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Review

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Ingestible Sensors

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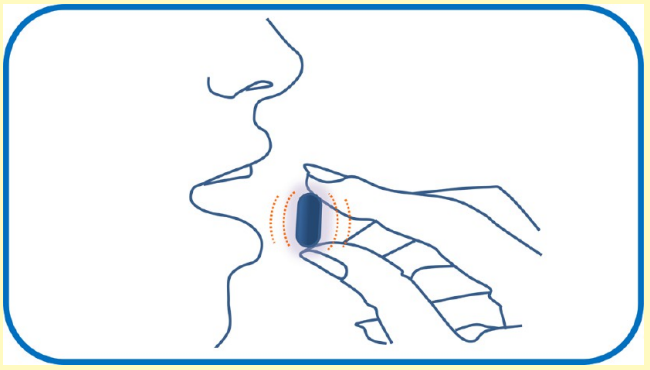
ABSTRACT: Ingestible sensing capsules are fast emerging as a critical technology that has the ability to greatly impact health, nutrition, and clinical areas. These ingestible devices are noninvasive and hence are very attractive for customers. With widespread access to smart phones connected to the Internet, the data produced by this technology can be readily seen and reviewed online, and accessed by both users and physicians. The outputs provide invaluable information to reveal the state of gut health and disorders as well as the impact of food, medical supplements, and environmental changes on the gastrointestinal tract. One unique feature of such ingestible sensors is that their passage through the gut lumen gives them access to each individual organ of the gastrointestinal tract. Therefore, ingestible sensors offer the ability to gather images and monitor luminal fluid and the contents of each gut segment including electrolytes, enzymes, metabolites, hormones, and the microbial communities. As such, an incredible wealth of knowledge regarding the functionality and state of health of individuals through key gut biomarkers can be obtained. This Review presents an overview of the gut structure and discusses current and emerging digestible technologies. The text is an effort to provide a comprehensive overview of ingestible sensing capsules, from both a body physiology point of view as well as a technological view, and to detail the potential information that they can generate.



KEYWORDS: *wireless capsules, smart pills, telemetry, stomach, small intestine, colon, swallowable, biomarker*

Advancements in electronic components have made electronic devices increasingly smaller, smarter, and more power efficient. Microprocessors have been reduced in size and are now more efficient and multifunctional. Furthermore, significant advancements in battery technologies have seen a substantial increase in energy and power density, resulting in reduced physical dimensions that can operate for longer. This unprecedented progress has enabled high fidelity telemetry and high performance data analysis using very small devices, while requiring less power.

Apart from the electronic components, sensors have also "seen" much needed progress in recent years. Thanks to the developments made in electronics, optics, materials science, and chemistry, sensors are now more reliable, sensitive, and smaller in size than ever before. Additionally, enhanced capabilities of new microcontrollers and signal processing have allowed for more reliable extraction of the noisiest sensor signals in a very short time.

The aforementioned advancements have led to a revolution in the development of wearable electronics.[1−3] They are now used in a variety of applications such as fitness trackers, interactive communications, medical devices for health monitoring and diagnostics, detectors for alertness, navigation tools, and also increasingly as communications and media devices. Wearable sensors are now a big sector of the wearable electronics market with accelerometers, gyroscopes, magnetometers, and barometers appearing in many common gadgets.[3−8] Such wearables incorporate optical, chemical, electrode based, temperature, and acoustic sensors that are sold and used at very large numbers. Currently, the majority of wearables are based on sensing vital physical parameters (including motion and respiration rate) and or electrophysiology (including ECG and EMG). However, chemical markers that are relevant to health are being increasingly targeted.[7,9] Significant progress has recently been made in developing wearable electrochemical sensors that detect metabolites and electrolytes in sweat.[8,10,11]

So far, wearables operate based on physical sensing of electrical signals, mechanical alterations, and temperature have shown led to strong commercial successes. However, the same success is yet to be seen for chemical sensing. Unfortunately, skin is not easily surmountable and therefore is a natural impediment present against the ultimate chemical sensing for wearable technologies. Thus far, sweat sensing has shown great promise,[8,10,12−16] but nevertheless, high quality sweat sensing depends on the body temperature and persistent physical activity for inducing it. Several developments tried to overcome this by sensor patches with microspikes for piercing the skin to surpass the epidermis and gain access to the body liquid directly.[17] However, there are many practical issues, such as longevity, reliability, and used

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microneedles left within the skin, that have hampered the eventual commercial value of these technologies.

The other major category of body monitors and sensors is the family of implantable devices. Implantable sensors have been very successful in products such as cochlear implants and also a variety of neurostimulators/sensors.[18−20] Nonetheless, obviously their invasive nature makes them the least favorable by patients.

A noninvasive and safe approach to reach some of the target body fluids is to use ingestible devices. This paradigm will allow for direct access to the gut environment during the passage of ingestibles along the gastrointestinal (GI) tract. The mucous membrane of the gut provides facile and rapid transfer/exchange of chemicals within the gut, and hence, a wide range of biomarkers and therapeutic targets are available to measure. Some of these chemicals of interest that are exchanged inside the GI tract include electrolytes, metabolites, and enzymes.[21] In addition to these, our gut hosts a microbiome with a symbiotic relationship with our body where the microorganisms also produce a range of chemical byproducts as a result of their various activities that impact the state of the health of the gut.[22,23]

Progress in ingestible devices benefited from recent advances in sensors and functional materials. These have allowed for the realization of faster sensor response times, increased reliability, higher sensitivity, enhanced selectivity, and with less demand for power. One of the major obstacles for ingestibles in the development has been the power supplies. These have primarily been batteries that had to last for several days during the passage of the ingestible device in the gut. Fortunately, battery technology has also experienced significant progress in recent years. To date, ingestible sensing capsules can provide information about the internal condition of the gut through images, pH readings, pressure measurements, core temperature data, and also measurement of chemical constituents inside the gut. According to the report "Smart Pills Technologies Market (2012−2017)" (http://www.marketsandmarkets.com/), the global smart pills, or ingestible devices, market is expected to nearly reach the one billion dollar mark by 2017, specially focused on two primary functions of wireless patient monitoring and diagnostic imaging.

This Review aims at describing and analyzing the current range technologies that make up ingestible sensor devices. The text depicts the environment of the gut and the potential analytes and variables of interest for sensing. It presents the different capsule technologies currently being used and researched, discusses them carefully, concludes with the presentation of the future direction of ingestible sensing capsules and pills.

GUT ORGANS AND SENSING TARGETS

The gut is made of distinct organs (Figure 1): the esophagus, stomach, small intestine, and large intestine with the oral cavity (mouth) as its entrance. The small intestine itself is made of subsegments that are fundamentally different from one another including the duodenum, jejunum, and ileum.

To understand the significance and operation of ingestible sensors, it is important to first become familiar with the organs of the GI tract and the chemistry and biology (Figure 2) of the GI environment. In this section, the physiology of different organs in the gut is carefully presented and the sensing targets will be discussed.

Oral Cavity. The first stop for food digestion is the oral cavity. The physical activity of chewing (mastication) combined with the secretion of enzymes (Table 1) and chemicals are the first

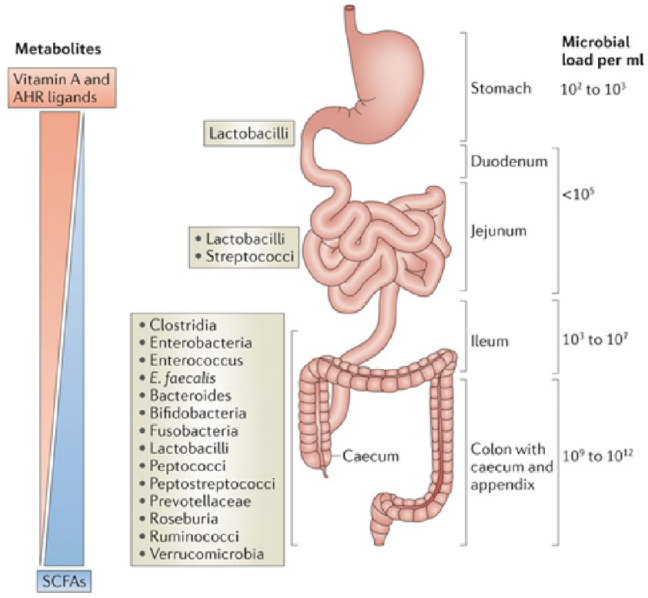

Figure 1. Extended schematic of the GI tract excluding the mouth and esophagus. The major type of bacteria colonizing each region and the common metabolites are presented. The estimated concentrations of the bacterial community and main metabolites in each organ are also depicted.[24] Reprinted with permission from ref 24. Copyright 2014 The Nature Publishing Group.

