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Smart capsules for sensing and sampling the gut: status, challenges and prospects

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ABSTRACT

Smart capsules are developing at a tremendous pace with a promise to become effective clinical tools for the diagnosis and monitoring of gut health. This field emerged in the early 2000s with a successful translation of an endoscopic capsule from laboratory prototype to a commercially viable clinical device. Recently, this field has accelerated and expanded into various domains beyond imaging, including the measurement of gut physiological parameters such as temperature, pH, pressure and gas sensing, and the development of sampling devices for better insight into gut health. In this review, the status of smart capsules for sensing gut parameters is presented to provide a broad picture of these state-of-the-art devices while focusing on the technical and clinical challenges the devices need to overcome to realise their value in clinical settings. Smart capsules are developed to perform sensing operations throughout the length of the gut to better understand the body's response under various conditions. Furthermore, the prospects of such sensing devices are discussed that might help readers, especially health practitioners, to adapt to this inevitable transformation in healthcare. As a compliment to gut sensing smart capsules, significant amount of effort has been put into the development of robotic capsules to collect tissue biopsy and gut microbiota samples to perform in-depth analysis after capsule retrieval which will be a game changer for gut health diagnosis, and this advancement is also covered in this review. The expansion of smart capsules to robotic capsules for gut microbiota collection has opened new avenues for research with a great promise to revolutionise human health diagnosis, monitoring and intervention.

INTRODUCTION

The gastrointestinal (GI) tract has historically been a region of intense interest for the assessment of health. The diagnosis of gut disorders initially relied on external observation via x-ray, endoscopy and surgery until 1957 when two papers[1 2] from the same research group simultaneously reported the development of a swallowable capsule, termed an Endoradiosonde. The ingestible device could sense the gut physiological parameters internally and transmit the data through radio communication.[3 4] One capsule reported the measurement of pH, while the other reported the measurement of pressure and temperature with a capsule size of 28 mm in length and 9 mm in diameter.[1 2] Another group of researchers in the same year reported the development of a pressure measuring capsule with a capsule size of 30 mm in length and 10 mm in diameter.[5]

These advancements allowed the development of similar sized capsules to sense different parameters within the gut, but the detection of bleeding through ingestible sensors remained a challenge. In the 2000s a capsule endoscope was invented that used a small camera to record a video to detect gut lesions.[6 7] This technology was approved by the US Food and Drug Administration in 2001 and was followed by the launch of a series of other commercial endoscopic capsules.[8–10] However, these capsule endoscopes neither controlled their motion (eg, by moving quickly through sites of little/no interest or slowing their movement at target-sites) nor accurately determined their position hence still lacked efficient diagnosis potential. These limitations were addressed by various locomotion, anchoring and localisation techniques, but they are out of the scope of this review, and are discussed in detail in other papers.[8 9 11–13]

Furthermore, the commercial capsule endoscopes that capture images of the gut lining have laid the foundation for similar-sized smart capsules that can perform monitoring, therapeutic and diagnostic functions such as sensing[10 14] and drug delivery[10 15] along the GI tract.[16–18] There are various review papers on the scope and development of medical devices for the gut,[8–12 14 15] however, latest progress on sensing and sampling capsule development have not been covered in literature. In this review, recent advances in the field of gut sensing and sampling devices are described with a focus on understanding their benefits while addressing the limitations of these devices.

The review starts with fundamentals of gut structure and physiology and details of gut microbiota. Then it continues with smart capsules for sensing different gut parameters and robotic capsules for sampling gut. Finally, the review discusses potential future avenues and implications of these capsules for personalised medicine, personal diet and early diagnosis of various gut diseases.

THE GI TRACT AND MICROBIOTA

The human GI tract is a 7–9 m long passage and in an average human lifetime, around 60 tonnes of food passes through it.[19] The food is digested and absorbed by the gut using a range of physical and chemical processes. The gut mainly comprises four distinct segments namely oesophagus, stomach, small intestine and large intestine. The segments have different pH levels, transit profiles, contain diverse chemical compounds and follow unique behaviour to move food through them, as outlined in figure 1. Any chemical or

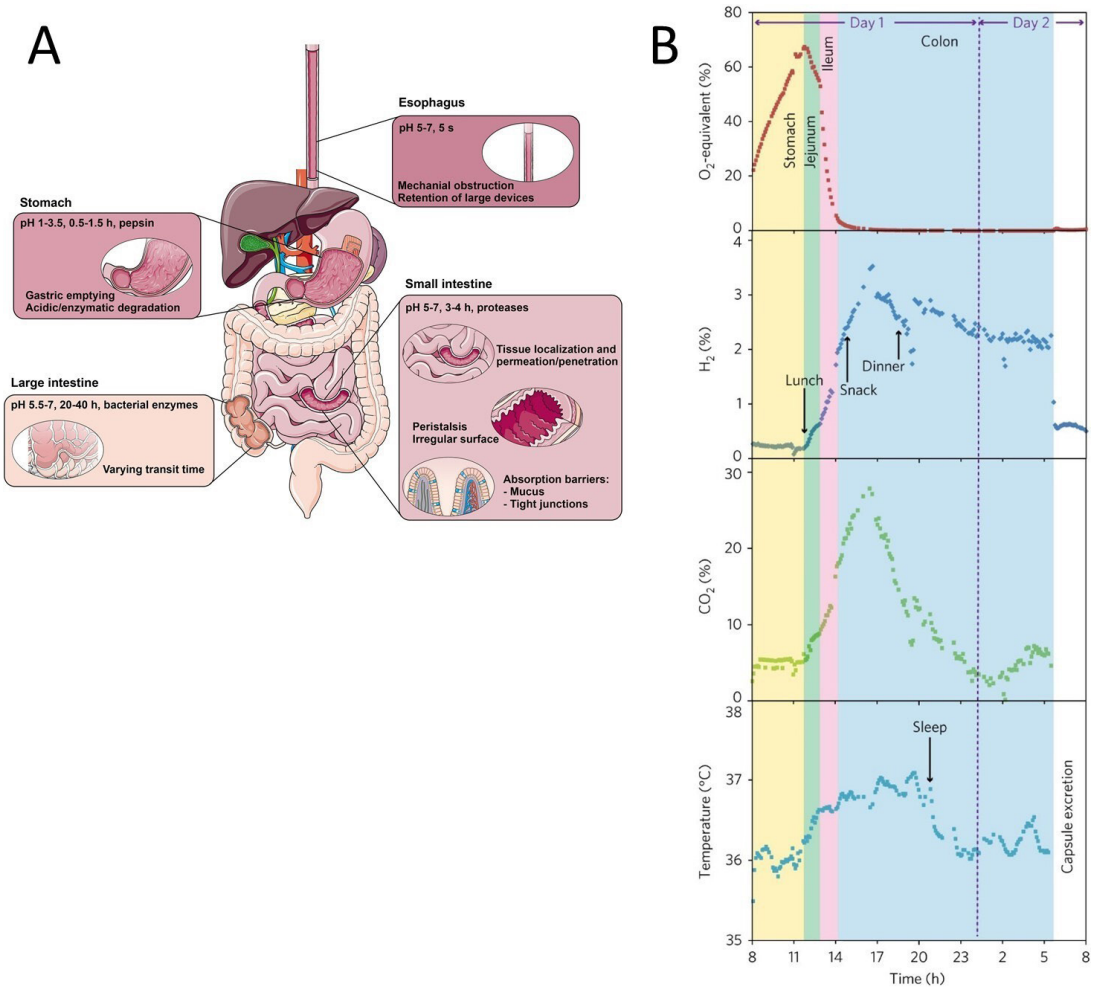

Figure 1 (A) Human GI (digestive) tract with each distinct segment of the gut identified.[15] (B) Temperature and gas profiles of the gut, measured internally, which shows the daily response in each segment.[16]

biological changes from normal within each segment can be used as a biomarker for a range of health conditions. The unique features of each of these segments is discussed in detail below.

Oesophagus

The oesophagus is a tube-like structure that connects the mouth or oral cavity with the stomach. The food is chewed in the mouth and broken down into smaller particles and mixed with saliva that prepares the food for absorption. The food transits through the oesophagus in a few seconds to the stomach where it stays for a few hours depending on the type of food, activity level and fluid intake. The oesophagus and stomach are separated by a sphincter that allows passage of the food from the oesophagus to the stomach while stopping the backflow of stomach fluid into the oesophagus.

Gastro-oesophageal reflux disease (GORD) is a health condition that produces irritation, heart burn and inflammation in the oesophagus, if the oesophageal sphincter is not closed properly.[20] This allows stomach acid to enter the oesophagus creating acid reflux episodes that may damage oesophageal tissue. Another health condition affecting the oesophagus is achalasia in which the lower oesophageal muscles fail to relax which restricts the passage of food to the stomach.[21] Furthermore, dysmotility is a dysfunction in which contraction from the oesophageal muscles are impaired resulting in imbalanced and uncoordinated peristaltic movement, leading to gut-related diseases.[22] The peristaltic movement of the oesophagus is an important physiological process transporting food into the stomach and any disorder can be harmful. Therefore, this region sometimes requires monitoring to observe potential health problems related to the upper gut.

Stomach

The stomach is a J-shaped, hollow and dilated part of the upper gut that holds the food once it passes through the oesophagus. The gastric glands of the stomach generate hydrochloric (HCl) acid which maintains the pH at low levels (1–3.5 pH) that has two main functions. First, it kills any unwanted bacteria ingested with the food, and second, it starts the digestion of the food by activating the digestive juices (enzymes), and breaking down the mixture into a paste, known as chyme. The stomach wall secretes the digestive enzyme in an inactive form (eg, pepsinogen), which is activated by the acid into a functional enzyme (eg, pepsin). The muscular contractions (peristaltic movements) from the stomach wall blends the food and digestive enzymes creating chyme, which is released in the small intestine, with the gastric emptying time dependent on the type of food consumed.

Achlorhydria is a health condition that results from low gastric secretions by the stomach glands.[23] This leads to insufficient amounts of HCl and digestive enzymes being produced which impairs food digestion. Furthermore, gastric motility disorder is an impairment that leads to gastroparesis in case of delayed gastric emptying or dumping syndrome in case of rapid gastric emptying.[24 25] Therefore, several parameters in the stomach require monitoring. First, the

amount and time of HCl acid secretion from the stomach glands to maintain the low pH, and the impacts of this on the digestion process are very important components. Second, the gastric emptying time is also extremely important for the digestion process and sometimes requires monitoring for nutritional studies, and lastly, pH sensing at various segments of the gut is critical to the diagnosis of gut-related problems.

