Rivera, U.H., Kasi, V., Park, K., Johnson, J.S., Verma, M.S., Rahimi, R., 2022b. Smart capsule for targeted proximal colon microbiome sampling. Acta Biomater 154, 83–96. https://doi.org/10.1016/j.actbio.2022.09.050

Ng, S.C., Shi, H.Y., Hamidi, N., Underwood, F.E., Tang, W., Benchimol, E.I., Wu, J.C., Chan, F.K., Sung, J.J., Kaplan, G., 2017. The Worldwide Incidence and Prevalence of Inflammatory Bowel Disease in the 21 st Century: A Systematic Review of Population-Based Studies. Gastroenterology 152, S970–S971. https://doi.org/10.1016/s0016-5085(17)33292-4

O'Driscoll, C.M., Bernkop-Schnürch, A., Friedl, J.D., Préat, V., Jannin, V., 2019. Oral delivery of non-viral nucleic acid-based therapeutics - do we have the guts for this? European Journal of Pharmaceutical Sciences 133, 190–204. https://doi.org/10.1016/j.ejps.2019.03.027

Parasrampuria, D.A., Kanamaru, T., Connor, A., Wilding, I., Ogata, K., Shimoto, Y., Kunitada, S., 2015. Evaluation of regional gastrointestinal absorption of edoxaban using the enterion capsule. J Clin Pharmacol 55, 1286–1292. https://doi.org/10.1002/jcph.540

Park, J., Cho, Y.K., Kim, J.H., 2018. Current and future use of esophageal capsule endoscopy. Clin Endosc 51, 317–322. https://doi.org/10.5946/ce.2018.101

Park, S., Park, H., Park, S., Byungkyu, K., 2006. A paddling based locomotive mechanism for capsule endoscopy. Journal of Mechanical Science and Technology 20, 1012–1018.

Park, Sanghyeon, Lee, H., Kim, D.I., Kee, H., Park, Sukho, 2022. Active multiple-sampling capsule for gut microbiome. IEEE/ASME Transactions on Mechatronics 27, 4384–4395. https://doi.org/10.1109/TMECH.2022.3155534

Parr, A.F., Sandefer, E.P., Wissel, P., McCartney, M., McClain, C., Ryo, U.Y., Digenis, G.A., 1999. Evaluation of the feasibility and use of a prototype remote drug delivery capsule (RDDC) for non-invasive regional drug absorption studies in the GI tract of man and beagle dog. Pharm Res 16, 266–271.

Pithavala, Y.K., Heizer, W.D., Parr, A.F., O'Connor-Semmes, R.L., Brouwer, K.L., 1998. Use of the InteliSite® capsule to study ranitidine absorption from various sites within the human intestinal tract. Pharm Res 15, 1869–1875.

Plano, D., Kibler, S., Rudolph, N., Zett, O., Dressman, J., 2024. Silicon-Based Piezo Micropumps Enable Fully Flexible Drug Delivery Patterns. J Pharm Sci 113, 1555–1565. https://doi.org/10.1016/j.xphs.2024.01.003

Ramadi, K.B., Mcrae, J.C., Selsing, G., Su, A., Fernandes, R., Hickling, M., Rios, B., Babaee, S., Min, S., Gwynne, D., Jia, N.Z., Aragon, A., Ishida, K., Kuosmanen, J., Jenkins, J., Hayward, A., Kamrin, K., Traverso, G., 2023. Bioinspired, ingestible electroceutical capsules for hunger-regulating hormone modulation. Sci Robot 8, eade9676.

Rehan, M., Al-Bahadly, I., Thomas, D.G., Young, W., Cheng, L.K., Avci, E., 2023. Smart capsules for sensing and sampling the gut: Status, challenges and prospects. Gut. https://doi.org/10.1136/gutjnl-2023-329614

Rey, J.F., Ogata, H., Hosoe, N., Ohtsuka, K., Ogata, N., Ikeda, K., Aihara, H., Pangtay, I., Hibi, T., Kudo, S.E., Tajiri, H., 2012. Blinded nonrandomized comparative study of gastric examination with a magnetically guided capsule endoscope and standard videoendoscope. Gastrointest Endosc 75, 373–381. https://doi.org/10.1016/j.gie.2011.09.030

Rezaie, M., Rafiee, Z., Choi, S., 2023. A biobattery capsule for ingestible electronics in the small intestine: Biopower production from intestinal fluids activated germination of exoelectrogenic bacterial endospores. Adv Energy Mater 13. https://doi.org/10.1002/aenm.202202581

Rimawi, I.B., Muqedi, R.H., Kanaze, F.I., 2019. Development of gabapentin expandable gastroretentive controlled drug delivery system. Sci Rep 9. https://doi.org/10.1038/s41598-019-48260-8

Roda, G., Chien Ng, S., Kotze, P.G., Argollo, M., Panaccione, R., Spinelli, A., Kaser, A., Peyrin-Biroulet, L., Danese, S., 2020. Crohn's Disease. Nat Rev Dis Primers 6. https://doi.org/10.1038/s41572-020-0156-2

Roda, G., Jharap, B., Neeraj, N., Colombel, J.F., 2016. Loss of Response to Anti-TNFs: Definition, Epidemiology, and Management. Clin Transl Gastroenterol 7. https://doi.org/10.1038/ctg.2015.63

Saad, R.J., Hasler, W.L., 2011. A technical review and clinical assessment of the wireless motility capsule. Gastroenterol Hepatol (N Y) 7, 795.