step to make the food ready for body absorption. Saliva is a bodily fluid formed in the mouth and is of very high physiological importance comprising electrolytes, mucus, white blood cells, epithelial cells, glycoproteins, and enzymes (such as amylase and lipase, Table 1) and antimicrobial agents including IgA and lysozyme. Enzymes released here break down carbohydrates to catalyze them into smaller sugars. Basic saliva electrolyte content is suggested to contain KCl, KH_2PO_4, $NaHCO_3$, NaCl, $MgCl_2(H_2O)_6$, and $(NH_4)_2CO_3$.[25] There are certain sicknesses that can be related to the oral cavity such as mouth ulcers, cold sores (canker sores caused by bacteria and viruses), yeast infections (thrush), gum problems, and the common bad breath.

What Can Be Sensed in the Oral Cavity? A visual inspection of the oral cavity is carried out by general physicians in search for ulcers, cold sores, lacerations, and/or inflammation. The mouth is a point of most facile and noninvasive access to the secreted bodily fluid for diagnostics,[26−28] and DNA samples are generally extracted from saliva.[29,30] There is a possibility to conduct tests that provide information about metabolism of the body based on the chemical makeup of saliva. Electrolyte imbalances and disturbances are also obvious targets. The most common clinical targets through saliva testing include hormone disorders, cancer, infectious conditions (including HIV and viral hepatitis), and allergy disorders. The problem of using saliva contents as biomarkers for diagnosis is that the biomarkers are generally present in concentrations that are too low to be analyzed reliably.

Esophagus. The esophagus is the connection between the mouth and stomach. Generally, the passage of food through esophagus is quick, in the order of a few seconds, and only minimal food digestion occurs here. However, several significant gut disorders impact this area including acid reflux, from the stomach. Reflux, in its severe form, can also harm the mouth and deteriorate teeth and gums.

What to Sense in the Esophagus? The integrity of the esophagus wall is very important, and many imaging capsules, optical coherence tomography, and endoscopy systems have

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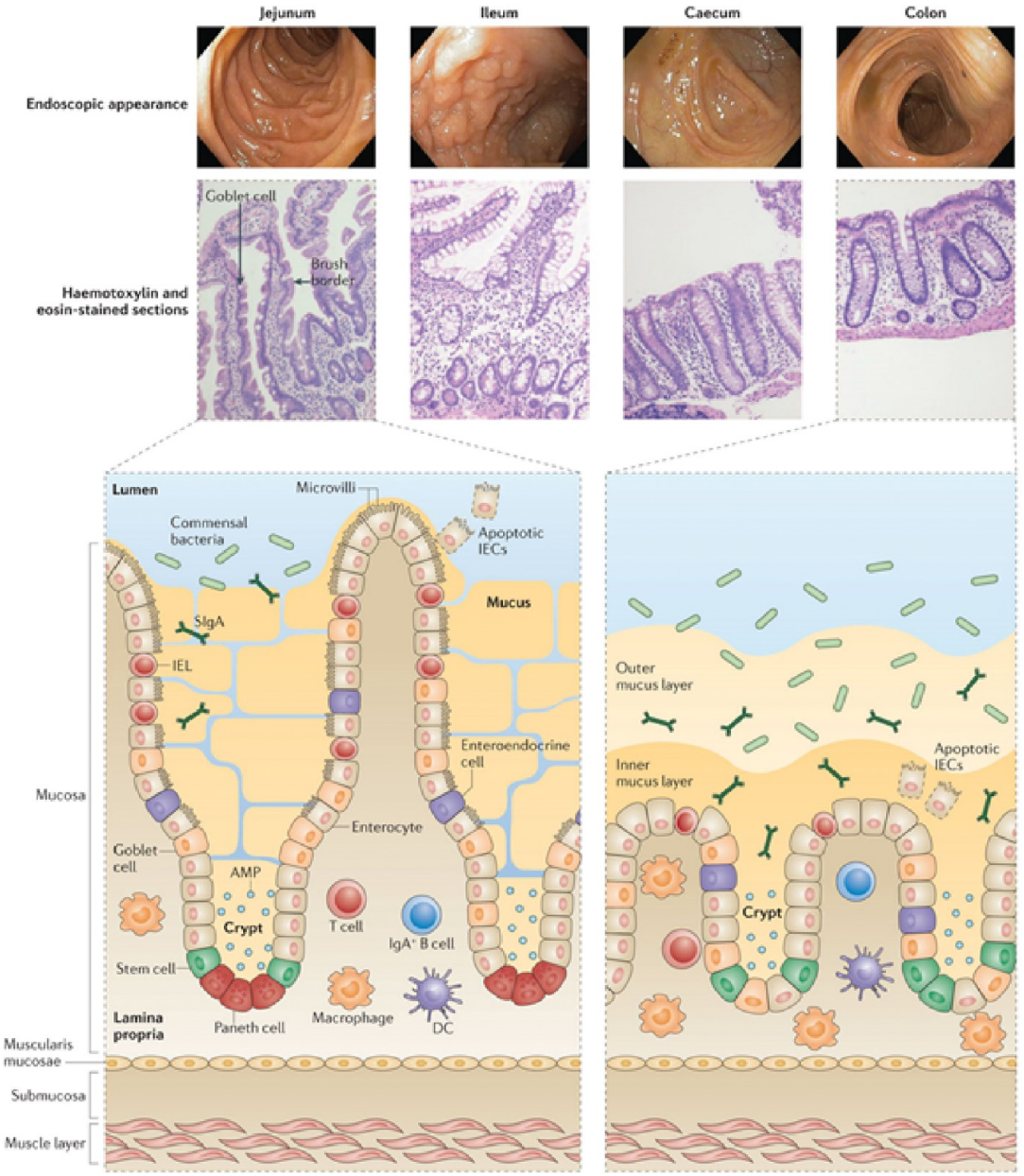

Figure 2. Endoscopy images of different segments of the gut (top panels) and cross sections of the mucosa for each section (middle panels). Schematics of mucosa components for different sections of the gut (bottom panel). The jejunum has long thin villi covered by a surface epithelium, comprising microvilli incorporating digestive enzymes. Stem cells in the crypts generate the mucus-secreting goblet cells found on the villus, and Paneth cells with antimicrobial peptides (AMPs). The majority of intestinal immune cells are in the central part of the villus, whereas intraepithelial lymphocytes (IELs) are found. The cecum and colon have no villi, and the mucosa consists mainly of crypts with only short regions of flat surface epithelium. Goblet cells are numerous and are found throughout the crypts. Paneth cells are rare. Villi are absent from all parts of the colon, and crypts are relatively small. A large number of goblet cells exist here to the produce protective mucus. Paneth cells and IELs are very rare in the colon.[24] Reprinted with permission from ref 24. Copyright 2014 The Nature Publishing Group.

been designed to assess the presence of inflammation and lacerations in this area. Additionally, the mucosa of the esophagus is monitored for diagnosing disorders where the quality of the mucosa can show signs of problems such as eosinophilic esophagitis.[31,32]

Stomach. The stomach is a muscular, hollow, dilated organ of the upper part of the gastrointestinal tract (Figure 1). The stomach lies under the diaphragm, and positioned behind it is the pancreas. The pancreas has the function of producing the digestive enzymes. The acid (HCl) that is generated by the gastric glands of the stomach keeps the pH low (Figure 3A), helps with digestion, and also reduces the proliferation of unwanted bacteria from the food. Glands of the stomach walls (Figure 2) secrete digestive enzymes (Table 1) and gastric acid for food digestion. The stomach secretes many chemicals and compounds including proteases (protein-digesting enzymes including pepsin) and other enzymes such as gastric lipase, hormones (including gastrin, histamine, endorphins, serotonin, cholecystokinin, and somatostatin), and other chemicals. Gastric juice is made of 0.05−0.1 M HCl that reduces the pH and potassium chloride (KCl) and sodium chloride (NaCl). There is also the secretion of bicarbonate, a base to buffer the gastric fluid