Small intestine

This is the largest section of the gut measuring about 6–7 m in length and has a diameter of around 25–30 mm. The small intestine is also referred to as the small bowel and is further divided into three main segments, that is, duodenum, jejunum and ileum. The duodenum is the section nearest to the stomach and is the shortest of the segments. This segment initially secretes sodium bicarbonate to neutralise the acid contained in chyme from the stomach which increases the pH level to around 7 (neutral level). This smooth section soon gives way to more folded tissue covered with finger-like projections called villi, which are further covered in microvilli that increases the surface area. Duodenal tissue also secretes hormones to signal the release of digestive enzymes to prepare the small intestine for nutrient absorption and generates peristaltic movements to push the chyme towards the distal end of the gut, so the remaining food is moved to the next segment, the jejunum. The jejunum is around 2.5 m long, and is also covered with villi/microvilli that helps in absorption. Its main function is to absorb amino acids while moving the content further in the ileum segment through peristaltic movements. The ileum is about 3 m in length and also contain villi/microvilli similar to duodenum/jejunum. This segment helps bile acid to be absorbed by the host along with fatty acids, glucose, fructose and glycerol.

The small intestinal region can be affected by a number of health conditions that require diagnosis and treatment. Small intestinal bacterial overgrowth (SIBO) can result is malabsorption, diarrhoea, osteoporosis and nutritional deficiencies.[26] Furthermore, dysmotility is a condition in which contraction from the intestinal muscles are impaired resulting in imbalanced and uncoordinated peristaltic movement, leading to gut-related diseases, for example, pseudo-obstruction.[27] In addition, the release of gases due to fibre fermentation, bacterial overgrowth in the small intestine, reduced digestion or absorption of food nutrients (malabsorption) and abnormal (slow or fast) movement of food through small intestine can indicate various health conditions. Lastly, IBS, IBD and many other diseases are linked to this region that require monitoring for diagnosis and treatment purposes.

Large intestine

The large intestine or colon is the last segment of the gut and comprises the caecum, ascending colon, transverse colon, descending colon, sigmoid colon and rectum which is followed by the anus which is the last connection of the gut in the body. The overall length is about 1.5 m, and it contains densely packed bacterial populations in order of 10^{10}–10^{12} organisms. The colon absorbs water and any remaining nutrients from the digesta and short chain fatty acids produced by microbial fermentation and excretes the residual undigestible food (faeces) from the body. This faecal matter is used worldwide for the diagnosis of various gut disorders, for example, detecting infections, identifying bleeding disorders, determining poor nutrient absorption, diarrhoea, constipation and in colon cancer diagnosis.[28 29]

Gut microbiota

A huge population of microorganisms (bacteria, archaea and fungi), collectively known as the microbiota, live inside the gut and play a major role in fibre fermentation and the synthesis of short chain fatty acids, and some nutrients (eg, vitamins).[30] This population of microorganisms have been studied for a long time, and numerous studies on the relationship between microbiota and human health reveal that the microbiota can act as a biomarker for human health.[31] The human meta-organism comprises bacterial colonies which include approximately 10^{13} prokaryotic organisms with a biomass of around 0.2 kg.[32] Although the human microbiota is still not fully explored, it is pertinent that it colonises the mucosa layer, which covers the columnar epithelium of the GI tract and the digesta within the intestinal lumen,[33] as depicted in figure 2.

The knowledge of the relationship between the host and its microbiota has progressed significantly and suggests that the microbiota is a crucial component of human health. Researchers are exploring obesity, IBD, biochemical processes and diabetes with the help of microbiota.[34–38] It is considered that microbiota can be informative of the health status over the life of the host and can even assist in early diagnosis of diseases like cancer, obesity and diabetes.[34 35 39] Furthermore, the analysis of microbiota can lead to improved treatment of diseases such as ulceration, coeliac disease, Crohn's disease and IBS.[40] Microbiota can also help to study the relationship or interaction between nutrition and human health.[40 41] Comprehensively, it can be inferred that the human gut microbiota is greatly influential to human health.

Recent research studies suggest that the microbiota can potentially determine the mood, behaviour and several other characteristics of the host.[42] The gut microbiota has been shown to influence brain function and behaviour, and play a role in stress and anxiety, depression and mental disorders.[43–45] Studies have looked at the impact of microbiota on mood, and revealed that the microbiota regulate emotions and cognition through the gut-brain axis which is a bidirectional communication link between the GI tract and the central nervous system.[46]

Impact of microbiota on host health and the limitations of sampling methods

Recent studies suggest the assessment of the human intestinal microbiome can reveal negative impacts on host health from some bacterial interactions with food. A study conducted on 40 human volunteers revealed that microbiota in the intestine produce trimethylamine-N-oxide from phosphatidylcholine (a chemical present in some foods), which has been shown to contribute towards the physiopathology of heart disease.[47] The gut microbiota is an important tool to observe the effects on physiopathological parameters and on controlling inflammation. Rodent studies have observed the impact of an increase in bifidobacteria within the gut microbiota following consumption of a high fat diet which induced diabetes, suggested that the gut microbiota can be indicative of inflammation during the occurrence of diabetes and obesity.[48] A study also determined that artificial sweeteners induced glucose intolerance by altering the gut microbiota.[37] Furthermore, the same group of researchers revealed that dietary effects on individual animals were different due to the response of their gut microbiota in a related study.[38]

In general, obesity is co-related with the consumption of food. Studies using rodent models have revealed that weight regain is highly dependent on the gut microbiota,[34] suggesting that the weight regain phenomenon may be understood and resolved by targeting the microbiota.

The changes in diversity of microbiota is prominent in early life but gradually decreases with age,[49] and is also dependent on various other factors like diet[50–53] and living conditions.[54] The human gut microbiome may contribute towards the

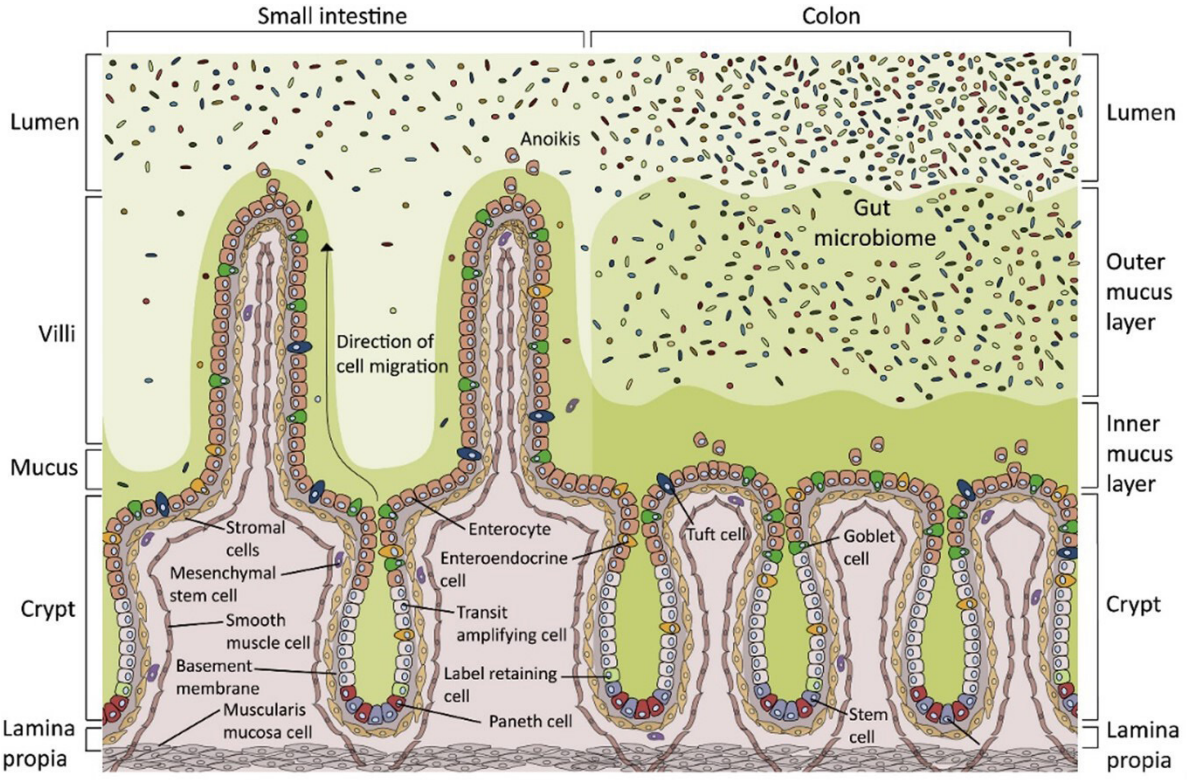

Figure 2 Representation of microbial population across the lumen and mucosa layer in both the small intestine and colon. The villi structure is only present in the small intestine along with a mucus layer whereas the colon contains two mucus layers. Reproduced from Fellows and Varga-Weisz[159] licensed under CC BY 4.0.

development of several diseases including type 2 diabetes,[55] metabolic diseases,[56 57] arterial dysfunction,[58] IBS[59] and cancer.[60] A study using an unsupervised machine learning algorithm without age information on available 16S rRNA sequencing data from newborns to centenarians showed the ageing progression of microbial communities.[61] The compiled data identified 35 genera related to age progression and when compared with the literature, they showed the loss of some beneficial genera and indicated an increase in inflammation and cancer-related genera in elderly subjects. Another study looked at the linkage between ageing and gut microbiome, and identified distinct groups of taxa that changed with ageing and discovered that the alterations were different in healthy and unhealthy ageing.[62]

The most common samples used as a proxy for intestinal microbiota are faecal samples, as they are easy to collect non-invasively and can be collected repeatedly from the same individual. However, faecal samples are collected at the end of the 9 m long gut that restricts extraction of spatial and temporal information from these samples as they are not collected from the actual site of digestion.[63 64] This is a major limitation to data interpretation since associating diseases to certain location of the gut and site-specific treatment is not possible. This has been demonstrated in animal studies that show major changes in the intestinal microbiota are not always reflected in the faecal microbiota.[65] Furthermore, the faecal sample is contaminated downstream from the site of disease by subsequent microbial populations and gut secretions during transit to the end of the GI tract.[66 67] Another method used to study gut microbiota is by using flexible endoscopy with biopsy tools. However, biopsy tools are designed to collect tissue samples, and they cannot reliably capture microbial content. Hence, the current conventional tools available to collect microbial samples from the intestine without contamination have limitations. These methods are also tethered which limits their reach into the small intestine and the section of small intestine closest to colon (ileum) is a home to a different population of microbiota to the hind gut.[68] This method also involves a risk of gut perforation and bleeding, and the procedure is invasive and unpleasant for a patient.[69–71]

In next sections, the latest methods used for sensing gut parameters and the use of untethered tools for sampling the gut microbiota are covered.