Saccher, M., Kawasaki, S., Dekker, R., 2021. The long-term reliability of pre-charged CMUTs for the powering of deep implanted devices, in: IEEE International Ultrasonics Symposium, IUS. IEEE Computer Society. https://doi.org/10.1109/IUS52206.2021.9593683

Sadeghi Boroujeni, P., Nejat Pishkenari, H., Amiri Chimeh, H., Moradi, H., Vossoughi, G., 2023. Five-degree-of-freedom robust control of a magnetic endoscopic capsule using an electromagnetic system. Control Eng Pract 134, 105484. https://doi.org/10.1016/j.conengprac.2023.105484

Senekowitsch, S., Schick, P., Abrahamsson, B., Augustijns, P., Gießmann, T., Lennernäs, H., Matthys, C., Marciani, L., Pepin, X., Perkins, A., Feldmüller, M., Sulaiman, S., Weitschies, W., Wilson, C.G., Corsetti, M., Koziolek, M., 2022. Application of in vivo imaging techniques and diagnostic tools in oral drug delivery research. Pharmaceutics 14. https://doi.org/10.3390/pharmaceutics14040801

Shalon, D., Culver, R.N., Grembi, J.A., Folz, J., Treit, P. V., Shi, H., Rosenberger, F.A., Dethlefsen, L., Meng, X., Yaffe, E., Aranda-Díaz, A., Geyer, P.E., Mueller-Reif, J.B., Spencer, S., Patterson, A.D., Triadafilopoulos, G., Holmes, S.P., Mann, M., Fiehn, O., Relman, D.A., Huang, K.C., 2023. Profiling the human intestinal environment under physiological conditions. Nature. https://doi.org/10.1038/s41586-023-05989-7

Shiner, M., 1963. A capsule for obtaining sterile samples of gastrointestinal fluids. The Lancet 281, 532–533. https://doi.org/doi:10.1016/S0140-6736(63)91328-X

Simi, M., Valdastri, P., Quaglia, C., Menciassi, A., Dario, P., 2010. Design, fabrication, and testing of a capsule with hybrid locomotion for gastrointestinal tract exploration. IEEE/ASME Transactions on Mechatronics 15, 170–180. https://doi.org/10.1109/TMECH.2010.2041244

Sivaneswari, S., Karthikeyan, E., Chandana, P.J., 2017. Novel expandable gastro retentive system by unfolding mechanism of levetiracetam using simple lattice design – Formulation optimization and in vitro evaluation. Bulletin of Faculty of Pharmacy, Cairo University 55, 63–72. https://doi.org/10.1016/j.bfopcu.2017.02.003

Söderlind, E., Abrahamsson, B., Erlandsson, F., Wanke, C., Iordanov, V., Von Corswant, C., 2015. Validation of the IntelliCap® system as a tool to evaluate extended release profiles in human GI tract using metoprolol as model drug. Journal of Controlled Release 217, 300–307. https://doi.org/10.1016/j.jconrel.2015.09.024

Spanogiannopoulos, P., Bess, E.N., Carmody, R.N., Turnbaugh, P.J., 2016. The microbial pharmacists within us: A metagenomic view of xenobiotic metabolism. Nat Rev Microbiol 14, 273–287. https://doi.org/10.1038/nrmicro.2016.17

Staib, A.H., Beermann, D., Harder, S., Fuhr, U., 1989. Absorption differences of ciprofloxacin along the human gastrointestinal tract determined using a remote-control drug delivery device (HF-capsule). Am J Med 87, 66–69.

Staib, A.H., Loew, D., Harder, S., Graul, E.H., Pfab, R., 1986. Measurement of theophylline absorption from different regions of the gastro-intestinal tract using a remote controlled drug delivery device. Eur J Clin Pharmacol 30, 691–697.

Steinberg, W.H., Mina, F.A., Pick, P.G., Frey, G.H., 1965. Heidelberg Capsule I: In vitro evaluation of a new instrument for measuring intragastric pH. J Pharm Sci 54, 772–776.

Steiner, J.A., Pham, L.N., Abbott, J.J., Leang, K.K., 2022. Modeling and analysis of a soft endoluminal inchworm robot propelled by a rotating magnetic dipole field. J Mech Robot 14. https://doi.org/10.1115/1.4053114

Tojo, R., Suárez, A., Clemente, M.G., De Los Reyes-Gavilán, C.G., Margolles, A., Gueimonde, M., Ruas-Madiedo, P., 2014. Intestinal microbiota in health and disease: Role of bifidobacteria in gut homeostasis. World J Gastroenterol 20, 15163–15176. https://doi.org/10.3748/wjg.v20.i41.15163

Torres, J., Mehandru, S., Colombel, J.F., Peyrin-Biroulet, L., 2017. Crohn's disease. The Lancet 389, 1741–1755. https://doi.org/10.1016/S0140-6736(16)31711-1