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Table 1. Digestive Enzymes of the Gut, Their Target Substrates and Products

digestive juices and *example enzymes*	digested substances	products
saliva		
amylase	long chain carbohydrates	short chain carbohydrates
gastric juice		
pepsin	proteins	partly broken down proteins
pancreatic juice		
trypsin	proteins	peptides and amino acids
lipases	fats emulsified by bile	fatty acids and glycerol
amylase	long chain carbohydrates	short chain carbohydrates
intestinal enzymes		
peptidases	peptides	amino acids
sucrase	sucrose	glucose and fructose
lactase	lactose	glucose and galactose
maltase	maltose	glucose

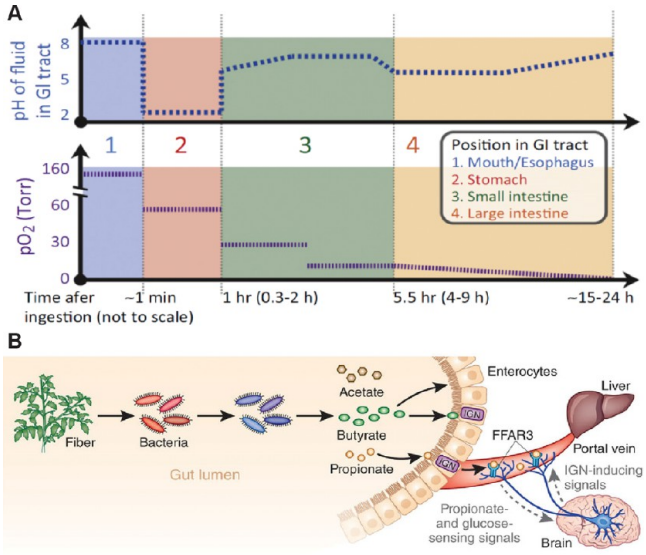

Figure 3. (A) Demonstration of the pH and oxygen profiles in different organs of the gut. Blue, purple, green, and brown areas are the esophagus/mouth, stomach, small intestine, and colon regions, respectively.[33] Reprinted with permission from ref 33. Copyright 2015 Elsevier. (B) Short-chain fatty acids produced by microbial fermentation of plant fibers.[34] Reprinted with permission from ref 34. Copyright 2014 The Nature Publishing Group.

and reduce its acidity when needed. The gastric fluid also contains mucus, as a viscous physical barrier to protect the stomach epithelia in the acidic environment. In the stomach, the food is churned by muscular contractions (peristalsis). Some small portion of the food ingested can be absorbed through the stomach mucosa; this includes water, medication of small molecular sizes, selected amino acids, and small concentrations of methanol and caffeine. The most prevalent stomach disorders include peptic ulcers, gastritis, and stomach cancer, for many of which the cause is the *Helicobacter pylori* infection.[31,32]

Dietary metabolites such as retinoic acid and aryl hydrocarbon receptor (AHR) ligands are found in both the stomach and, in much higher concentration, the small intestine. Retinoic acid is a metabolite of vitamin A (retinol) that mediates the operation of vitamin A which is required for growth and development. The AHR is a ligand-activated transcription factor involved in the regulation of biological responses to planar aromatic hydrocarbons. AHRs appear in important developmental pathways such as lymphoid systems, T-cells, and neurons.

What to Sense in the Stomach? The gastric juice balance is very important. Parameters such as pH, metabolite concentrations, electrolyte production (such as bicarbonate), and enzymes are all important parameters to monitor in the stomach. It is important to visually check the quality of mucosa in the search of stomach ulcer and other disorders. Searching for bacteria such as *Helicobacter pylori* which is the cause of ulcers is an important medical diagnostic process.

Small Bowel. The length of the small intestine (or otherwise referred to as the small bowel) can vary between 3 and 11 m, but on average it is about 6 m, with a diameter of 2.5−3 cm. It is subdivided into three segments: the duodenum, jejunum, and ileum (Figure 1).

The duodenum is the shortest section of the small intestine which is located in close proximity to the pancreas, gallbladder, and liver (Figure 1). The pancreas produces digestive enzymes (Table 1), and the gallbladder generates bile. Bile is a dark green to yellowish brown liquid. Gallbladder bile consists of bilirubin, fats (cholesterol, fatty acids, and lecithin), and inorganic salts. Additionally, Brunner's glands are found in the duodenum and help in neutralizing the acid moved from the stomach. The duodenum secretes hormones that signal the liver and gallbladder to release alkaline bile and digestive enzymes. The duodenum also produces the hormone secretin as a signal for the release of sodium bicarbonate to increase the pH to 7.

Further along the small bowel is the jejunum which is about 2.5 m long with a mucosa layer containing microvilli (Figure 1) that increase the surface to volume ratio. Small chained sugars, amino acids, and fatty acids are absorbed here.

The final segment of the small bowel is the ilium which is about 3 m long, and similarly the mucosa layer contains microvilli where most of the bile acid is absorbed. These microvilli also allow for very efficient absorption of digested food in this region including fatty acids, small sugar units (such as glucose and fructose), and glycerol. Digestive enzymes in the small intestine include those that catalyze proteins (such as pepsin), lipids (such as lipase), and carbohydrates (such as dextrinase and glucoamylase).[35]

An approximate microbial density of $<10^5$ CFU/mL is found in the jejunum area, and this increases by up 2 orders of magnitude to 10^7 at the transition to the ileum. The microbial community of the small intestine is diverse, and a short list is shown in Figure 1.[24] The bacteria of the gut live in symbiosis with us, primarily consuming the nondigested fibers to produce short chain fatty acid (SCFAs) as metabolic byproducts which are absorbed by the mucosa of the jejunum, ileum, and colon.

Other metabolic byproducts produced from bacteria include different gases dependent on their activities and fermentation of fiber.[36−39] These gases can be consumed in subsequent bacterial pathways or they can be absorbed by the mucosa. However, a large volume of such gases are released as flatus.

What Can Be Sensed in the Small Intestine? About 10−15% of the global population, at some stage of their lives, suffer from diseases of the small intestine. Overgrowth of bacteria, different types of irritable bowel syndrome (IBS), malabsorption of carbohydrates, and different types of cancers are among such conditions.

Balances of the electrolytes, gases, and metabolites are all valuable parameters for assessing the operation of the each

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individual segment of the small bowel. The integrity of the mucosa and presence of lacerations/inflammations are important and can be found through imaging. Bacterial counts and taxonomic profiling will help in understanding the microbial community of the small bowel in individuals.

Colon. The colon starts with the cecum which continues to the ascending colon and then the transverse, descending, and rectum areas and then continues to the anal channel (Figure 1). The colonic region is about 1.5 m long and contains bacterial concentrations in the order of 10^{10}–10^{12} CFU/mL. The colon absorbs water and the final remnants of absorbable nutrients from the processed food intake and then excretes the indigestible matter to the rectum. Colonic bacterial communities account for over 1.5 kg of the colon weight. The genome of the colonic bacteria is approximately 150 times larger than the human genome. The bacterial cohort harbors between 1000 and 1150 prevalent bacterial species, and each individual has at least 160 such species, which are also largely shared between different humans (Figure 1).[23,24,40] It is well established that changing the diet alters the composition of the gut microbiota. David et al. explored this phenomenon by measuring the rates at which changes in dietary fiber intake translates into changes in the composition and transcriptional profile of the gut microbiota in humans.[41] The environment of the colon is highly anaerobic (Figure 3A) and as such allows the proliferation of the anaerobe bacteria.

The three main SCFAs, acetate, propionate, and butyrate, which are produced by the bacterial community of the colon, stimulate colonic sodium and fluid absorption (Figure 3B).[42−45] They also help in the proliferation of the epithelial cells (gut walls). It has been shown that acetate improves colonic blood flow that this in return stimulates the gut motility. Butyrate is the preferred energy substrate for epithelial cells promoting their growth.[42,43] It has been suggested that low fiber diets, that decrease the butyrate concentration, can cause the occurrence of many peculiar colonic disorders in Western societies.[46] Similar to fermentation within the small intestines, gases are also produced in the colon. However, the concentrations of gases are much greater than that in the ileum.