SMART CAPSULES FOR SENSING THE GUT

The wireless capsule endoscope (WCE), M2A, was developed as an alternative to tethered endoscopes by Given Imaging in the beginning of 21st century.[6] This WCE was a pill-sized capsule (26 mm×Ø 11 mm) that was swallowed and used intrinsic peristaltic forces to move along the GI tract until it could be recovered from human faecal waste. Through its passage, it captured images that were transferred wirelessly to a recorder, which were examined after the trial.[9] Although this device assisted with diagnostic procedures, provided ease and comfort to the patient as compared with tethered endoscope, the visual analysis provided incomplete information about gut diseases. Therefore, subsequent similar-sized capsules with a wider range of sensors as shown in figure 3 used to measure the physiological, biological and chemical parameters are detailed below and shown in table 1.

pH sensing

GORD producing irritation, heart burn and inflammation in the oesophagus has been traditionally monitored though catheter-based pH measurement tools which are uncomfortable and restrict the daily activities of patients. A wireless Bravo reflex

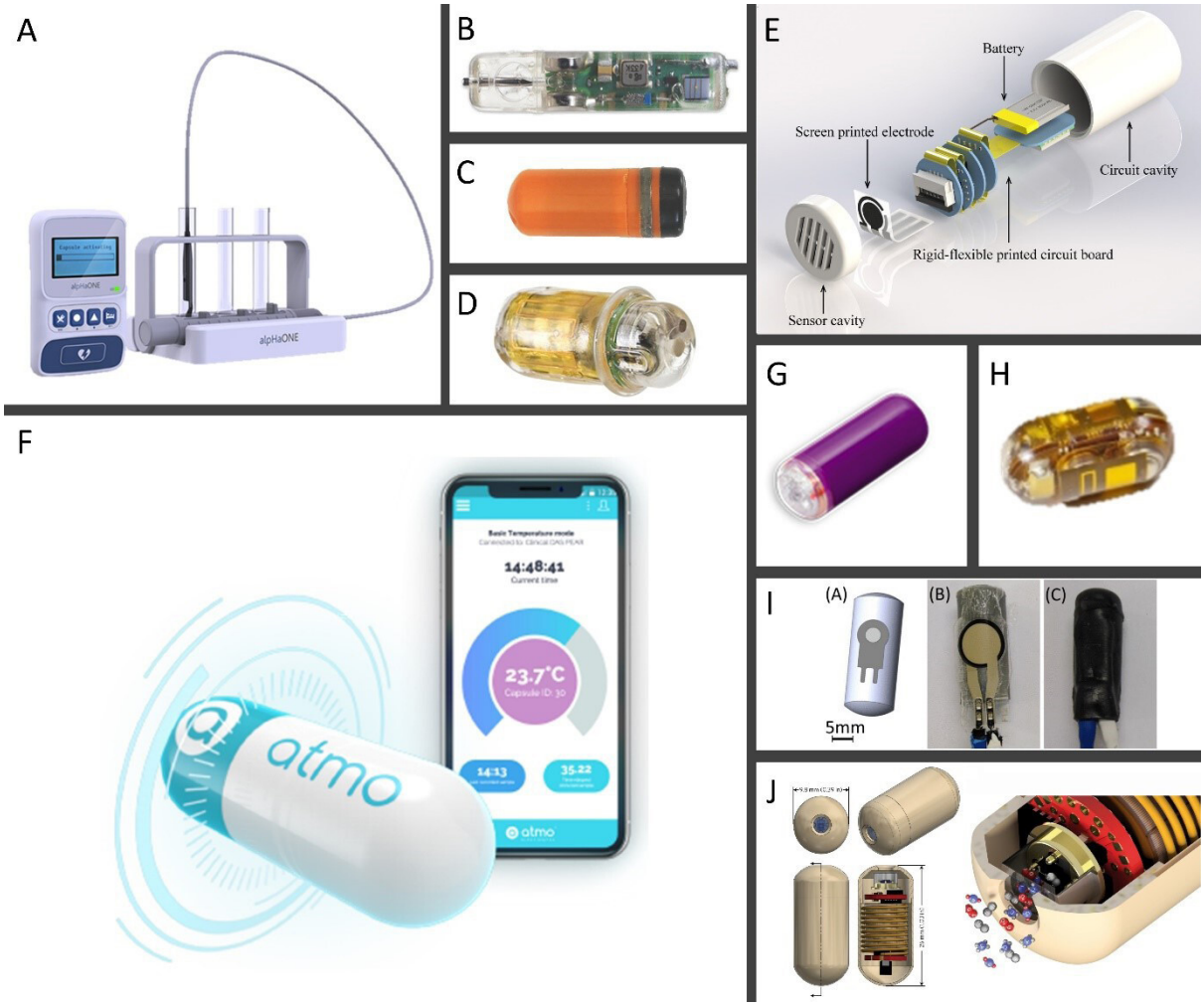

Figure 3 Gut sensing devices for measuring various gut parameters. (A) alphaOne pH monitoring capsule by the Jinshan group[75] and (B) Bravo reflex capsule by Medtronic[72] are used to record acid reflux episodes to diagnose gastro-oesophageal reflux disease by attachment to the oesophageal wall. (C) Heidelberg pH capsule for upper GI tract use to determine achlorhydria by holding it inside the stomach.[78] (D) SmartPill by Medtronic to measure pH, temperature and pressure throughout the gut that can also generate a transit profile.[81] (E) Laboratory prototype to measure pH.[87] (F) Atmo Gas Capsule by Atmo Biosciences to measure gases from inside the gut that simultaneously generates the gas profile (results) on a phone application.[112] (G) VitalSense by Philips Respironics[97] and (H) eCelsius by BodyCap[96] used to measure core body temperature. (I) Capsule prototype to measure peristaltic pressure.[106] (J) Capsule to measure gases in the gut.[16]

capsule (Medtronic, USA)[72] overcame these limitations by attaching the capsule to the oesophageal wall using an endoscope and continuous pH monitoring became possible for several days.[73 74] Recently, Jinshan group (China) launched the alphaONE pH monitoring capsule (26.5 mm×6 mm×5.5 mm)[75] as shown in figure 3A that was formerly known as JSPH and had proven its efficacy for patients with GORD in clinical trials.[76 77] The wireless capsule technology showed similar results to the traditional catheter while improving the feasibility and safety for performing GORD tests.

An insufficient amount of HCl in the stomach due to low gastric secretions results in achlorhydria that can be detected by a Heidelberg pH capsule (Heidelberg Medical, Germany),[78] a method invented in 1960s.[79] The Heidelberg pH capsule is used in the upper GI tract and is held in the stomach using tethered methods, that is, a thread is attached to the capsule that is tied outside mouth, to continuously measure the pH level while sodium bicarbonate is introduced in the stomach to neutralise the gastric juice.[80] Afterwards, the time taken by the gastric secretions to convert the gastric juice from a base to acid nature is used to determine the health of the patient. This capsule is a unique tool for detecting achlorhydria by measuring the acidic content in the stomach which can impair the food digestion process.

The normal pH level of distinct segments of the GI tract changes with the development of some GI-related diseases (eg, ulcer, UC, Crohn's disease, GORD), that require pH monitoring of the whole GI tract and wireless capsules are best suited to monitor such situations. A commercial capsule SmartPill (Medtronic, USA)[81] measures the pH of the entire gut along with temperature and pressure measurements, and offers an alternative to gastric emptying scintigraphy (GES) for measuring gastric emptying times. It has been used to determine the complete transit profile of the GI tract including small and large bowel transit times to help treat patients with chronic constipation.[82 83] Another commercial capsule IntelliCap (Medimetrics, The Netherlands),[84] used for drug delivery, has also been used to determine the transit times of the whole gut by measuring the pH and temperature in humans and animals.[85 86] The capsule technology offers significant benefits over traditional GES method as the capsule generates complete transit profile of the gut and the method has not reported any after-effects on gut motility (peristaltic movement).

Table 1 Sensing technologies using smart capsules

Name	Dimension (mm)	Sensing parameters				Evaluation
		pH	Temperature (°C)	Pressure (mm Hg)	Gas	
Bravo[72]	25×6×5.5	1–7	NA	NA	NA	CA, in vivo
alphaONE[75]	26.5×6×5.5	1–9	NA	NA	NA	CA, in vivo
Heidelberg[78]	21×Ø 8	1–8	NA	NA	NA	CA, in vivo
SmartPill[81]	26.8×Ø 11.7	0–9	25–49	0–350	NA	CA, in vivo
eCelsius[96]	17.7×Ø 8.9	NA	25–45	NA	NA	CA, in vivo
VitalSense[97]	23×Ø 8.7	NA	32–42	NA	NA	CA, in vivo
CorTemp[98]	22.4×Ø 10.9	NA	10–50	NA	NA	CA, in vivo
myTemp[99]	20×Ø 8	NA	30–45	NA	NA	CA, in vivo
IntelliCap[84]	26.7×Ø 11	1–8	20–40	NA	NA	CA*, in vivo
BEST[88]	38×8×4	1.9–12	NA	NA	NA	LP, in vivo
Cheng *et al*[87]	26×Ø 14.5	1–9	NA	NA	NA	LP, in vivo
Xu *et al*[89]	26×Ø 11	0–14	35–42	95–110	NA	LP, in vivo
Zhao *et al*[90]	22×Ø 11	1–10	34–42	70–150	NA	LP, in vivo
Benken and Gianchandani[102]	24×Ø 12	NA	NA	0–262	NA	LP, in vivo
Kim *et al*[107]	30×Ø 13	NA	NA	0–1103	NA	LP, in vivo
Rehan *et al*[106]	30×Ø 12	NA	NA	0–265	NA	LP, ex vivo
Kalantar-Zadeh *et al*[16]	26×Ø 9.8	NA	Yes	NA	Yes	LP, in vivo
Atmo Biosciences[112]	28×Ø 11	NA	Yes	NA	Yes	CA, in vivo

CA*, discontinued; CA, commercially available; LP, laboratory prototype; NA, not available.