Tortora, G., Valdastri, P., Susilo, E., Menciassi, A., Dario, P., Rieber, F., Schurr, M.O., 2009. Propeller-based wireless device for active capsular endoscopy in the gastric district. Minimally Invasive Therapy and Allied Technologies 18, 280–290. https://doi.org/10.1080/13645700903201167

Tran, K., Brun, R., Kuo, B., 2012. Evaluation of regional and whole gut motility using the wireless motility capsule: Relevance in clinical practice. Therap Adv Gastroenterol 5, 249–260. https://doi.org/10.1177/1756283X12437874

Travers, G.J.S., Nichols, D.S., Farooq, A., Racinais, S., Périard, J.D., 2016. Validation of an ingestible temperature data logging and telemetry system during exercise in the heat. Temperature 3, 208–219. https://doi.org/10.1080/23328940.2016.1171281

Uboldi, M., Melocchi, A., Moutaharrik, S., Palugan, L., Cerea, M., Foppoli, A., Maroni, A., Gazzaniga, A., Zema, L., 2022. Administration strategies and smart devices for drug release in specific sites of the upper GI tract. Journal of Controlled Release 348, 537–552. https://doi.org/10.1016/j.jconrel.2022.06.005

Van der Schaar, P.J., Dijksman, F., Shimizu, J., Wanke, C., Siersema, P.D., 2011. First in human study with a novel ingestible electronic drug delivery and monitoring device: The Intellicap. Gastroenterology 140, S-766. https://doi.org/10.1016/s0016-5085(11)63178-8

Van Der Schaar, P.J., Dijksman, J.F., Broekhuizen-De Gast, H., Shimizu, J., Van Lelyveld, N., Zou, H., Iordanov, V., Wanke, C., Siersema, P.D., 2013. A novel ingestible electronic drug delivery and monitoring device. Gastrointest Endosc 78, 520–528. https://doi.org/10.1016/j.gie.2013.03.170

Varum, F., Freire, A.C., Bravo, R., Basit, A.W., 2020a. OPTICORE™, an innovative and accurate colonic targeting technology. Int J Pharm 583, 119372. https://doi.org/10.1016/j.ijpharm.2020.119372

Varum, F., Freire, A.C., Fadda, H.M., Bravo, R., Basit, A.W., 2020b. A dual pH and microbiota-triggered coating (PhloralTM) for fail-safe colonic drug release. Int J Pharm 583. https://doi.org/10.1016/j.ijpharm.2020.119379

Verma, S., Nagpal, K., Singh, S.K., Mishra, D.N., 2014. Unfolding type gastroretentive film of cinnarizine based on ethyl cellulose and hydroxypropylmethyl cellulose. Int J Biol Macromol 64, 347–352. https://doi.org/10.1016/j.ijbiomac.2013.12.030

Vllasaliu, D., Thanou, M., 2022. Of devices and drugs – Ingestible bots for diagnosis and therapy. Adv Drug Deliv Rev 183. https://doi.org/10.1016/j.addr.2022.114174

Wang, W., Yan, G., Han, D., Meng, Y., Pu, P., 2020. Design and testing of a novel gastrointestinal microrobot. Biomed Microdevices 22. https://doi.org/10.1007/s10544-019-0438-1

Weitschies, W., Müller, L., Grimm, M., Koziolek, M., 2021. Ingestible devices for studying the gastrointestinal physiology and their application in oral biopharmaceutics. Adv Drug Deliv Rev 176. https://doi.org/10.1016/j.addr.2021.113853

Wilding, I., Hirst, P., Connor, A., 2000. Development of a new engineering-based capsule for human drug absorption studies. Pharmaceutical Science & Technology Today 3, 385–392.

Woo, S.H., Kim, T.W., Lee, J.H., Kim, P.U., Won, C.H., Cho, J.H., 2009. Implemented edge shape of an electrical stimulus capsule. International Journal of Medical Robotics and Computer Assisted Surgery 5, 59–65. https://doi.org/10.1002/rcs.235

Wu, L., Lu, K., 2022. Experimental investigation of a new type of driving concept for capsule robot. Intell Serv Robot 15, 661–669. https://doi.org/10.1007/s11370-022-00443-5

Xu, Y., Li, K., Zhao, Z., Meng, M.Q.H., 2022. Adaptive simultaneous magnetic actuation and localization for WCE in a tubular environment. IEEE Transactions on Robotics 38, 2812–2826. https://doi.org/10.1109/TRO.2022.3161766

Yadav, V., House, A., Matiz, S., McCoubrey, L.E., Bettano, K.A., Bhave, L., Wang, M., Fan, P., Zhou, S., Woodhouse, J.D., Poimenidou, E., Dou, L., Basit, A.W., Moy, L.Y., Saklatvala, R., Hegde, L.G., Yu, H., 2022. Ileocolonic-targeted JAK inhibitor: A safer and more effective treatment for inflammatory bowel disease. Pharmaceutics 14. https://doi.org/10.3390/pharmaceutics14112385

Yim, S., Goyal, K., Sitti, M., 2013. Magnetically actuated soft capsule with the multimodal drug release function. IEEE/ASME Transactions on Mechatronics 18, 1413–1418. https://doi.org/10.1109/TMECH.2012.2235077

Yim, S., Sitti, M., 2012. Design and rolling locomotion of a magnetically actuated soft capsule endoscope. IEEE Transactions on Robotics 28, 183–194. https://doi.org/10.1109/TRO.2011.2163861