What to Sense in the Colon? Stool (colonic content) analysis is an important medical diagnostic process.[47−49] The conditions that this analysis can help to diagnose include infection (from parasites, viruses, or bacteria), poor nutrient absorption, or in extreme cases cancer. The colonic content may be examined for blood traces as well as the presence of fat, proteins, and fibers. The breakdown of the electrolytes in the colon is also important in assessing its functionality.

Colonoscopies are an important process to assess the quality of the colon mucosa in search for inflammation and wounds. The main three SFCAs of butyrate, acetate, and propionate as well as other metabolites are important chemicals that show the health of the colon. Gene sequencing of the microbiome of this area and its analysis are becoming increasingly critical for addressing many disorders in the body, especially regarding the concept of leaky colon.[50,51]

GENERAL REQUIREMENTS FOR INGESTIBLE DEVICES

There are many factors that are important in the design of ingestible sensing and monitoring capsules.[52−55] This includes their physical dimensions, aerodynamics, and density that allows for facile ingestion and whether they rely on passive or active locomotion, as capsule retention is an issue of great importance.

Critical factors for ingestible devices include: high fidelity and private transmission of data from the capsules to an external receiver; the lifetime of the battery with low power internal electronic circuits; and biocompatibility of the materials used in the capsule. In this section, the general requirements of ingestible devices for reliable and durable operation will be discussed.

Power Supplies. Due to the duration of operation and the need to not only gather data but also transmit data, the power consumption of ingestible devices needs to be kept low. Most commercially available ingestibles use silver-oxide coin batteries. Such batteries provide voltage of 3 V at ∼80 mAh with a diameter of 8 mm and thickness of 2.5 mm where the max pulsed current can be as high as 70 mA. Li ion batteries, while having a much higher energy density than that of silver-oxide, are not suitable due to their health and hazard issues if they are exposed to the gastric juice. If left with no sealant, they increase the pH in the gastric juice which can cause serious illnesses.[56] Generally, several batteries are used in a capsule to provide the needed lifetime. The small bowel image capsules have a lifetime of up to 8 h, allowing the capsule to reach most of the small intestine region.

Telecommunications. Wide bandwidth communication is critical for image acquiring capsules that have to process and transmit large amounts of data.[53,57] In such capsules, high image quality and high frame rates are important features. Generally, image compressor subsystems are used to limit the data transmission. For the Given Imaging capsules, the 433 MHz commercial communication band is used and a data rate of 2.7 Mb/s is implemented. It seems that this frequency is also one of the most suitable as the associated electromagnetic waves pass through the body tissues at low propagation loss.[58] Commercial transmitter chips are often used for telecommunications, and data encoding is recommended to maintain patients' privacy. There have also been recent efforts in increasing data rate transmission by increasing the transmission carrier frequency.[59] Additionally, a variety of antennae have been shown to be implemented in capsules.[60]

Microcontrollers and Processors. Microcontrollers and processor units have the responsibility of ordering the commands to and from sensors and transmitters. In camera capsules, they have a much more important role as they are required to compress the images for efficient use of the bandwidth and reliable data transfer. They can be custom designed depending on the requirements.

Power Switches. Magnetic reed switches are generally used for turning the ingestible devices on before their use.

Cladding. The claddings of ingestible electronic devices are required to be made of materials that are biocompatible and remain intact in the caustic environment of the gastrointestinal tract.[33] They also need to be robust to retain their physical integrity during the peristaltic movement throughout the devices' passage. If chemical sensors are used, then the ingestible device must employ membranes that allow for the target chemical to permeate and for rapid equilibrium to be reached between the environment of the gut and the headspace above the sensors.

Sensors. The sensors, for sensing either physical or chemical parameters, are the core components that define the operation of the ingestible electronic capsule. The different types of sensors and their driver units, which are used in the various ingestible sensing capsules, will be described in more detail in the Application section when the technologies are described.

Passive and Active Capsule Locomotion. Most of the ingestible sensing capsules rely on passive progression in the gut, allowing the body to do the work. There is a strong correlation

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ACS Sens. 2017, 2, 468−483

between the passage of food and capsule in the gut which will be discussed in a later section. However, it is also possible to remotely control the movement of the ingestible device along the GI tract. It is important to consider that the peristaltic movements in the GI tract can be unpredictable, resulting in unreliable diagnoses in 20% of the trials using passive progression.[61] Active control of the electronic capsules' locomotion and camera orientation have shown to be invaluable, as not having such control leads to low diagnostic specificity and false-positive results, mainly in the colonic tract. Therefore, integrating mechanisms for active locomotion are important.[62,63] One of the most common methods is to integrate an internal permanent magnet in the capsule that responds to an external magnetic field generator. Such a system can be used for guiding, steering, and rotating the capsule[64] and even allow imaging at 360°. Such capsules have been made by companies including Siemens, Olympus, and Jinshan Science & Technology.

Localizing the Electronic Capsule. Accurate knowledge of the position and orientation of the capsule when it moves along the GI tract is important to analyze any sensor profiles or images to ensure that the parameters are correctly correlated with the location of the capsule in the gut.[65] Magnetic fields and antenna arrays are used for locating the capsules. This can be based on using permanent magnets, magnetoresistors, or coils embedded in the capsules that respond to an external electric field. The location can also be based on imaging of absorbed or scattered magnetic waves. Electromagnetic waves at various frequencies ranging from X-rays down to very long wavelengths in radio frequency ranges have been implemented. Obviously, the hazards of very high wavelengths have to be considered. Ultrasound has also been used for estimating the location of the capsules.[66] Another method for localization of the ingestible device is by using the physical environmental parameters that change from one region of the gut to another. As previously discussed (Figure 3A), the environment of the gut generates step changes in the oxygen and pH concentrations. As such, oxygen and pH sensors and the output profiles can be embedded into capsules for accurately identifying the passage from one organ to another.

Ingestible Device Safety and Retention. Capsule retention in healthy users has not been often reported. The passage of the electronic capsule in healthy subjects may take up to several weeks, depending on the type of food intake, but overall it has been considered 100% safe for capsules smaller than 11 mm in diameter and 28 mm in length. However, the retention rate is very different in patients with gut disorders. Bowel obstruction due to capsule retention represents the most serious potential adverse event for ingestible devices. A report from electronic capsule manufacturers shows a retention rate of 0.33%. This is based on 20 prolonged capsule retention events in 6000 individual device trials.[67] The capsule retention can also be a serious issue for patients who have undergone multiple medical interventions in their gut. Capsules are suggested to be not suitable for use in people with pacemakers due to possible mutual interferences.

Ingestible Senors and Their Applications. As presented in the previous section, there many physical and chemical entities that can be sensed along the GI tract.

There are ingestible sensors that are developed for measuring physical parameters such as core temperature and pressure. There are chemical and biochemical components that are related to the balances in the gut and the functionalities, but the field is still relatively new with a great prospect for growth. The potential monitored markers include: electrolytes that are responsible to keep the gut environment at the right pH and ionic concentrations; metabolites, including digestion and fermentation metabolites, which play great roles in the function of the body and gastrointestinal tract; enzymes that are the catalysts for digestion and also perform other activities in the gut; and additionally, a large number of microbial communities. Ingestible sensors can directly measure these components and may also target the byproduct of chemical and biochemical activities such as gases.

Ingestible sensors (other than image capsules) can operate in the normal gut environment while the food or liquid is there to understand normal gut functionality, or they can be stimulated with a specific food substrate to show the impact on the environment or function. Ingestible sensors may need specific pre-preparation before their implementation. For instance, imaging capsules need a gut environment which is cleared of any non-transparent object in advance, requiring the patient to go on a stringent diet for a few days.

MOUTH SENSORS—STATIONARY SENSING SYSTEMS

The first organ to monitor is the mouth. As discussed previously, saliva is the first target media that contains valuable information for sensing, including enzymes and electrolytes. Saliva sensors can be kept in the mouth for a long duration and then removed. In true evaluation, such sensors may not be considered ingestible as they do not pass through the GI tract, but because they also target the GI tract liquid, they are included in this Review.