Some prototypes tested in vivo to measure pH have also been reported in the literature. A recyclable smart capsule prototype has used an iridium oxide-based sensor to precisely monitor the pH in a beagle dog study, however, the overall size was slightly bigger and battery life was shorter than commercial capsules.[87] A battery-less prototype has also been used to determine acid reflux episodes from a pig's oesophagus and performed well when compared with the Bravo capsule in similar in vivo experiments.[88] Another capsule prototype tested in humans monitored pH with a high resolution of 0.001, in addition to measuring temperature and pressure.[89] The improved design with better power consumption of sensors allowed the device to measure gut parameters for almost 10 days.[90]

Drug absorption is highly dependent on transit times which vary from animal to animal and depend in turn on feeding rate and time. Therefore, pH sensing throughout the gut using the Bravo capsule has been performed to determine individual (stomach, small intestine, large intestine) transit times, with the capsule allowed to pass through the gut instead of being attached to the oesophageal wall.[91]

The pH measurement of different segments of the gut can now be accurately and precisely measured with smart capsules, which can help diagnose abnormal conditions and assist in generating transit profiles that are useful tools in gut health diagnosis. The smart capsules for pH sensing can assist in better understanding of diseases like GORD,[20] inflammation, achlorhydria,[23] ulcer, UC, Crohn's disease, chronic constipation, diarrhoea[29] and has a potential to replace some of the traditional methods. These smart capsules sometimes embed a temperature sensor to measure the core body temperature and specifically to determine the time of excretion of the capsule from the body.

Temperature sensing

The normal body temperature of a healthy human is 37°C and when the body loses more heat than it generates, this condition leads to hypothermia when the core (internal) body temperature falls below 35°C. Conversely, if the core body temperature increases above 40°C, it leads to hyperthermia and can result in heat stroke that could be life threatening. For hypothermia or hyperthermia, temperature monitoring is extremely important and can help in determining safe and appropriate treatment.[92] For accurate monitoring of the core body temperature, the gut is a promising candidate as sometimes axillary (outside) temperature readings via thermometer or contactless infrared pyrometer are inaccurate.[93 94] Therefore, measurement of the core body temperature through ingestible devices like smart capsules which continuously measure the gut temperature can be more accurate when compared with other methods.[94] Other applications include the monitoring of internal body temperatures of athletes continuously while they are training or performing as the core body temperature changes with exercise intensity and activity time which is useful in determining optimum performance level.[95]

A commercial ingestible capsule (eCelsius) measured the core body temperatures of athletes during the road cycling world championship.[95] The temperature of 25% of the athletes was recorded above 40°C (with the highest individual measurement of 41.5°C). Although none of the athletes were treated for heat stroke (hyperthermia), it is likely that their performance was affected.[95] Several commercial capsules are available to measure the core body temperature such as eCelsius (BodyCap, France),[96] VitalSense (Philips Respironics, USA),[97] CorTemp (HQ, USA)[98] and myTemp (myTemp, The Netherlands).[99] A study compared the accuracy and responsiveness of four commercial capsules (eCelsius, VitalSense, CorTemp and myTemp) and showed small differences across the tested capsules.[100] Another study on eight participants compared the performance of eCelsius and myTemp capsules by measuring the rectal temperature simultaneously during and after the exercise. The myTemp device showed better performance while the eCelsius had an average systematic error of about 0.2°C, which could be eliminated by calibration of the capsule before the trial.[101] Smart capsules that measure the core body temperature are more accurate than existing instrumentation and can perform measurement during exercise, which is not possible with traditional methods.[95 101]

One of the functions of the gut through which the temperature sensing smart capsule transits from one segment to the next and eventually is excreted from the body is peristaltic movement. Peristaltic movements apply a diverse range of forces, and sometimes these can be measured to diagnose potential health problems.

Pressure sensing

The food moves from mouth to the stomach through the oesophagus using peristaltic movement to push the food in a distal direction. Achalasia is a condition in which lower oesophageal muscles fail to relax which restricts the passage of food to the stomach. Oesophageal manometry is traditionally performed using tethered devices to monitor the oesophagus for movement of food towards the stomach by measuring the pressure applied by the peristaltic movements.[21] A wireless capsule (24 mm×Ø 12 mm) has measured the peristaltic pressure in a beagle dog for 26-hour period, which showed that a smart capsule can be used for long-term monitoring as opposed to tethered devices.[102] Another capsule prototype with better sensor power consumption allowed measurement of gut parameters including peristaltic pressure through a full gut transit, with the authors claiming that the smart capsule had a battery life of 233 hours.[90] Another group tested a capsule prototype in 24 human subjects which monitored peristaltic pressure with a maximum error of 0.15 kPa and an 80% success rate in detecting poor gastric motility in the tested patients, along with measuring temperature and pH.[103] Smart capsules that measure the peristaltic pressure of the oesophagus allows health practitioners to assess disorders of the lower oesophageal muscles, providing a better diagnosis.

Dysmotility is a dysfunction in which contraction from the intestinal or oesophageal muscles are impaired resulting in imbalanced and uncoordinated peristaltic movement, leading to gut related diseases. For monitoring the manometry of the entire gut, a few commercial capsules are available, for example, the SmartPill motility capsule and the Bravo capsule.[72 81] A capsule prototype tested in both healthy and constipated subjects revealed that the colonic contraction in normal patients was significantly higher than the patients with constipation which resulted in the chyme (food residue) staying longer in the colon of constipated patients and higher absorption of water leading to dryer stools and more difficult defecation.[90]

The pressure measured by commercial capsule, for example, SmartPill, Bravo and other laboratory prototypes mentioned earlier, is intraluminal pressure that is the cumulative pressure within each distinctive region (eg, stomach, small intestine, large intestine) and is different from peristaltic forces so provides less information on the amount and frequency of peristaltic contraction. A prototype used two Micro Electromechanical Systems (MEMS)-based sensors to nullify the impact of intraluminal pressure and removed the disturbances from breathing and heartbeat signals of live subjects, hence successfully estimated the peristaltic contraction forces.[104 105] In another paper, peristaltic forces were measured using a force sensor that provided real-time information on gut motility including contraction frequency and the amount of peristaltic forces generated by the intestines for better diagnosis of the gut health.[106]

Another application area for pressure sensing capsules is the estimation of transit times through distinct sections of the gut, for example, oesophagus, stomach and colon. A capsule prototype used MEMS-based pressure sensor to measure the intraluminal pressure of the gut, determined that the pressure in each region represented different cumulative pressures so pressure signals could be used for estimating transit times.[107]

Smart capsules with pressure sensing capability provide a viable solution for the diagnosis of gut disorders (eg, achalasia and dysmotility) as they offer accurate information on gut motility, for each distinctive segment of the gut that is a crucial factor used to determine overall gut health. These capsules can also be used to determine transit profiles which are helpful in determining the digestion and absorption that provide better insight of the gut health.

Another way to determine the transit profile is by sensing the gases throughout the length of the gut as each segment generates different types and quantities of gases.

Gas sensing

Gases are present inside the gut partly because of swallowed air, but other significant sources are fibre fermentation, bacterial overgrowth in the small intestine, reduced digestion or absorption of food nutrients (malabsorption) and unnatural (slow or fast) movement of food through small intestine. These gases are key in detecting various gut-related disorders like IBS, carbohydrate malabsorption and SIBO. The current gold standard is breath testing as it is easy to perform and non-invasive, but it does not provide any information about the origin (point of gas generation) of the detected gases.[108] A hydrogen sensing capsule was developed to overcome the limitations of breath tests and tested in vivo in a pig model as a proof-of-concept demonstration.[109] The sensing parameters were then extended to include the measurements of methane and carbon dioxide gases.[110] Finally, the gas-sensing capsule with the capability to measure oxygen, hydrogen and carbon dioxide was tested in human subjects and gathered precise information on the origin of the gas generation which was unable to be obtained by a breath test performed simultaneously in human subjects.[16 111] The Atmo Gas Capsule (Atmo Biosciences, Australia)[112] as shown in figure 3F was tested in humans and compared with the SmartPill Motility Capsule (Medtronic, USA)[81] to generate gut transit profiles.[113]

An important parameter considered in gut health diagnosis is accurate digestion and absorption measurement, which is assisted by gas-sensing smart capsules that provide accurate measurement of gut performance.

ROBOTIC CAPSULES FOR SAMPLING THE GUT

The study of gut microbiota is gaining massive attention due to its significant impact on human health. The gut microbiota is an important factor in human health, and it can act as a biomarker for early diagnosis of diseases like diabetes, cancer and obesity. The gut microbiota can also be used for better identification of IBD, ulcer, coeliac disease, Crohn's disease and IBS. The current gold standard for collecting a sample of gut microbiota is faecal sampling but it is highly contaminated, and it is not possible to localise faecal samples which means it is not possible to associate a particular disease to a certain location within the 9 m long gut. The microbiota contains a depth of information that cannot be fully captured by smart capsules through sensing or imaging, so robotic capsules are being developed to collect samples from the gut to allow detailed examination after capsule retrieval. Devices that can collect a sample from the gut are divided into two broad categories. First, biopsy devices that can collect a small tissue sample from the gut wall, and second, sampling devices that can collect gut content-based (fluid) samples which contain digesta, mucus, microbiota and exfoliates.

Biopsy devices for tissue sampling

Due to the limitations of tethered endoscopy with biopsy tools in terms of their reach into the gut and risk of gut perforation and bleeding, robotic capsules were developed to perform tissue biopsy. In 2003, a patent application proposed a wireless capsule system to collect a biopsy specimen in a biological body using microspectroscopy and/or biosensors.[114] This capsule contained two motorised blades to capture solid tissue or a liquid specimen that could be stored in two dedicated compartments to avoid contamination until its recovery. Another design consisted of a razor connected to a torsional spring was proposed that triggered the biopsy process by melting a paraffin block which allowed the razor to rotate at high speed with the help of torsion spring to capture a tissue sample.[115] Both approaches required the capsule to be in close contact (almost rubbing) with the intestinal wall to capture the tissue. To allow this to occur, a magnetic biopsy capsule was used and an external magnet held the capsule's lateral hole against the intestinal wall while a cylindrical razor blade cut the tissue with magnetic actuation.[116] However, this design lacked a triggering mechanism to effectively locate the target-site. Therefore, a design with a micro reed switch that triggered the biopsy process based on external magnetic field was presented that included an elliptical hole to affix the target tissue and a spiral spring to produce the rotational force.[117] Once the capsule reached the target-site, the reed switch was triggered by an external magnetic field that heated a shape memory alloy (SMA) spring. This resulted in the cutting of a special polymer string which allowed the torsional spring to rotate the biopsy cutting tool, hence collecting the affixed tissue from the elliptical hole.