Yu, A., Baker, J.R., Fioritto, A.F., Wang, Y., Luo, R., Li, S., Wen, B., Bly, M., Tsume, Y., Koenigsknecht, M.J., Zhang, X., Lionberger, R., Amidon, G.L., Hasler, W.L., Sun, D., 2017. Measurement of in vivo gastrointestinal release and dissolution of three locally acting mesalamine formulations in regions of the human gastrointestinal tract. Mol Pharm 14, 345–358. https://doi.org/10.1021/acs.molpharmaceut.6b00641

Yuan, S., Wan, Y., Mao, Y., Song, S., Meng, M.Q.-H., 2019. Design of a novel electromagnetic actuation system for actuating magnetic capsule robot, in: 2019 IEEE International Conference on Robotics and Biomimetics (ROBIO). IEEE, Dali, China, pp. 1513–1519.

Zarate, N., Mohammed, S.D., Newell, M., Yazaki, E., Williams, N.S., Lunniss, P.J., Semler, J.R., Mark Scott, S., 2010. Accurate localization of a fall in pH within the ileocecal region: validation using a dual-scintigraphic technique. American Journal of Physiology-Gastrointestinal and Liver Physiology 299, 1276–1286. https://doi.org/10.1152/ajpgi.00127.2010.-Stereotypical

Zhang, K., Liu, C., Yang, X., Liu, X., Guo, H., 2017. An ingestible capsule system for in-body core temperature monitoring. Microw Opt Technol Lett 59, 2670–2675. https://doi.org/10.1002/mop.30801

Zhang, S., Bellinger, A.M., Glettig, D.L., Barman, R., Lee, Y.A.L., Zhu, J., Cleveland, C., Montgomery, V.A., Gu, L., Nash, L.D., Maitland, D.J., Langer, R., Traverso, G., 2015. A pH-responsive supramolecular polymer gel as an enteric elastomer for use in gastric devices. Nat Mater 14, 1065–1071. https://doi.org/10.1038/nmat4355

Zhao, N., Luo, Y., Shen, Y., 2023. Design, modeling and validation of a deformable capsule-like crawling robot based on scissor elements. Mech Mach Theory 181. https://doi.org/10.1016/j.mechmachtheory.2022.105173

Zhou, H., Alici, G., 2022. A magnetically actuated novel robotic capsule for site-specific drug delivery inside the gastrointestinal tract. IEEE Trans Syst Man Cybern Syst 52, 4010–4020. https://doi.org/10.1109/TSMC.2021.3088952

Zhu, Y., Deng, K., Zhou, J., Lai, C., Ma, Z., Zhang, H., Pan, J., Shen, L., Bucknor, M.D., Ozhinsky, E., Kim, S., Chen, G., Ye, S.H., Zhang, Y., Liu, D., Gao, C., Xu, Y., Wang, H., Wagner, W.R., 2024. Shape-recovery of implanted shape-memory devices remotely triggered via image-guided ultrasound heating. Nat Commun 15. https://doi.org/10.1038/s41467-024-45437-2

Tab. 1. Overview of various strategies employed for the targeted treatment of gastrointestinal (GI) diseases with advantages, disadvantages, and examples; GRAS, generally recognized as safe

Strategy	Advantages	Disadvantages	Examples	References
pH-dependent polymer coatings	○ Applicable for a wide range of drugs ○ GRAS ingredients	○ Inter- and intraindividual variabilities in pH levels ○ No patient-specific customisation	Eudragit® S, Eudragit® L, Eudragit® FS 30 D, ColoPulse, Duocoat®, CODES™, Phloral®, OPTICORE™	(Awad et al., 2022; Katsuma et al., 2002; McCoubrey et al., 2023; Schellekens et al., 2012; Varum et al., 2020b, 2020a)
Microbiota-dependent polymer coatings	○ Applicable for a wide range of drugs ○ GRAS ingredients ○ Fibre fermentation function highly conserved in the microbiome	○ Inter- and intraindividual variabilities in microbiome composition ○ No patient-specific customisation	Pectin, guar gum, chitosan, resistant starch, COLAL™, Phloral®, OPTICORE™	(Awad et al., 2022; McCoubrey et al., 2023; Varum et al., 2020a, 2020b)
Time-dependent polymer coatings	○ Applicable for a wide range of drugs ○ GRAS ingredients	○ Inter- and intraindividual variabilities in transit times ○ No patient-specific customisation	Eudragit® RS 100, Eudragit® RL 100, CODES™, Chronotropic	(Awad et al., 2022; Katsuma et al., 2002; McCoubrey et al., 2023)
Prodrugs	○ Successfully used for almost a century	○ Allergic reactions and adverse events ○ Drug-specific design and therefore lengthy development ○ More complicated market entry as a novel drug	Sulfasalazine, olsalazine, 5-aminosalicylic acid-p-aminobenzyl alcohol-diamine system	(McCoubrey et al., 2023; Sousa et al., 2014; Zhao et al., 2022)
Smart capsules	○ Applicable for a wide range of drugs ○ Market entry as a medical device ○ Interaction with the user ○ Complete remote control of point of release ○ Additional features such as sensing ○ Independence from inter- and intraindividual variabilities	○ Insufficient release of particulate formulations and in the colon reported ○ Difficulties with remote capsule activation ○ Substantial dimension and therefore issues with retention ○ Potential toxicity problems related to batteries ○ Lack of sustainability ○ Expensive production	InteliSite®, Enterion™, IntelliCap®	(Al-Jawadi et al., 2018; Cummins, 2021; Rezaie et al., 2023; Wilding et al., 2000)