Many of the techniques used to analyze the oral phase include sensors mounted onto a mouthguard (Figure 4A) platform.[68] The electronic components including the batteries, microcontroller, and transceivers (Bluetooth) are generally incorporated into the mouthguard in such sensing systems. It has been shown with this type of technology that they can measure chemicals in the mouth including salivary uric acid[68] and pH.[69] Other emerging applications for mouth based sensors have included biosensors fabricated from edible materials that detect microbial populations in food substrates or on tooth enamel.[70]

COMMERCIAL INGESTIBLE IMAGING AND SENSING CAPSULES

The first report on a swallowable electronic capsule emerged in 1957 by Jacobson and Mackay using radiofrequency (RF) transmission of internal temperature and pressure readings.[71] From this very beginning, the idea was based on designing a capsule as small as 33 mm in length to navigate passively along the GI tract by means of peristaltic contractions. There is no actual report on the outcomes of using such capsules in humans for decades after it was introduced. The field did not advance much until the early 1990s when the electronic circuits reduced significantly in size and became more prevalent.

In the following sections, the current commercial systems and emerging technologies of ingestible sensors are presented.

Imaging Capsules. The focus was initially diverted to endoscopy, and this remains the largest part of the ingestible devices market. The driving factor behind this was to find a method to replace relatively invasive endoscopies based on tube endoscopes that are inserted into the oral or rectal orifices.[72] The rigidity of the endoscopy instruments and their relatively large dimensions limit the access to many areas of the gut, making endoscopic procedures poorly tolerated by patients.

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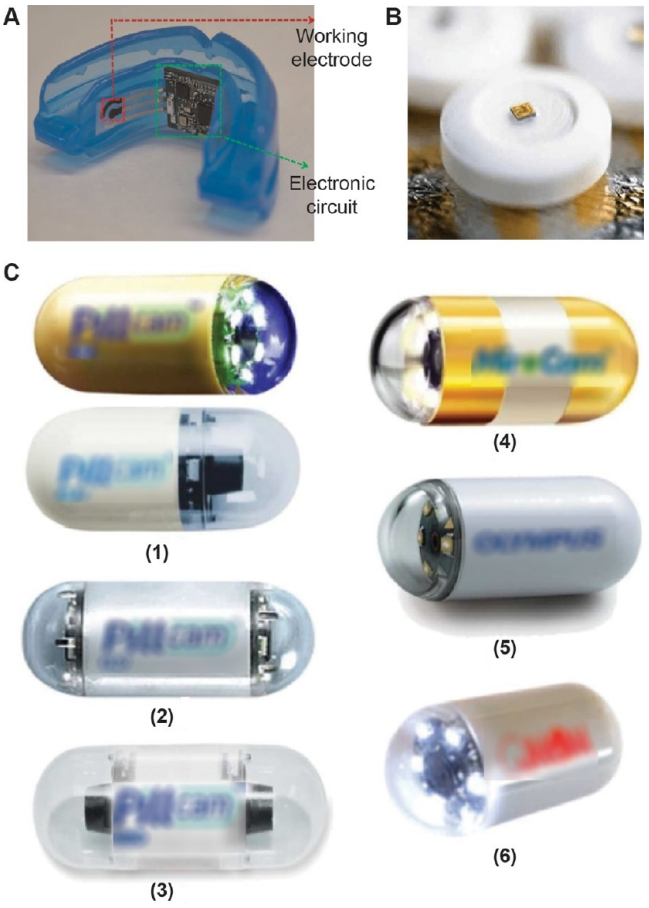

Figure 4. (A) Picture of the mouthguard with integrated biosensors, amperometric and wireless circuit board.[68] Reprinted with permission from ref 68. Copyright 2015 Elsevier. (B) Ingestion monitoring pill developed by Proteus Digital Health.[33] Reprinted with permission from ref 33. Copyright 2015 Elsevier. (C) The most used commercially available camera capsules: (1) PillCam SB and PillCam SB2; (2) PillCam ESO; (3) PillCam COLON by Given Imaging Inc.; (4) MiroCam by Intromedic Co.; (5) EndoCapsule by Olympus, Inc.; and (6) OMOM of Chongqing Jinshan Science and Technology Group.[53] Reprinted with permission from ref 53. Copyright 2011 The Institute of Electrical and Electronics Engineers.

Pain, problems with sedation, and potential repeated screening are also other problems.[73] In 2000, Given Imaging Inc. (Yoqneam, Israel), based on G. Iddan patents (first patent granted in 1981), introduced the wireless capsule endoscopy (WCE) that incorporated a small camera, LEDs for lighting, transmitter, batteries, and microcontrollers.[74]

Generally, before taking the small intestinal and colon camera capsule, patients are administered with a laxative and are to fast up to 24 h. Additionally, sodium phosphate, prokinetic, and rectal suppository are also prescribed for ensuring an effective lumen cleaning to obtain clean images. The fasting period is 4 h before an esophagus capsule.

Here we present a brief description of different camera capsules by Given Imaging Inc. that currently covers the most diverse types of products for examining the GI tract. The company is now under the full ownership of Medtronic (Fridley, MN).

PillCam SB. Given Imaging Inc. officially introduced their first swallowable camera capsule (PillCam SB) for small intestine (small bowel, hence the term SB is used) imaging, at the Digestive Week Conference in 2000 (Figure 4C).[75] Since then, new capsule versions (e.g., PillCam SB2 in Figure 4C) with more battery power and better images have emerged.[76] The images are collected by the receiver and later examined by gastroenterologists. The battery life of the capsule is generally in the order of 8−10 h.

PillCam ESO. PillCam ESO capsule (Figure 4C) passes through the esophagus tube very quickly (in tens of seconds), and to reduce the passage time the patient lays down on his/her side during the imaging process. Due to the short progression time, the esophageal passive capsules require a high frame rate and do not need long battery life. The PillCam ESO by Given Imaging Inc. has been equipped with two cameras: one at each end to increase the information gained through the imaging in a short time.

PillCam COLON. The colon tube diameter is much wider than the small intestine's diameter. As such, wide angle imaging is required to reduce the chance of going out of focus. This capsule is used today as a complementary tool to traditional colonoscopy. To provide better image,s the PillCam COLON (Figure 4C) is larger than the SB type with a length of 31 mm and diameter of 11 mm and is equipped with two cameras on each end.[77,78]

Other Commercial Image Capsules and Image Processing Aspects. In addition to Given Imaging, there are other companies producing camera capsules with a variety of capabilities (Figure 4C). This includes endoscopic capsules, such as Olympus Inc., Endo capsule, (Japan), Chongqing Jinshan Science and Technology, OMOM capsule (China), and Intromedic Co. (China), MiroCam capsule (South Korea).[79]

There has been significant progress in video capsule endoscopy in recent years, mainly involving signal processing and computational methods that have been developed to enhance the diagnostic possibilities and improve the accuracy when using camera capsules. These include algorithms for detecting hemorrhage and lesions, thus reducing the review time for practitioners, localizing the capsule or lesion, assessing intestinal motility, enhancing the video quality, and managing the data. A good review on such techniques can be found in a work by Iakovidis and Koulaouzidis.[80]

Temperature Sensing Capsules. The ingestible temperature sensors are commonly used for monitoring body temperature mainly to measure heat stress in patients, workers in industrial environments, and also possibly soldiers in the field.[81] Capsules such as CorTemp (23 mm in length 8.6 mm in diameter) by VitalSense (Mini Mitter Co., Inc., Bend, OR) consist of a thermistor-based temperature sensor and are used for core body temperature measurements. Recently, most of the new ingestible devices have embedded temperature sensors in them.

pH Monitoring System. Gastric juice inside the stomach is highly acidic due to the secretion of HCl. The abrupt pH rise (>3 pH units) from gastric baseline marks the passage of the capsule to the alkaline duodenum. The ileocecal junction (the junction between the ileum and colon) is generally identified as an abrupt pH drop of at least 1 pH unit. Given Imaging Inc. acquired the Bravo pH monitoring system in early 2010. The Bravo system is able to measure pH (also temperature and pressure) of the GI tract during its passive progression.[82] The capsule lifetime is generally several days, and the test is conducted while the patients maintain their regular diets and daily activities. Recently, pH tests are increasingly being considered as the gold standard for monitoring of gastric reflux, helping clinicians to diagnose and manage gastroesophageal reflux disorders (GERD).