The biopsy tools that remained inside the capsule shell could not guarantee tissue collection despite the external magnetic holding mechanism, therefore some designs were presented that actively moved the tools outside the capsule shell to ensure tissue collection as shown in figure 4. A motor with a rack and pinion gear system moved a biopsy tool (forceps with barbs) from inside of a capsule shell to biopsy, but this compromised the limited power available to the capsule endoscope to perform usual imaging tasks.[118] Another device used two ring-shaped permanent magnets to move the biopsy forceps outside the shell to actively cut intestinal tissue.[119] An SMA actuator was used to project a biopsy razor out of the capsule shell once the capsule was at the target-site, then the rotating magnetic field rotated the capsule prototype helping the razor to cut the tissue from the gut wall and finally two restoration magnets were used to bring the cutting tool back inside the capsule shell to secure the sample.[120]

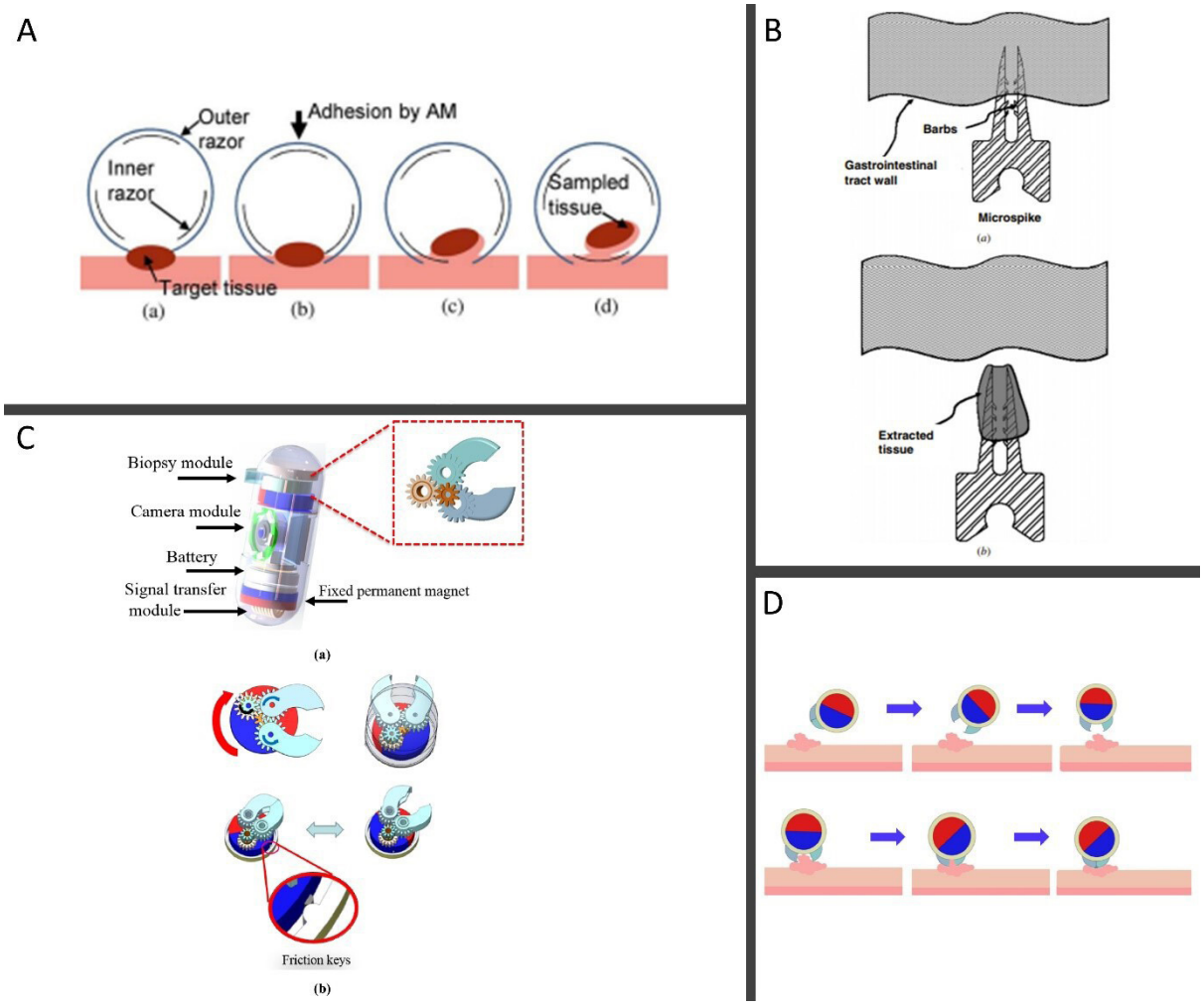

Figure 4 Tools for tissue biopsy. (A) Cylindrical razors to cut a targeted tissue sample.[126] (B) A barb-based design to penetrate the gut wall to extract a tissue sample.[124] (C) A scissor-shaped razor to clamp tissue inside the jaws.[121] The razor used magnetic actuation to eject from the capsule shell and cut the targeted tissue with scissor motion that could be visualised with the camera module. (D) The elaboration of tissue extraction method using the scissor-shaped razor.[121]

However, the two magnets used for restoration of the biopsy module to bring the ejected blade back inside the capsule, were too large and did not allow a telemetry system for triggering the biopsy process to fit inside traditional endoscopes. Another design used a gear-assembly to move forceps-style blades in and out of the capsule shell as shown in figure 4C that allowed the biopsy system to fit inside a traditional endoscope.[121]

All these designs presented a biopsy tool, and some also included a triggering method but most of them lacked locomotion to help the capsule reach the target-site. A biopsy capsule with an active locomotion mechanism that could move flexibly within the gut and extract a tissue sample with rotating blade mechanism from the target location by magnetic actuation was presented.[122] Later, this research group modified the blade design with a retractable biopsy punch to fit inside a traditional endoscope so the biopsy procedure could be effectively performed with visual aid from the camera module.[123]

Some designs considered obtaining a biopsy sample from the mucosa layer, as superficial collection from the epithelial layer was not sufficient for in-depth microbiota analysis. A unique design of a micro-spike with barbs was proposed as shown in figure 4B that was triggered by heating an SMA wire that moved the micro-spike outside the capsule shell by a slider crank mechanism with a torsion spring used to penetrate into the mucosa layer.[124] The barbs helped to tear the biopsy samples which was then stored inside the capsule to avoid contamination. Another capsule captured a fine-needle aspiration biopsy, and was triggered with a magnetic actuation that squeezed the capsule allowing a sharp hollow needle to penetrate into the mucosa layer to obtain a sample, which was not explored previously by the earlier biopsy capsules.[18 125]

One of the challenges for most of the biopsy capsules is the lack of control of their motion as they rely on peristaltic forces to reach the target-site and stopping the capsule at the target-site is not possible. Some of the designs used an external magnetic field to anchor the capsule at the target-site but this increased the complexity and cost of the overall system while the capsule anchoring could not be precisely controlled. A complete solution with a tissue monitoring module using a camera, anchoring module using SMA springs to stop the capsule at the target-site and a biopsy module using two cylindrical razors and a spiral spring to extract the tissue did show clinical promise.[126] However, the capsule required further miniaturisation as it was oversized for in vivo testing and supplying the power to all modules was challenging as the size of the battery was too big to fit inside a swallowable capsule. Another capsule used a single magnetic actuator to drive both the anchoring mechanism and biopsy spike tool using a ratchet mechanism to overcome the power limitations, but intestinal trials are yet to be realised.[127]

In order to collect biopsy samples from the stomach, a magnetically actuated capsule was developed that released a large number of temperature-sensitive microgrippers that self-fold themselves due to a change in temperature.[128] The capsule then collected the microgrippers with an adhesive patch using its camera module.

The biopsy devices are promising tools for collecting tissue samples from the gut wall and they can overcome the limitations of tethered devices by accessing the entire gut. The biopsy tools are used with locomotion and localisation mechanisms to efficiently capture the target tissue. However, these devices cannot be used for sampling the gut microbiota as they cannot capture content-based samples.

Sampling devices for content-based sampling

Patent applications

The development of tools for sampling the gut contents are gaining attention based on the impact microbiota have on human health and the amount of information microbiota can reveal. The promising benefits of sampling devices for the collection of gut microbiota has resulted in many patents with an intent to produce a commercial device. A patent filed in 1957 which was later published in 1962, intended to track a capsule through X-ray to determine the target-site and to open an inlet through radiant energy from outside of the subject, to collect a sample.[129] However, this design did not specify how to protect the sample from downstream contamination, that is, if sealing the sample storage compartment completely was not possible then samples from other locations further down the gut may continue to enter the storage. Another patent suggested the use of a low melting point spring that could be heated from outside the host using an electromagnetic field, hence detaching the spring which then opened the chamber for sample collection.[130] The spring was connected to a piston inside a slider that allowed the piston to move to the other end once the fluid chamber was filled, which closed the inlet of the chamber and secured the sample from contamination. Another patent proposed to use an ether-filled bellows inside a capsule that could expand on heating from an external electromagnetic field resulting in collection of the surrounding fluid, with the capsule returned to its original position once the magnetic field was removed which secured the collected sample.[131]

Most of the designs used separate opening and closing mechanisms, hence making them complicated. Second, a lot of the capsules were designed for one-off use, which increased the overall cost and reduced sustainability. Therefore, SMA materials were introduced that allowed the reuse of capsules multiple times. An SMA spring was latched inside the capsule chamber which was compressed when the temperature was changed by passing electric current through the spring that allowed the chamber to sample content from an orifice.[132 133] Another design with a rotatable mechanism was based on twisted concentric cylinders that used an SMA polymer which were heated to open apertures on the circumferential wall, allowed the surrounding fluid to enter the capsule.[134] The device moved back to its original position when heating was stopped which secured the collected sample from contamination. Another patented design used an SMA polymer for the inlet (door) of the capsule.[135] The SMA polymer shape was designed to block the outside fluid from entering the chamber. When the SMA polymer was heated using induction heating, it allowed the outside fluid to enter the capsule, once heating was stopped the polymer returned to its original shape which secured the sample inside the chamber and avoided cross-contamination.