Tab. 2. Overview of capsule endoscopes available on the market with name, company, size (in mm), weight (in g), number of cameras, field of view, number of lights, frame rate (in fps) and operation time (in h); N.I., no information

Name	Company	Size [mm]	Weight [g]	Number of cameras	Field of view	Number of lights	Frame rate [fps]	Operation time [h]	Reference
PillCam™ SB3	Medtronic	26.2 x 11.4	3.0	1	156°	4	2 – 6	8	(Erber, 2017; "FDA approval for PillCamTM SB3," 2021; "Medtronic, PillCamTM SB 3 - Specifications," n.d.; "PillCamTM capsule endoscopy platform," 2022; Kurniawan and Keuchel, 2014)
PillCam™ COLON2	Medtronic	32.3 (+ 0.5) x 11.6	2.9 (+ 0.1)	2	2x 172°	4	4 – 35	10	("FDA approval for PillCamTM COLON2," 2014; "Medtronic PillCamTM COLON 2 - Specifications," n.d.; "PillCamTM capsule endoscopy platform," 2022; Kurniawan and Keuchel, 2014)
PillCam™ Crohn's Disease	Medtronic	32.3 (+ 0.5) x 11.6	2.9 (+ 0.1)	2	2x 172°	4	4 – 35	10	("Medtronic PillCamTM Crohn's - Specifications," n.d.; "PillCamTM capsule endoscopy platform," 2022)
ENDOCAPSULE 10	Olympus Medical Systems	26 x 11	3.3	1	160°	N.I.	2	12	(Erber, 2017; "FDA approval for ENDOCAPSULE 10," 2015; "Smart and safe: ENDOCAPSULE 10," 2021; Kurniawan and Keuchel, 2014)
OMOM® HD	JINSHAN Science & Technology	25.4 x 11	3	1	172°	4	2 – 10	12	(Kurniawan and Keuchel, 2014; "OMOM® HD: Capsule endoscopy system," n.d.)
CapsoCam Plus®	CapsoVision	31 x 11	4	4	360°	N.I.	20	15	("CapsoCam® - Specifications," n.d.; "FDA approval for CapsoCam Plus®," 2020; Erber, 2017; Kurniawan and Keuchel, 2014)
MiroCam® MC1600	IntroMedic	24.5 x 10.8	3.25 ± 0.1	1	170°	6	6	12	("FDA approval for MiroCam®," 2018; "MiroCam®: Capsule endoscpy advantages," n.d.; Kurniawan and Keuchel, 2014)
MiroCam® MC200	IntroMedic	30.1 x 10.8	3.5 ± 0.1	2	2x 170°	12	6	12	("FDA approval for MiroCam®," 2018; "MiroCam®: Capsule endoscpy advantages," n.d.; Kurniawan and Keuchel, 2014)

Tab. 3. Advantages, disadvantages and previous applications of different approaches to smart drug delivery capsule localisation in the GI tract; HF, high frequency

		Strategy	Advantages	Disadvantages	Applications	References
Mechanical Strategies		Cogwheel	○ Gamma radiation-free ○ Determination of velocity	○ Doubtful accuracy ○ Only in the small intestine ○ Large size leading to stomach retention	INSERM U61 capsule	(Lambert et al., 1991; Wilding et al., 2000)
		Thread	○ Gamma radiation-free ○ Low cost	○ Inter- and intraindividual variabilities in GI anatomy	Smith Kline French Cylinder	(Eriksen et al., 1961)
Sensing		pH/ temperature sensing	○ Gamma radiation-free ○ Additional information on GI tract	○ Inter- and intraindividual variabilities ○ Initial pH dependent on food and beverage intake	IntelliCap® capsule	(Koziolek et al., 2015; Maurer et al., 2015; Söderlind et al., 2015; Van Der Schaar et al., 2013; Van der Schaar et al., 2011; Weitschies et al., 2021)
		Pressure sensing	○ Gamma radiation-free ○ Additional information on GI tract	○ Inter- and intraindividual variabilities	N/A	(Benken and Gianchandani, 2019; Cummins, 2021; Li et al., 2017; Liao et al., 2021)
Indirect imaging		X-ray	○ Gamma radiation-free	○ Health risks ○ Ingestion of contrast medium	HF-Capsule, Smith Kline French Cylinder	(Eriksen et al., 1961; Harder et al., 1990; Staib et al., 1989, 1986)
		Gamma scintigraphy	○ Well-described ○ Observation of drug distribution possible	○ Radiation leading to health risks ○ Restricted in many countries ○ Incorporation of markers necessary ○ Difficulties in identifying anatomical features ○ Radiopharmaceutical facilities and nuclear medicine support necessary	InteliSite® capsule, InteliSite® Companion device, Enterion™ capsule	(Clear et al., 2001; Mc Caffrey et al., 2008; McGirr et al., 2009; Parasrampuria et al., 2015; Parr et al., 1999; Pithavala et al., 1998; Wilding et al., 2000)
		Magnetic resonance imaging	○ Gamma radiation-free ○ Good definition	○ Limited to a range of materials ○ Subjects must remain rotated ○ Not suitable for patients with metal implants	N/A	(Senekowitsch et al., 2022)
		Magnetic marker monitoring	○ Gamma radiation-free ○ 3D images	○ Low sensitivity ○ Few machines available ○ No anatomical imaging	N/A	(Senekowitsch et al., 2022)
Direct imaging		Push endoscopy	○ Available in many facilities ○ Collection of luminal fluids possible	○ Invasive ○ Alteration of GI physiology ○ No access to entire GI tract ○ Possible interference with smart capsule	N/A	(Mehedi et al., 2023)
		Capsule endoscopy	○ Minimal invasive ○ High temporal resolution	○ Problems with swallowability ○ Single-use	N/A	(Senekowitsch et al., 2022)