The passage of the digestible device from the stomach to the small bowel has always been a question. However, it has been

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ACS Sens. 2017, 2, 468−483

shown that there is a very strong relationship between the emptying of a meal to the emptying of the capsule. Kuo et al. reported that there is a correlation of $r = 0.73$ between the two events.[83] As such, pH capsules are also effectively used for assessing the passage time of the GI tract as a whole or in the discrete organs for individuals with disorders of upper GI, constipation, and idiopathic and diabetic gastroparesis (delayed gastric emptying). Rao et al. showed that in constipated patients both colonic transit time and gastric emptying were significantly delayed.[84] The pH sensing capsules are also used for diagnosing small bowel dysfunctions, colonic disorders, and functional nonulcer dyspepsia.[53,85]

Despite the suggestions that generally the pH capsule should leave the stomach in less than 5 h, transit through the small intestine in less than 6 h, and should transit the colon in less than 60 h, many different scenarios for the capsule transit times have been observed.[67,86] Sometimes the capsule passes through a gut organ very quickly, and sometimes the passive movement is very slow (Figure 5). The timing depends on the body characteristics,

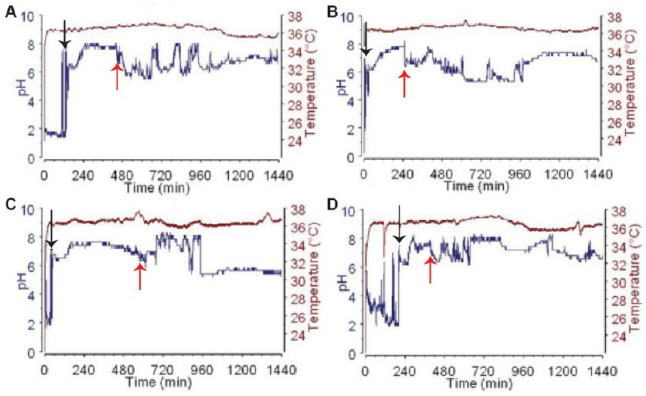

Figure 5. Four examples of pH and temperature profiles.[86] Gastrointestinal motility tracing can be conducted using the wireless pH capsules. Black arrows are the onsets of gastric emptying, and the red arrows are the colon entrance. (A) and (B) are close the most commonly observed pH profiles, while the capsule retention in the gastric phase in much shorter in (B). Panel (C) shows a prolonged small intestine passage, and panel (D) shows a longer than usual retention in the stomach. The increases in the pH in the stomach section are likely due to the response of the pH measuring capsule to the taken water. Reprinted with permission from ref 18. Copyright 2015 Elsevier.

the environment, and the degree of body hydration and also more importantly on the food ingested. Generally, fibrous food slows down the capsule's journey in the small intestine, while laxatives accelerate it. Interestingly, fibrous food activates the bacteria in the colon and speeds up its excretion from the colon.

Pressure Sensing Capsules. Capsules such as the Given Imaging Bravo capsule are also able to obtain pressure profiles of the GI tract. The true values of pressure measurements are still unknown, and more human trials are required.[67] Some of the normal contractility reference values have been reported by Kloetzer et al. for the stomach and proximal small intestine.[87] However, the pressure capsules have not been able to give any accurate information regarding peristaltic wave propagation and the pressure profiles remain confounding. Proper standards should be developed to aid in the identification of various pressure patterns and associations with the gut motility.[67]

Medication Monitoring Pills. A more recent entrance to the market is the medication ingestion monitoring pill by Proteus Digital.[33] This pill is used for reminding/signaling the users that medicine needs to be taken and monitors the amounts ingested. The Proteus pills are passive and upon hitting acidic electrolyte are activated, transmitting a signal to a small, battery-powered body patch and sending the data via Bluetooth to possibly a smartphone in the vicinity. The pills are very small, and the actual circuit attached to pill (Figure 4B) is only in the order of millimeters in dimension.

Advanced Capsule Device Concepts. Philips Inc. (Philips Electronics Inc., Amsterdam, Netherlands) produced IntelliCap, a capsule system which incorporates a microprocessor, battery, pH sensor, temperature sensor, RF wireless transceiver (to receive commands), fluid pump, and drug reservoir. The system is able to measure body internal parameters and to deliver a pharmaceutical treatment agent on command, thus also providing a therapeutic functionality to specific target areas.[53] The OdoCapsule is also a new concept that includes lesion localization units and video stabilization capability.[88]

OTHER ADVANCES IN INGESTIBLE ELECTRONIC CAPSULES

Significant advances have been made regarding ingestible capsule devices that incorporate various gas sensors, wavelength spectrometry, fluorescence and Raman spectroscopy, optical coherence tomography, confocal microendoscopy, electrochemical sensing, and ultrasound imaging units. A brief overview of such systems will be presented in this section.

Gas Sensing Capsules. Gas sensing capsules are one of the newest additions to the ingestible electronic capsules market. Sensing gases as byproducts of the gut activities is a novel idea for monitoring the functionality of the gut (Figure 6A).[89−91] A comprehensive overview regarding the roles that gases play in our gut, their importance, and also the technologies for measuring and assessing such gases can be found in our previous concept paper.[89] The capsule has been under development since 2011 by our group. It has passed stringent animal tests and also the first successful phase of human trials. The capsule has been equipped with oxygen, hydrogen, carbon dioxide, and methane gas sensors (Figure 6B). Step changes in the oxygen profile associate with the location of the capsule, while other gases are digestive and fermentation gases associated with the gut activities (Figure 6C and D). Gas sensors operate in both aerobic and anaerobic environments and are protected by gas permeable membranes of high integrity.

Some gases of the gut are produced as a result of the endogenous chemical and enzymatic interactions in the gut. The chemical interactions are responsible for changes in the O_2 and CO_2 gas profiles in the stomach (Figure 6C and D). However, the majority of the gas production is associated with fermentation by bacteria in the small intestine (jejunum and ileum) and colon (Figure 6D). These bacteria ferment the undigested and unabsorbed food substrates, produce SCFAs, and also produce hydrogen, carbon dioxide, and methane as well as traces of odorous (sulfide containing gases such as H_2S) byproducts.

These gas sensing capsules are a great replacement for breath test analysis. While the breath test is considered the gold standard for diagnosis of carbohydrate malabsoption, IBS, small intestine overgrowth of bacteria, and many other gut disorders, it still suffers from significant inaccuracies due to reliability on low concentrations of gases measured at the mouth and also interferences from the body metabolism. Gas sensing capsules measure the gases in the gut at the source point and raise the accuracy of gas measurements and hence can offer higher reliability for diagnosis.