However, most of these designs required a strong external (magnetic or electromagnetic) field to trigger the sampling process which required an expensive external setup. Therefore, some internal triggering mechanisms have been proposed that rely on internal resources from within the capsule device. One capsule used wireless communication to trigger a set of spring-loaded concentric cylinders that were joined with a meltable thread.[136] The wireless receiver was used to ignite the heater that melted the thread and allowed the spring to open the concentric cylinders which in turn collected the sample via suction from a small inlet. This capsule was designed for one time use, while another patent proposed a wireless triggering mechanism that used a motor to open the sampling chambers. The capsule

Table 2 Sampling devices to collect gut microbiota samples

Name	Dimensions (mm)	Storage capacity (µL)	Type of sampling	Actuation mechanism	Target location	Evaluation
Cui *et al*[146]	30×Φ 10.2	262	Active	Motor	SI	LP, in vivo
Yaw *et al*[147]	31×Φ 11	83.8*3	Active	Motor	SI	Unspecified
RSS capsule[148 149]	31×Φ 11.6	–	Active	Motor	SI and colon	CP, in vivo
Du *et al*[150]	20×Φ 14	300	Active	Vacuum suction	SI	LP, benchtop experiments
MSCE[151]	32×Φ 11.6	400	Active	Vacuum suction	SI	CP, in vivo
Osmotic pill[140]	21.6×Φ 7.6	120	Passive	–	SI and colon	LP, in vivo
IMBA capsule[141]	26.1×Φ 9.9	74	Passive	Spring loaded latch	SI	LP, in vivo
Salem *et al*[142]	26.1×Φ 9.9	200	Passive	Sponge	SI	LP, benchtop experiments
Hydrogel capsule[143 144]	15×Φ 9	282.7	Passive	Hydrogel	SI	LP, ex vivo
Hydrogel capsule[145]	15×Φ 9	282.7	Passive	Hydrogel	Colon	LP, in vivo
BCMAC[152]	11×Φ 8	42	Active	Magnets	SI	LP, in vivo
Diller *et al*[153]	26×Φ 12.4	1500	Active	Magnets	SI	LP, ex vivo
Park *et al*[154]	26×Φ 11	15*3	Active	Magnets	SI	LP, ex vivo
Finocchiaro *et al*[155]	30.5×Φ 11.5	261*2	Dynamic	Magnets	SI	LP, benchtop experiments
Rehan *et al*[156]	30×Φ 12	500	Dynamic	SMA springs	SI	LP, ex vivo
Rehan *et al*[158]	45×Φ 12	250	Dynamic	SMA spring	SI	LP, ex vivo

*Indicates multiple compartments.
.BCMAC, blindly controlled magnetically actuated capsule; CP, commercial prototype (awaiting US Food and Drug Administration approval); IMBA, intestine microbiome aspiration; LP, laboratory prototype; MSCE, magnetically controlled sampling capsule endoscope; RSS, recoverable sampling system; SI, small intestine; SMA, shape memory alloy.

consisted of two motorised blades to capture solid tissue or a liquid specimen that could be stored in two dedicated compartments to avoid contamination until recovery.[114]

The embedded designs that incorporated both sampling and triggering mechanisms inside the capsule, left less capacity for the sample storage itself. Therefore, a simplified design was proposed that collected the content from the intestine with both active and passive mechanisms.[137] The capsule had a vacuum compartment with a seal which could be dissolved by a chemical reaction when the target location was reached. For the active mechanism, the compartment opening was covered by a magnet which was displaced using an external magnetic field. However, neither the active nor passive mechanisms proposed, defined any method to close the compartment to stop downstream contamination so targeted sampling was not possible. Another patent proposed using a fluid-sensitive membrane to cover the inlet of the chamber which was dissolved by interacting with the stomach or intestinal fluid and allowed the accumulation of a sample inside the chamber. The inlet then got closed by a spring-operated valve that blocked the orifice once the chamber was filled with fluid.[138] Wrigglesworth *et al* proposed an extendable mechanism to collect digesta from the ileum (small intestine) of animals to study nutrient absorption and digestion, the capsule had a mechanism to extend from the centre at the target-site to collect a sample size up to 1.5 mL.[139]

Commercial and laboratory prototypes

The laboratory prototypes of sampling devices that have been developed, as shown in table 2, can be classified into three major types. First, uncontrolled or passive sampling devices, as shown in figure 5, that activate the sample collection by dissolving the covering (enteric coating) over an inlet via a chemical reaction or any other method.[140–145] Second, controlled or active sampling devices, as shown in figure 6, that trigger the sampling process through wireless control (electronic or magnetic) to collect a sample at the target-site.[146–154] Third, dynamic sampling devices, as shown in figure 6B and H, that focus on collecting the microbiota from gut lining for in-depth analysis when the capsule reaches the target location.[155–158] The passive and active sampling approaches mainly collect the digesta fluid from the lumen only, whereas the dynamic sampling devices collect samples from both the lumen and intestinal wall.

Passive sampling capsules

The passive sampling capsule prototypes as shown in figure 5 mainly used an enteric coating that was dissolved at the target-site to collect a sample. An osmotic pill with four helical channels connected to a semipermeable membrane was developed that constantly passed the surrounding fluid through the channels while the membrane blocked the microorganisms inside the channels.[140] The pill was coated with a pH-sensitive enteric coating to avoid interaction with gastric juice, and the pill started sampling after the covering was dissolved in the small intestine. However, the sampling continued until the pill reached the colon as this design did not consider sealing the inlets. Another capsule prototype used a gelatin coating that dissolved in the small intestine and the inside chamber contained a hydrophilic fibre that absorbed the intestinal fluid.[141] The capsule used a spring-loaded latch that dissolved in 30 min and moved a piston to block the chamber inlet which secured the sample from cross-contamination, as shown in figure 5D. Similarly, another capsule prototype based on a bistable mechanism also used an external enteric coating to protect the capsule from sampling inside the stomach.[142] Once the capsule reached the small intestine, the outer covering was dissolved which exposed the inlet channel and allowed the chamber to fill with the surrounding fluid. A twofold mechanism was designed to hold a sponge inside the chamber which swelled after absorbing the intestinal content and triggered the bistable mechanism to close the orifice as shown in figure 5E, hence sealing the capsule from further collection. Another capsule prototype presented by Waimin *et al* proposed a passive sampling capsule whose enteric coating was dissolved at the target-site (small intestine) and allowed the surrounding fluid to fill the capsule.[143] A dehydrated hydrogel placed inside the capsule absorbed the sampling fluid which increased its volume, resulting in pressure increase against a polydimethylsiloxane membrane at the sampling aperture which sealed the storage chamber. The capsule design and its functionality are shown in figure 5B,C respectively, and it was tested under ex vivo conditions to prove its efficacy for detecting IBD.[144] Later, the design was modified with two enteric

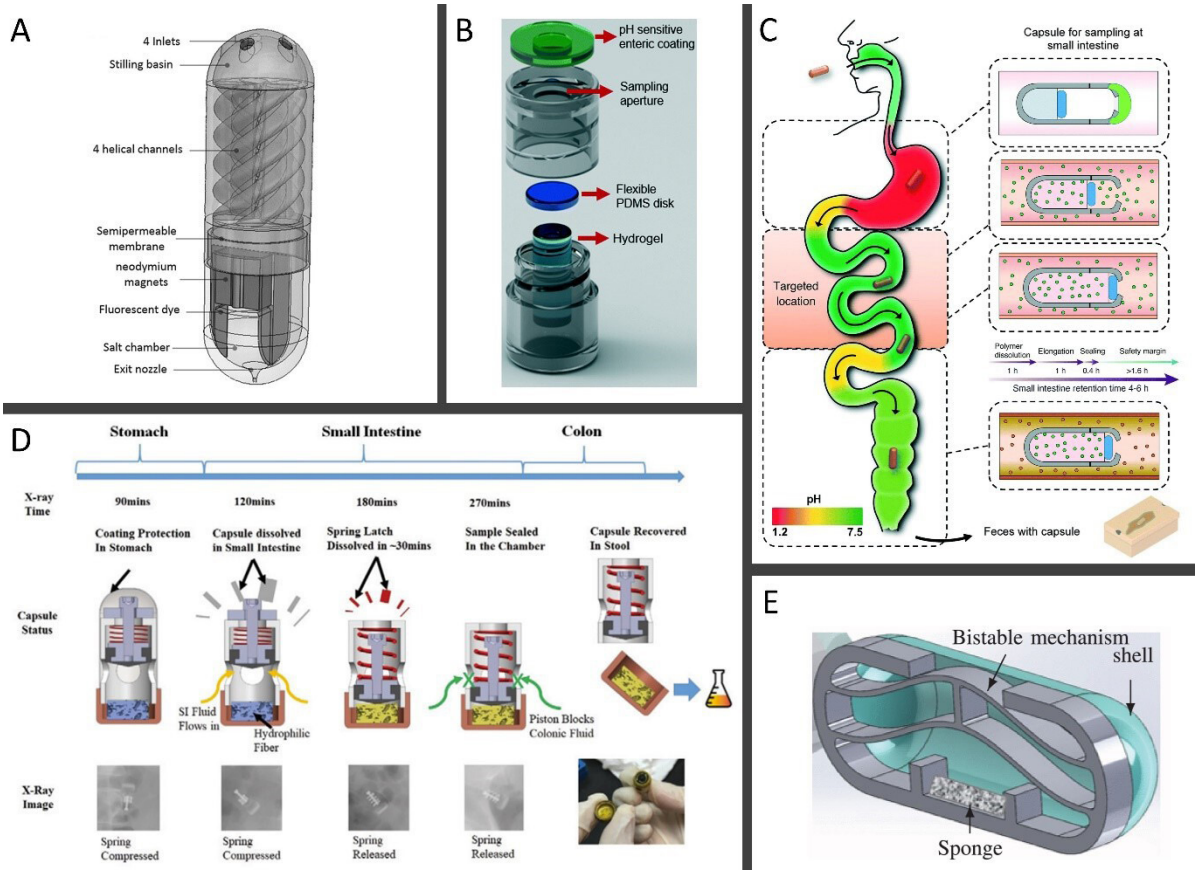

Figure 5 Passive sampling devices that use an enteric pH coating which dissolves by reacting with the target fluid allowing microbiota and digesta sample collection. (A) Osmotic pill sampler that continuously samples the microorganisms throughout its passage till recovery (reproduced from Rezaei *et al*[140] licensed under CC BY 4.0). (B) and (C) Collects the sample mainly from small intestine and secure it from contamination inside the colon by sealing the inlet through hydrogel (reproduced from Nejati *et al*[144] with permission from the Royal Society of Chemistry). (D) IMBA capsule with explanation of the collection process with timings in various regions throughout the gut (reproduced from Jin *et al*[141] 2019 AGA Institute). (E) Bistable mechanism to collect and store the sample (reproduced from Salem *et al*[142] 2018 IEEE). PDMS, polydimethylsiloxane.

coatings on top of each other, the first coating protected the capsule from sampling inside the stomach, while the second coating protected the capsule from sampling inside the small intestinal region. Both coatings were finally dissolved once the capsule reached the proximal colon where sampling started.[145] This modification allowed the capsule to collect samples from proximal colon for detecting colonic diseases.