Tab. 4. Details on previously developed smart drug delivery capsules including year of publication, size (in mm), achievable payload (in mL), strategy for signal transmission, mechanism of drug release, mode of drug delivery (active or passive) and method of localisation; EPM, external permanent magnet; EEM, external electromagnet; RF, radiofrequency; N/A, not applicable

Name	Published	Size [mm]	Payload [mL]	Signal Transmission	Drug Release Mechanism	Mode of Delivery	Detection of Location	Reference
Smith Kline French Cylinder	1961	16 x 8	0.5	RF pulse	Thermomechanical	Active	Thread, fluoroscopy	(Cummins, 2021; Eriksen et al., 1961)
HF-Capsule	1986	28 x 12	1	RF pulse	Thermomechanical	Passive	X-ray fluoroscopy	(Cummins, 2021; Harder et al., 1990; Staib et al., 1989, 1986)
INSERM U61	1991	39 x 11	N/A	EPM	Thermomechanical	Active	Rotation of a cog wheel	(Lambert et al., 1991; Wilding et al., 2000)
Gastrotarget Telemetric Capsule	1994	N/A	0.2	RF pulse	Thermomechanical	Active	Dummy unit	(D'Andrea and Schentag, 1994; Wilding et al., 2000)
InteliSite® Capsule	1999	35 x 10	0.8	RF pulse	Thermomechanical	Passive	Gamma scintigraphy	(Clear et al., 2001; Cummins, 2021; Parr et al., 1999; Pithavala et al., 1998)
Enterion™ Capsule	2000	32 x 11	1	EEM	Thermomechanical	Active	Gamma scintigraphy	(Cummins, 2021; Mc Caffrey et al., 2008; Parasrampuria et al., 2015; Wilding et al., 2000)
Gröning Capsule	2007	28 x 8.5	0.17	RF pulse	Electrochemical	Active	N/A*	(Cummins, 2021; Gröning et al., 2008, 2007; Gröning and Bensmann, 2009)
InteliSite® Companion Device	2009	35 x 10	1	RF pulse	Thermomechanical	Active	Gamma scintigraphy	(McGirr et al., 2009)
Yim & Sitti	2013	40 x 15 30 x 10**	0.8	EPM	Magnetical	Active	N/A*	(Yim et al., 2013)
IntelliCap® Capsule	2013	27 x 11	0.3	Wireless 2-way transceiver	Electromechanical	Active	pH, temperature sensor	(Cummins, 2021; Mirko Koziolek et al., 2015; Maurer et al., 2015; Söderlind et al., 2015; Van Der Schaar et al., 2013; Van der Schaar et al., 2011)
Munoz et al.	2016	26 x 11	0.63	EPM	Magnetical	Active	N/A*	(Munoz et al., 2018, 2016)

Guo et al.	2019	30 x 11	0.76	RF pulse	Magnetical	Active	N/A*	(Guo et al., 2019)
Lee et al.	2022	27 x 13	N/A***	EEM	Magnetical	Active	N/A*	(Lee et al., 2022)

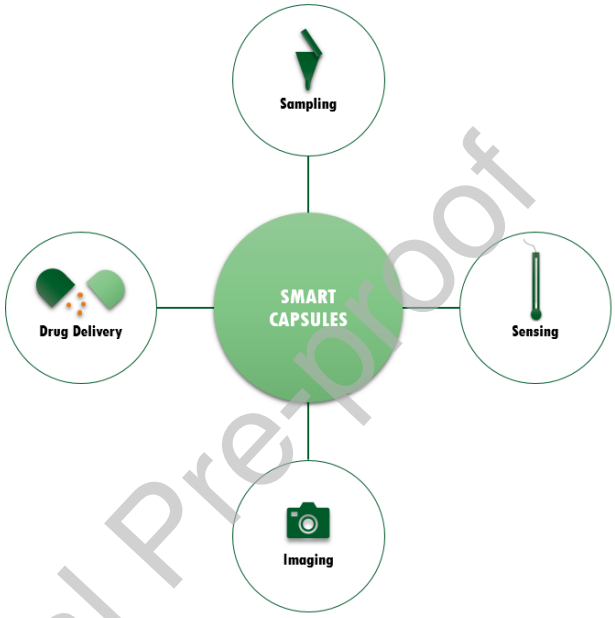


Fig. 1. Overview of therapeutic and diagnostic functionalities of smart capsules. These functionalities encompass drug delivery, imaging, sensing, and sampling.