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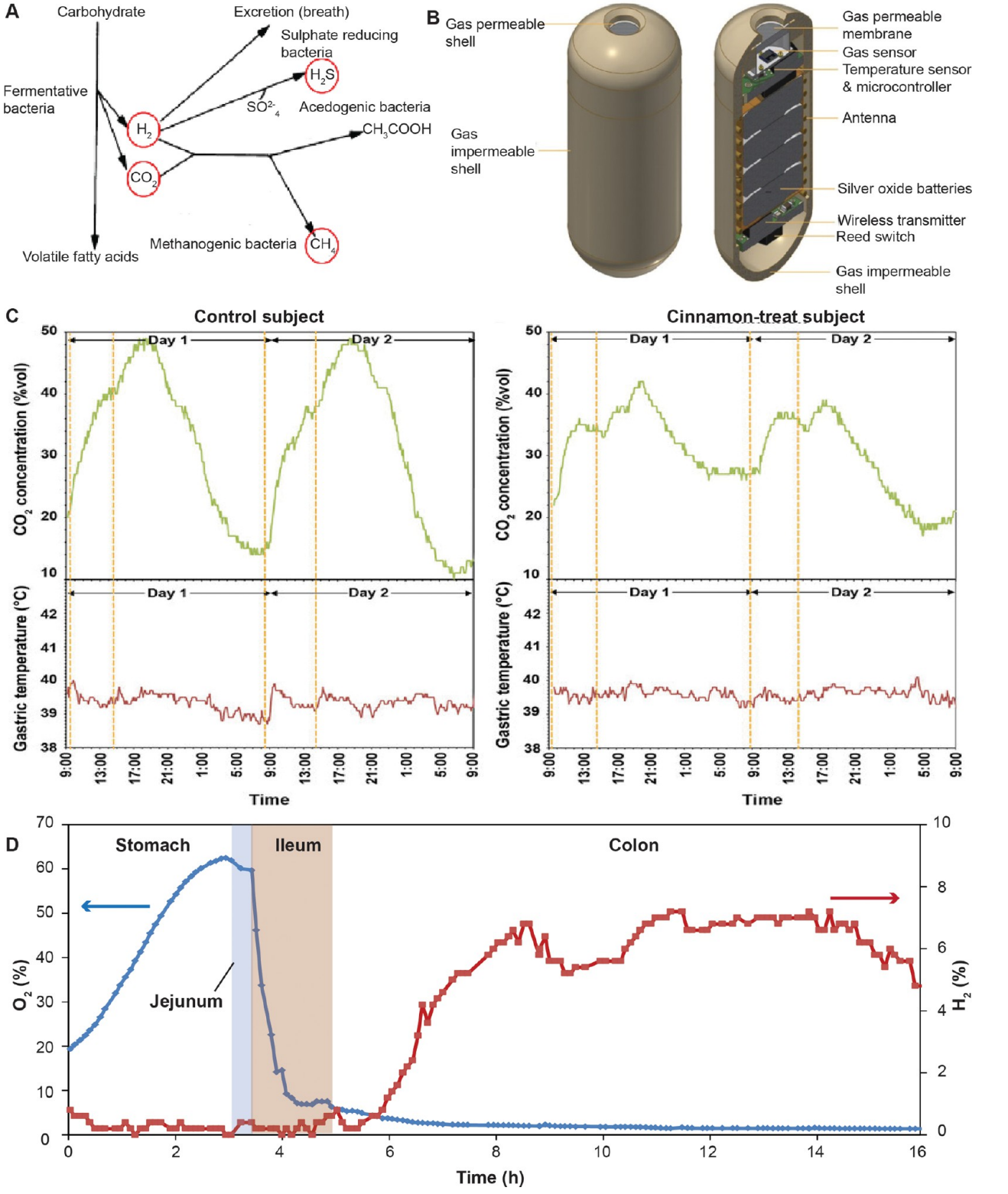

Figure 6. (A) Illustration of major intestinal gas production pathways. (B) Schematic of a gas sensing capsule.[91] (C) CO_2 gas and temperature profiles of the stomach in both control and cinnamon-treated conditions.[91] Reprinted with permission from ref 91. Copyright 2016 The Nature Publishing Group. (D) O_2 and H_2 gas profiles across the human stomach, jejunum, ilium, and colon in response to high fructose and oligosaccharide. The excess amount of such carbohydrates promotes the increase in the concentration of H_2 in the colon, reaching nearly 7%. O_2 increases in the stomach to above 21% of that of the ambient due to the response to oxidative reagents in the stomach. The steps in the oxygen profile show the transition between different segments of the colon.

Visible and Infrared Wavelength Spectroscopy. Light–tissue interaction can also be exploited for monitoring the health of the gut. One of the early projects regarding the development of capsules with visible spectroscopy systems was defined under the VECTOR project. The researchers involved in the VECTOR project demonstrated a basic spectroscopic capsule that is able to

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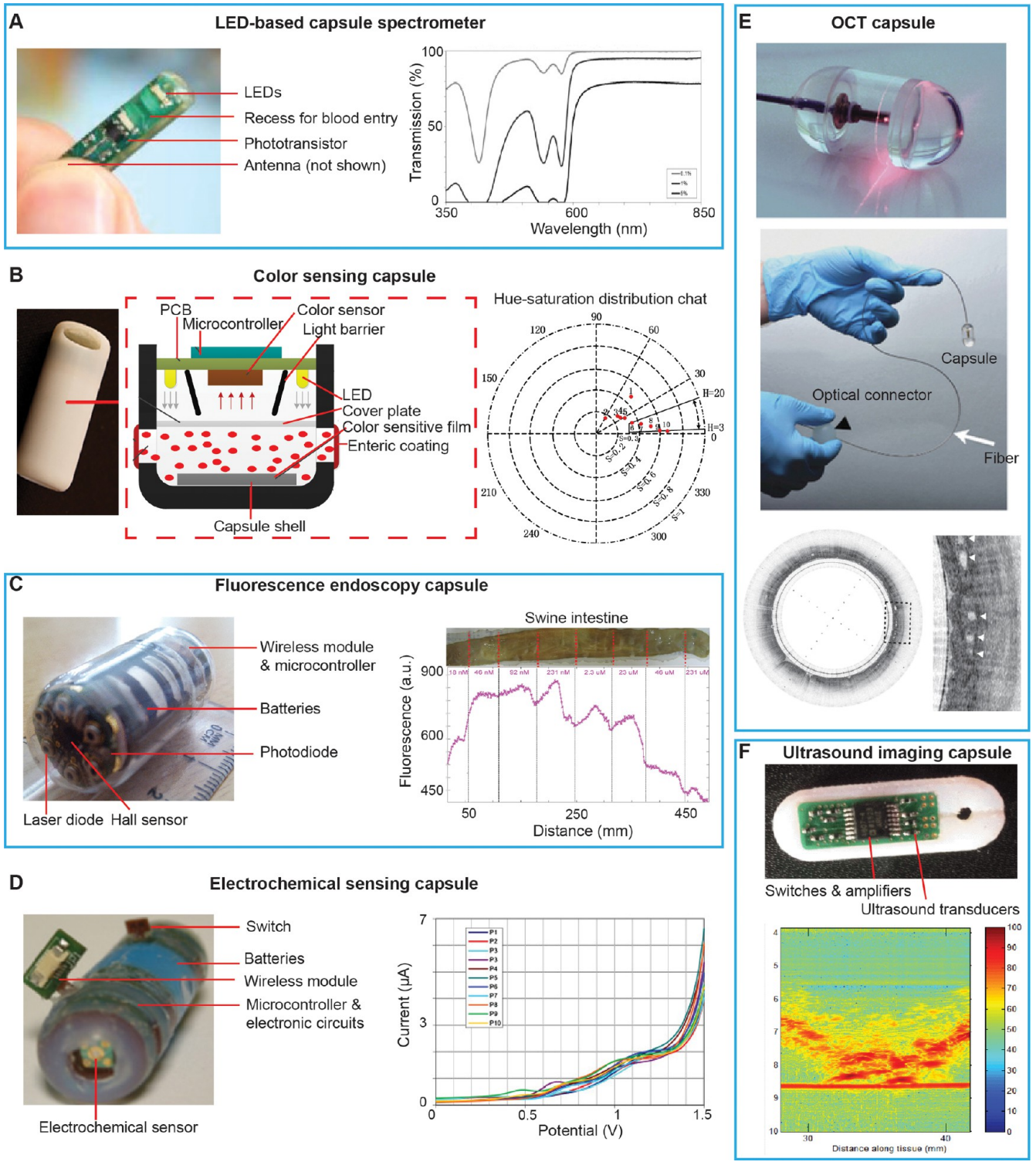

Figure 7. (A) Photograph of a LED-based capsule spectrometer and the transmission spectra of human blood at various blood/water ratios.[93] Reprinted with permission from ref 93. Copyright 2016 Elsevier. (B) Photograph and schematic of a color sensing capsule. The capsule output hue-saturation values correspond to different blood samples that are plotted in a chart.[94] Reprinted with permission from ref 94. Copyright 2016 Public Library of Science. (C) Photograph of a fluorescence endoscopy capsule and the capsule output for different concentrations of indocyanine green.[95] Reprinted with permission from ref 95. Copyright 2016 The Institute of Electrical and Electronics Engineers. (D) Photograph of an electrochemical sensing capsule and the pulse voltammograms of fecal waters sampled from 10 different healthy volunteers.[99] Reprinted with permission from ref 99. Copyright 2015 Elsevier. (E) Photograph of a tethered capsule endomicroscopy device and an endomicroscopy image obtained from a patient with histopathologically confirmed Barrett's esophagus. The white arrowheads in the output image show an irregular luminal surface, heterogeneous backscattering, and glands within the mucosa.[98] Reprinted with permission from ref 98. Copyright 2013 The Nature Publishing Group. (F) Photograph of a Sonocap and a microultrasound image of bowel tissue scanned at 48 MHz.[100] Reprinted with permission from ref 100. Copyright 2016 The Institute of Electrical and Electronics Engineers.