The capsule prototypes that rely on intestinal fluid to dissolve the pH-based enteric coatings for sample collection have certain limitations. First, sample collection cannot be started instantly, rather coating removal is a passive activity that requires time (around 30 min). Second, precise targeted sampling is not possible as closing the chamber for securing the sample is also a lengthy process (taking between 30 min and 1 hour). Hence, active sampling capsule prototypes that can quickly activate the sampling process were used.

Active sampling capsules

The active sampling capsule prototypes as shown in figure 6 used MEMS-based actuators to instantly trigger the sampling process at the target-site.

Motor-based prototypes

The first sampling prototype known to the authors was developed in 2008, and demonstrated simultaneous drug delivery and sampling by moving a piston that ejected a drug from the device while a small orifice at other end collected the surrounding content via vacuum suction.[146] The sampling prototype did not demonstrate any method to protect the sample as the orifice remained open after sample collection, hence may lead to cross-contamination. Another patent proposed to use a motor to sequentially expose three storage chambers to allow collection of intestinal content from three distinct locations.[147] The motor also closed the inlets after sample collection that resolved the contamination issue. A commercial company (Biora Therapeutics, USA formerly Progenity) patented this idea under the recoverable sampling system (RSS) and is in the process of carrying out clinical trials. The RSS capsule has the capability to detect five distinct sites within the gut before triggering the sampling process which reduces the need for tracking the device from outside the organism or relying on physiological cues like pH or transit profile.[148] The localisation technology flashed LED lights that were received by photodetectors and a microcontroller based on a preprogrammed algorithm predicted the intestinal or colon location using gut anatomy. The capsule design is shown in figure 6G and used a motor to open the sampling aperture to expose an absorbent pad that collected the intestinal fluid.[149] The absorbent pad was soaked with preservatives that maintain the microbial population until capsule recovery from faeces that ensures better analysis after capsule retrieval.

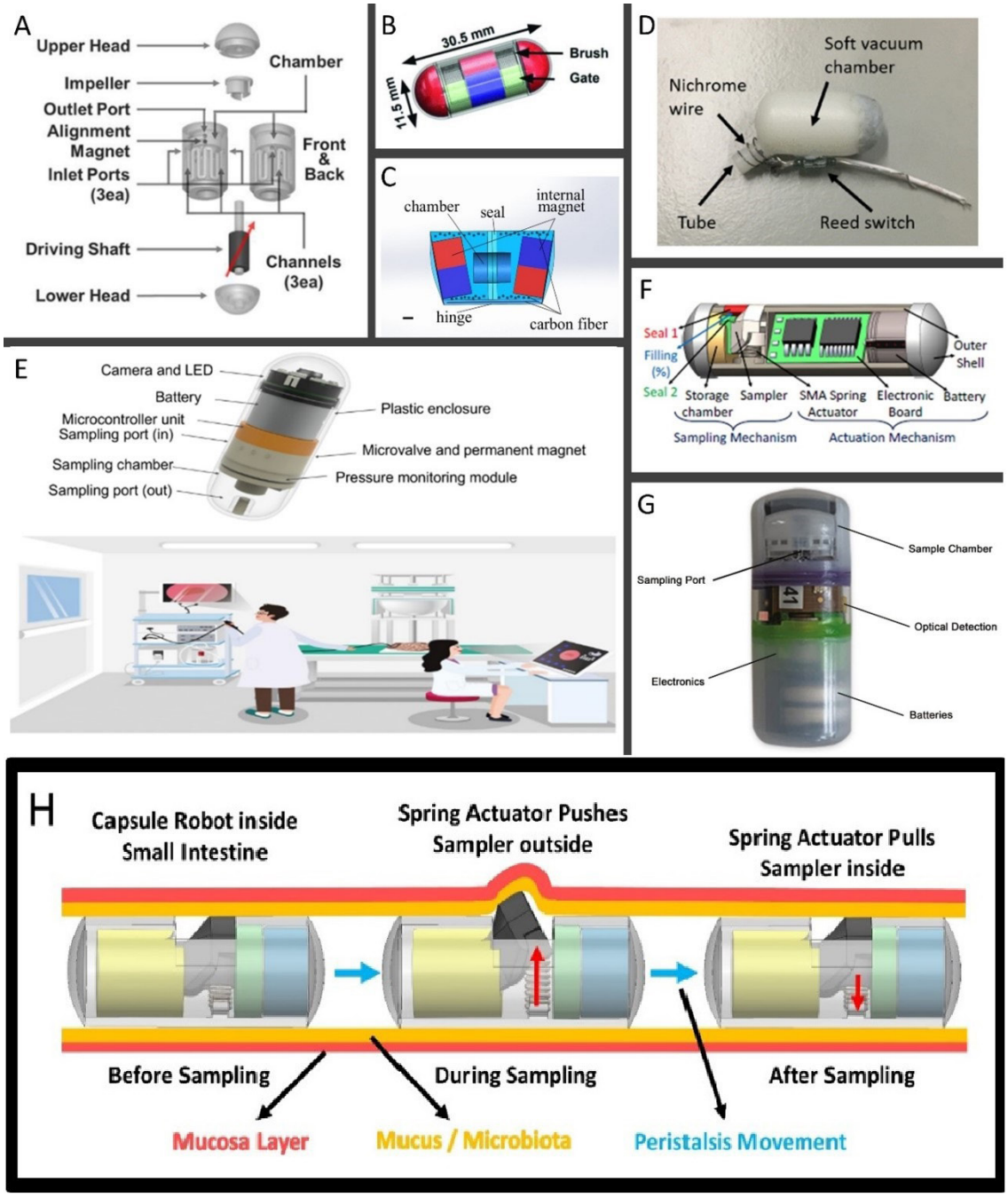

Figure 6 Active and dynamic sampling devices that use wireless triggering mechanism (except G) to collect microbiota and digesta samples. (A) A compact capsule with three separate channels to store the content (reproduced from Park *et al*[154] 2022 IEEE). (B) A dynamic sampling capsule that brushes the intestinal wall to collect microbiota (reproduced from Finocchiaro *et al*[155] 2021 IEEE). (C) A magnetic capsule with a hinge mechanism to collect digesta and microbiota sample with blind activation based on predicted transit time (reproduced from Shokrollahi *et al*[152] 2021 IEEE). (D) A flexible capsule triggered with a magnet to collect the surrounding fluid with suction (reproduced from Du *et al*[150] 2018 IEEE). (E) A commercial prototype with sophisticated external magnetic control mechanism to drag the capsule to the target-site and on-board camera to visualise the collection site (reproduced from Ding *et al*[151]). (F) Another dynamic sampling mechanism that scrapes the microbiota from intestinal wall. The capsule can be triggered by wireless transceiver (reproduced from Rehan *et al*[158] licensed under CC BY-NC-ND 4.0). (G) A standalone capsule that uses on-board camera (optical detection) to identify the target location and collect the sample based on an internal microcontroller signal (reproduced from Yau *et al*[149] 2021 Crohn's & Colitis Foundation.). (H) A dynamic sampling device that focusses on collecting the microbiota from gut lining (reproduced from Rehan *et al*[156] 2020 John Wiley & Sons). Dynamic sampling devices that focus on collecting the microbiota from the gut lining are shown in (B), (F) and (H).

Vacuum suction-based prototypes

A capsule prototype as shown in figure 6D, has a storage chamber consisting of a flexible material that was squeezed inside the capsule and the inlet was sealed with wax. Once the capsule reached the target-site, the sampling process was activated by magnetic actuation via a reed switch and a nichrome wire surrounding the inlet of chamber was heated so it melted the wax and allowed the collection of fluid via vacuum suction.[150] This design did not consider resealing

the inlet to avoid cross-contamination. A commercial company NaviCam (AnX Robotica, USA) has developed a magnetically controlled sampling capsule endoscope that can be manoeuvred to the target-site and its orientation can be precisely controlled using an external magnetic field.[151] The capsule contained three sampling ports sealed by a low melting point metal that was heated when the capsule reached the target-site allowing the external fluid to move inside the chamber due to pressure difference. The device position and orientation can be controlled by an operator using a built-in camera and external magnetic system which submerged the capsule in intestinal fluid for better sample collection, as shown in figure 6E. The capsule used a round-shaped stopping mechanism that automatically sealed the inlet once the chamber was filled with fluid.

Magnetic actuation-based prototypes

Both the motor and vacuum suction-based prototypes required electronic circuitry and a battery that occupy most of the capsule space while leaving little space for sample storage. Therefore, magnetic actuation-based capsules were proposed to instantly trigger inlet opening and closing functions for targeted sample collection. A magnetic capsule was designed to blindly collect the digesta from the intestine whereas the triggering time was estimated based on transit profile.[152] The capsule contained two small magnets embedded in the capsule shell as shown in figure 6C, fabricated in a way that it formed hollow space between them. The external magnetic field repelled the two magnets to allow the capsule to open using a hinge mechanism, and the removal of magnetic field allowed the magnets to collapse again which sealed the collected digesta. Furthermore, the authors modified the design to reduce the limitations of the actuation distance between the capsule and the magnetic field generator by reducing the magnetic force requirement to collect the sample.[153] Another magnetic capsule used an external magnetic field to perform locomotion and sampling.[154] First, the capsule was propelled to the target-site by a gradient magnetic field. Second, an inlet port (one of the three) was aligned with the sample collection channel by a uniform magnetic field, as shown in figure 6A. Third, a micropump was activated by a precessional magnetic field that collected the sample in an aligned microchannel via an aligned inlet port. The design was compact and showed commercial promise but needed to overcome the contamination issue as it used only one sampling port through which all inlet channels collect the samples hence led to a small amount of contamination in the second and third chambers.