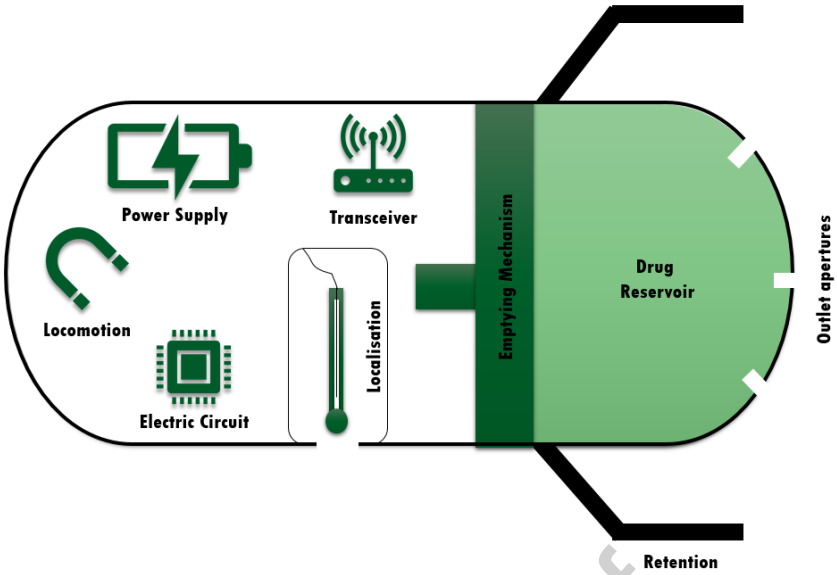


Fig. 2. Schematic overview of the main components employed in smart drug delivery capsules including drug reservoir, emptying mechanism, electric circuit, transceiver, power supply, localisation and retention strategies and locomotion module

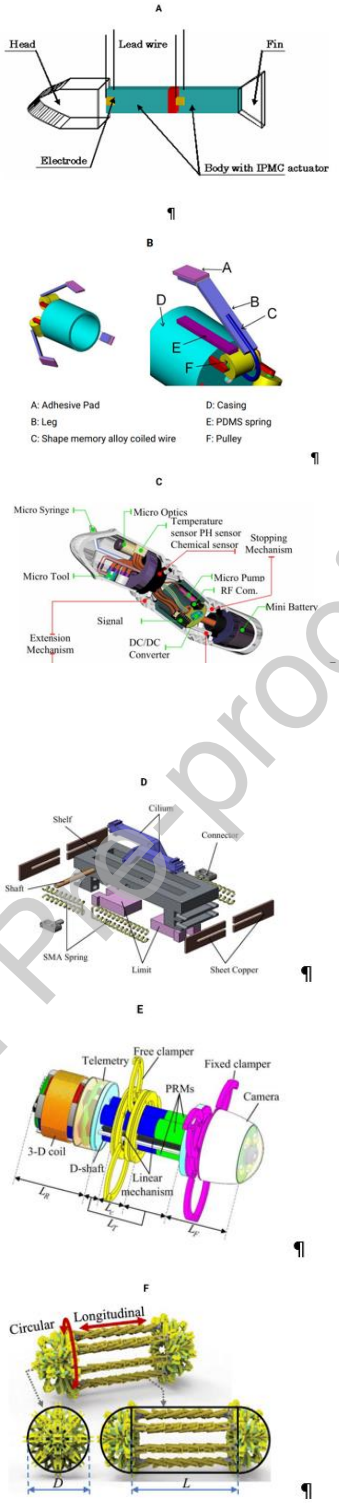


Fig. 3. Illustration of smart capsules featuring locomotion mechanisms developed by (**A**) Guo et al. (**B**) Karagozler et al. (**C**) Kim et al. (**D**) Li et al. (**E**) Gao et al. (**F**) Zhao et al.; IPMC, ionic polymer-metal composite; SMA, shape memory alloy; RF, radiofrequency; PRM, planetary reducer motor (Gao et al., 2021; Guo et al., 2006; Karagozler et al., 2006; Kim et al., 2005; Li et al., 2006; Zhao et al., 2023)

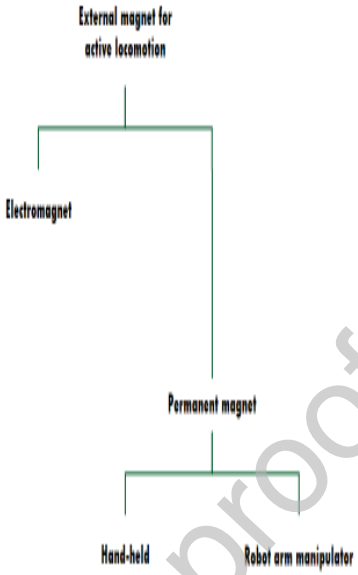


Fig. 4. Overview of various types of magnetically-controlled locomotion platforms: External electromagnets and external permanent magnets in handheld devices or robotic arm manipulators

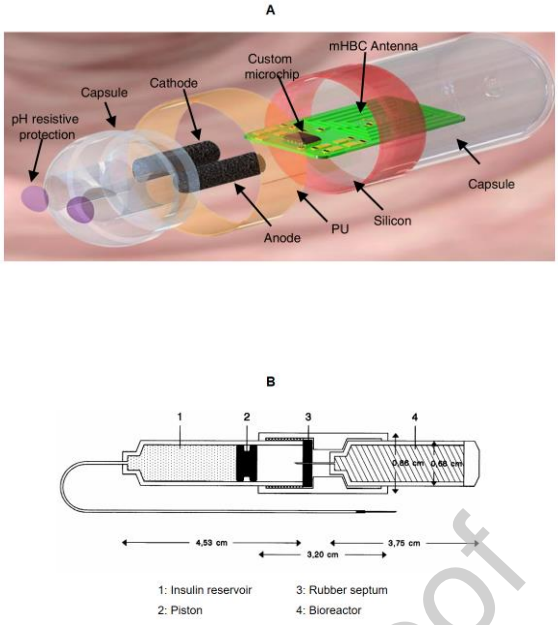
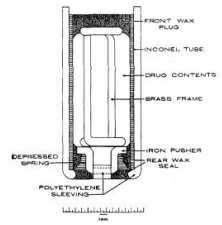
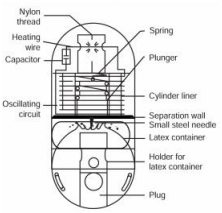


Fig. 5. Different previous approaches to bio-batteries for smart capsules: (**A**) capsule by De la Paz et al. (**B**) capsule by Gröning; mHBC, magnetically-coupled human body communications; PU, polyurethane; PEDOT:PSS, poly(3,4-ethylenedioxythiophene) polystyrene sulphonate (De la Paz et al., 2022; Gröning, 1997)

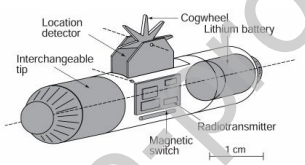
A



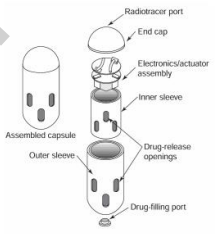
B



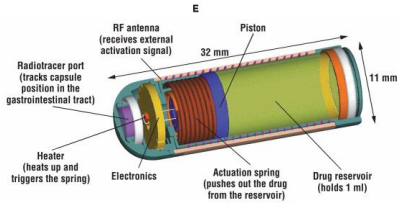
C



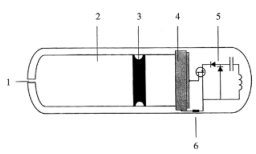
D



E



F



1: Feed opening
2: Drug reservoir
3: Piston
4: Gas-producing cell
5: High-frequency receiver
6: Resistor

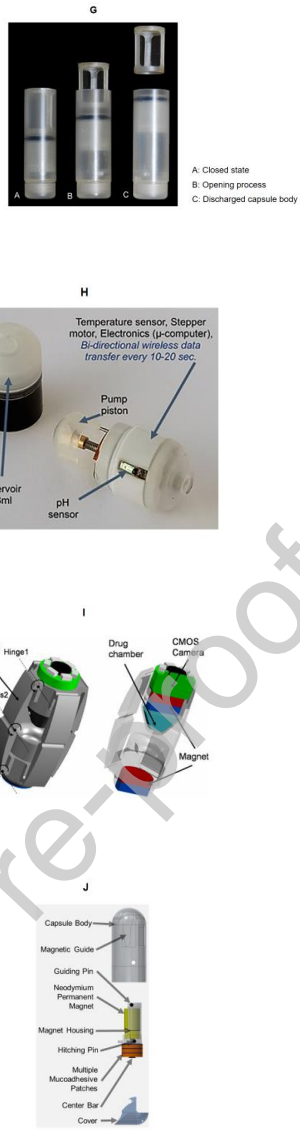


Fig. 6. Illustration of previously published smart drug delivery capsules: (**A**) Smith Kline French Cylinder (**B**) High frequency (HF)- Capsule (**C**) INSERM U61 Telemetric Capsule InteliSite® Capsule (**D**) InteliSite® Capsule (**E**) Enterion™ Capsule (**F**) Gröning Capsule (**G**) InteliSite® Companion Device (**H**) IntelliCap® Capsule (**I**) capsule by Yim & Sitti (**J**) capsule by Lee et al.; CMOS, complementary metal-oxide semiconductor; IPM, internal permanent magnet; RF, radiofrequency (Becker et al., 2014; Eriksen et al., 1961; Gröning and Bensmann, 2009; Lee et al., 2022; Mc Caffrey et al., 2008; McGirr et al., 2009; Wilding et al., 2000; Yim and Sitti, 2012)

Declaration of interests

☐The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☒The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

Brendan Griffin reports financial support was provided by University College Cork. Sophia Hoffmann reports financial support was provided by Horizon Europe. Vincent Jannin reports a relationship with Capsugel Colmar that includes: employment. Paul Galvin reports a relationship with Tyndall National Institute that includes: employment. Joseph O'Shea reports a relationship with University College Cork that includes: employment. If there are other authors, they declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Graphical Abstract