Dynamic sampling capsules

The designs presented so far, collect the fluid surrounding the capsule which cannot guarantee the collection of full spectra of microbiota, since microbiota are also present within the mucosal layer which cannot be collected by a simple opening and closing mechanism. The sampling location as well as the procedure used to collect the microbiota has critical implications for the quality of the information retrieved from sampling devices as the microbiota composition varies both longitudinally (eg, duodenum, jejunum and ileum) and radially (eg, within the lumen, epithelium, mucosa and submucosa) within the gut.[10] A magnetic capsule prototype as shown in figure 6B presented a brushing mechanism to collect microbiota from the gut lining (mucosal layer) that has not been explored before by the previous sampling devices.[155] First, the capsule was aligned with the intestinal wall using an external magnetic field. Second, the two gates of the sampling chambers were opened, and third, the brushing mechanism was rotated to collect microbiota by rubbing on the intestinal wall. Once the brushing was completed, the gates were closed to secure the sample inside two separate chambers. Another capsule prototype as shown in figure 6H targeted sampling from the mucosa layer demonstrated a unique way of scraping the microbiota from the intestinal wall.[156] Two SMA springs connected in an antagonistic configuration eject a round channel outside the capsule shell that scraped the content from gut lining due to natural pressure from peristaltic forces and stored the sample in a connected chamber. Once the sampling was completed, the other SMA spring moved the scraping channel inside the capsule shell to secure the sample from downstream contamination. Later, the design was improved by replacing the two one-way SMA springs with one two-way SMA spring that produced both upward and downward movement in response to two different temperatures which were generated by passing the current through the spring using an on-board battery.[157 158] However, both the designs that collected microbiota from gut lining are yet to perform in vivo trials which will demonstrate their effectiveness in terms of the quality of the sample collected.[155 158]

FUTURE PERSPECTIVES

Smart capsules with sensing technologies have provided low invasive access to locations within the gut that were not possible to access before these swallowable devices were developed. This allowed the sensing of parameters, for example, pH, temperature, pressure and, gases, at the point of origin that provided unique insights into the health of the host.[96–99 105 106 112] The pH measurement of different segments of the gut can now be accurately and precisely measured with smart capsules that now help diagnose abnormal conditions and assist to generate the transit profiles which are fruitful in gut health diagnosis.[72 75 78 81] Furthermore, the temperature measuring smart capsules that measure the core temperature of the body are more accurate than existing instrumentation and can perform measurement during exercise which was not possible before.[101] Similarly, gut motility is a crucial factor used to determine overall gut health, and this can now be measured through pressure-sensitive smart capsules for each distinctive segment of the gut.[81] In addition, an important parameter that is considered for gut health diagnosis is accurate digestion and absorption measurement which is made exclusively possible with the help of gas-sensing smart capsules that provide accurate measurement of gut performance.[16 112] These ingestible smart capsules have allowed the measurement of gut parameters at the site of origin which in turn are helping the health practitioners to get better insight into host health. The accurate measurements are a key to a successful treatment; therefore, it is expected with time, the smart capsules will improve the treatment of the patients further and increase the efficiency of medical treatment.

Sensing technologies have already significantly contributed towards better gut diagnosis, but they are limited in range and their capabilities. Another dimension in the smart capsule category has been begun with the development of robotic capsules that can collect gut microbiota samples from various locations.[148 151 152 156] The microbial population throughout the gut is unique and serves specific purposes. The study of microbiota collected from various locations has a potential to improve the understanding of relationship between distinct population of microorganisms living throughout the length of the gut which in turn can be used to diagnose various health conditions to improve the quality of treatment. In addition, sampling from different locations will help analyse the nutrition digestion and absorption to better understand the nutrition that can help prepare personalised foods in future.

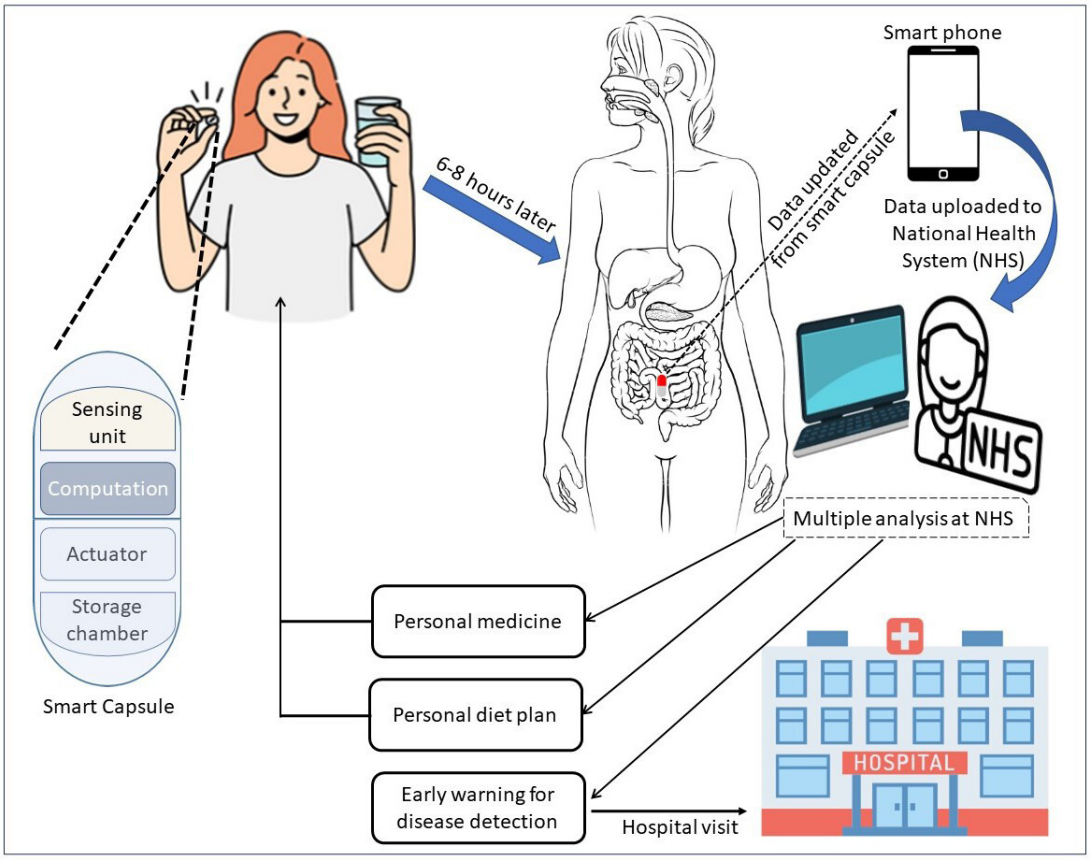

Figure 7 Future of smart capsule technology for monitoring gut health and disease detection for early intervention of health issues.

Most of the sensing devices can only sense a handful of gut parameters due to the size limitations of swallowable capsules. This has restricted the smart capsules to gather holistic information and purpose-built capsules were developed to perform single designated tasks only. The major challenge that needs to overcome by the smart capsules is miniaturisation to perform multiple sensing simultaneously using only one capsule. Most of the temperature and pH-sensing smart capsules are easy to activate before ingestion and they automatically record the designated parameters once swallowed and activated, using software that can be seen by the patient and doctor on their mobile device or from a PC using internet.[96 98] However, currently a separate capsule is used to sense each parameter which increases the overall cost and imposes a burden on the healthcare system. The current smart capsule solutions are expensive for personal use, as they require dedicated support from hospitals and doctors, and it will take a few decades to lower these costs to match diabetic (blood glucose) testing machines that people now keep at their homes for tracking their sugar levels. In future, smart capsule machines will be able to be used at home to continuously monitor gut parameters, in similar way to blood glucose testing machines, so doctors can be contacted if any abnormal changes are discovered which will allow timely precautionary measures to be taken, as patients with diabetes do currently on a regular basis.

Furthermore, there is an urgent need to expand the range of gut-sensing parameters assessed, as currently only a few parameters (eg, temperature, pressure, pH, gases) are measured by smart capsules. Gut motility is a key aspect of gut health and the development of smart capsules for measuring the motor activity of the gut muscles will help monitor individualised gut health, similar to our routine blood glucose tests on weekly or monthly basis. Similarly, the release of enzymes is crucial for metabolic activity and development of smart capsules for measuring various gut chemicals will lead to more insight into host health. Currently, our understanding of the gut parameters and their link with health is limited and that is mainly because of scarcity of technological tools we have to measure these parameters at the point of origin. In future, more capsules will be developed with smart sensors to measure a range of gut parameters that will create a family of smart capsules to present a holistic gut diagnostic that will eventually improve human health but allowing earlier intervention to reduce the burden on the existing healthcare system. However, this will require enormous effort from a diversified team including engineers, material scientists, clinicians, nutritionists, gastroenterologists, physicians, medical practitioners, hospitals and other stakeholders.

Realistically, there will always be limitations to developing smart capsules with dedicated sensing capabilities and it will not always be beneficial to only 'measure' gut parameters. Therefore, various approaches have been adopted to collect gut microbiota that can be assessed after capsule recovery from the faeces.[10] Most of the passive and active sampling capsules rely on arbitrary collection of surrounding fluid which does not capture the full microbiota as significant populations of microorganisms live on the gut lining[32] and the sampling mechanism needs to scrape or brush the intestinal wall to capture them.[155–158] A futuristic sampling device should be able to autonomously locate its target-site along the length of the gut and collect the sample from the mucosa layer that will guarantee the quality of the sample to study gut microbiota.[12] Currently, most of the laboratory capsule prototypes struggle to embed all of the required functions into a tiny capsule (with swallowable dimensions), which is a major hurdle for further in vivo testing.

The sampling devices, in the future, should focus on performing tasks in a standalone way without relying on external systems like magnetic or electromagnetic actuation, as shown in figure 7. The lower dependency will simplify the operational cost and will allow remote testing of the capsule for personalised treatments. This will put less burden on the healthcare system and will allow individuals to perform testing at home which can be monitored by the doctors using internet connectivity. Software on a mobile device can highlight any abnormalities to help doctors perform better diagnosis. The mobile software, with doctor support, may allow the preparation of personalised diet plans for optimum health outcomes. Smart sampling capsules could specify the optimal diets for individuals based on their microbiota composition, which may be realised in a few decades with support of doctors and nutritionists. The current rapid pace in sensor development could determine that this may happen in near future and the next generation may keep a log of their gut health from childhood to assess any significant changes in their gut health to treat themselves with the aid of prescriptions provided by doctors, which would be complimentary to current health practices.

The development of futuristic sensing and sampling devices may enable better treatment of gut-related problems like IBD, ulceration, coeliac disease, Crohn's disease and IBS. Furthermore, early diagnosis of diseases like cancer, obesity and diabetes might be realised, which could help to treat these deadly diseases efficiently. In addition, mental health issues may also be addressed by relating the gut microbiota with relevant biomarkers. Hence, in vivo sensing and sampling capsules are desired that will transform the traditional ways of gut diagnosis.

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