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ACS Sens. 2017, 2, 468−483

detect blood in the intestine using transmission based on a LED emission system.[92] Also recently, another LED-based capsule spectrometer has also been shown for blood detection in the gut with spectrometric quality that was comparable to that of more complex laboratory spectrophotometers (Figure 7A).[93] However, such spectroscopy systems are still in the laboratory and in vitro test phases.

Another recent development was demonstrated by Qiao et al.[94] which based on color detection (Figure 7B). They used a hue-saturation light color detection method with white LEDs, a membrane that allows the selective penetration of blood cells into the chamber, a color sensitive film, and a color sensor detector. The color sensitive film was made of anion exchange resin that allowed hydrophobic interactions with hemoglobulins and hence the change of color. The capsule was tested in the lab against different blood concentrations in a buffer, and human trials are yet to be conducted.

Very recently, a proof of concept for a fluorescence endoscopy capsule in the 650−900 nm range was presented by Demosthenous et al. (Figure 7C).[95] They incorporated a laser and photodiodes with an array of infrared sensors in a capsule for nanomolar detection of indocyanine green fluorophore. They successfully conducted ex vivo tests in the intestine of swines, although specificity of the system was not demonstrated.

Raman Spectroscopy. Inoue et al. implemented a blood detection system using a low energy wireless Raman spectrometry to scan for active bleeding or clots along the intestinal wall.[96] However, the information about this system is not properly presented and also no more information about the progress of capsule Raman spectroscopy has emerged since 2010.

Confocal Microscopy and Optical Coherence Tomography. Reflectance confocal microscopy using quasi-digestible capsules has been successfully shown.[97] Such capsules are tethered and communicate via optical fibers. Using the broadband nature of optical fibers, these quasi-capsules can acquire very large area confocal images. These systems have been used for detecting eosinophilic esophagitis (a disorder which is caused by food allergies, and defined by presence of eosinophil cells in the esophagus). High-speed reflectance confocal microscopy technology is capable of imaging individual eosinophils as highly scattering cells in the epithelium. The system has been successfully tested on patients and in semicommercial phase.

Optical coherence tomography is another medical imaging technique that has been implemented into tethered capsules (Figure 7E).[98] This method uses light to obtain 3D images of micrometer-resolution, from within optical scattering biological tissue. This method implements low-coherence interferometry, in infrared wavelengths. Tethered quasi-digestible capsules based on optical coherence tomography are now used for esophagus disorders and checking the mucosa integrity in patients. However, similar to the case of confocal microscopy systems, electronic and optical devices of these quasi-capsules are outside the body. So it is debatable how accurately such capsules can be considered as real ingestible devices.

Electrochemical Sensing. Incorporation of electrochemical sensors in ingestible capsule devices has been shown (Figure 7D).[99] It consists of a multielectrode sensor with potentiostatic circuits that can operate voltammetry. The capsule was tested in vitro on stool liquid, and consistency in measurement was shown. The developers also demonstrated both cyclic and pulsed voltammetry. The challenge with chemical sensors is assuring their integrity for continuous measurements in the caustic area of the gut.

Ultrasound Imaging. Another possibility of transducer integration with ingestible capsule devices has been recently shown for ultrasound imaging.[100] Lay et al. have developed a capsule that they named Sonopill (Figure 7F). This capsule contains ultrasound transducer arrays with a specifically designed IC for ultrasound receiver/transmitter circuits. They incorporated four single element piezoelectric transducers in the capsule with an operation frequency of 15−50 MHz. Ex vivo investigation on tissues have been conducted in the lab using this capsule, but it is not clear how the quality of images has been benchmarked. The capsule also interestingly contains white light fluorescence imaging with single photon avalanche detectors.

CONCLUSIONS AND FUTURE PERSPECTIVES

This paper provided an overview regarding the current state and prospective pathways of ingestible sensing capsule technology (refer to Table 2 for a summary). The gut structure and functionalities were discussed to give the readers an understanding about the sensing and monitoring targets within the gut. New advances were discussed to show the rapid progress of this field in recent years.

There is no doubt that the amount of information obtainable from various ingestible sensor capsules passing along the gut is potentially tremendous. As human beings, we still have nearly no knowledge about many of the functionalities of the gut. There are many unknowns about what occurs in the small intestine and colonic regions and their association with overall health. The importance of the microbiome and how it affects each organ of the body are increasingly being recognized. However, due to the diversity of the microbial families, their impacts in many areas are still unknown. The knowledge about what digestive enzymes are capable of doing is limited to their basic functionalities. The operation of gut metabolites and hormones is not fully understood in each and every organ. Knowledge of electrolytes of the gut and how they change in response to food, medical supplements, and the environment is vague.

Ingestible sensors for each and every aspect of the chemical changes of the gut should be developed to gain the needed knowledge and explore the functionality. Based on large measurements, and against specific references, comprehensive libraries for healthy cohorts should be established. Such libraries will establish the base for comparison and benchmarking when the ingestible sensors are used for screening, diagnostics, and monitoring.

The field of ingestible sensors is still in its absolute infancy. Our information about many different sections of the gastrointestinal tract is still rudimentary, and many discoveries are waiting to be made. Our acquisition of knowledge of the gut is so far limited to just a few ingestible sensors including pH, temperature, and pressure capsules as well as camera based devices. Even such capsules have only been used in relatively low numbers, considering the potential population in need of them. The costs associated with the use and administration of ingestible devices are still high, they have reliability issues, governmental regulatory barriers are still problematic, and lack of familiarity of medical doctors and food scientists with the output information from capsule signals is also a significant issue.

Ingestible sensing capsules have the capability to impact areas beyond their clinical applications for the prevention, diagnosis, and monitoring of gut disorders and gut related medical supplements. Smart pills can also provide invaluable information regarding food supplement influence on the individual including the effect of prebiotics and probiotics. They will be able to

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Table 2. Summary of the Ingestible Sensors: Commercial Products, Currently under Investigation and Future Possibilities

type of sensor in capsule	what it does	progress: advantage	technical issues	major manufacturer or references
camera	assessing visual conditions of the lumen walls	commercial: it has been successfully proven for diagnosing disorders with visual signs of inflammation and wounds	To be able to visually inspect the integrity, the gut is required to be completely cleansed beforehand. Therefore, it does not show a real world scenario where food and medical supplements are present. It is still limited to recognizing images and often difficult to assess the location of the capsule in the gut segment.	Medtronic (Given Imaging), CapsoVision, Olympus, Chongqing Jinshan Science and Technology, MiroCamRo capsule (South Korea)
pH	measuring acidity in different segments of the gut	commercial: capable of gut localization, can provide information about diseases which are related to gut motility or the acidity of the gut	The signal is noisy, still costly for the small amount of information it provides.	Medtronic (Given Imaging), Olympus
temperature	measuring the core body temperature	commercial: often used by soldiers in the field and also for sporting professionals, where accurate and remote measurement of body temperature is needed	Low cost temperature capsule cannot provide gut localization information.	Medtronic (Given Imaging), Olympus, HQInc.
pressure	measuring the gut pressure	commercial: not known	The signal is noisy and the clinical importance is still unknown, gut localization is not possible.	Medtronic (Given Imaging)
localization and monitoring	monitoring the arrival of the capsule in different sections	commercial: small size and can be efficiently used in monitoring adherence to therapeutic treatments	It is always used with other pills. The sensor only operates in two states, OFF and ON, activation occurs when the medicine/sensor is in contact with gastric fluid.	Proteus Digital Health
gas	measuring different types of gases in the gut	human trials: use gases as the byproduct of the gut activities to reveal food effect and diagnose gut disorders; signal to noise ratio is low for resistive based gas sensors; semiconducting, optical and thermal conductivity sensors have quasi linear responses and such high signal-to-noise ratio	Definition of gas profiles should be identified. Libraries for gas profiles of each gut disorders or food effect need to be established. Sensors should operate in both aerobic and anaerobic segments. Semiconducting and thermal conductivity sensors face selectivity challenges. Electrochemical gas sensors can be naturally noisy with unstable baselines.	90, 91
visible and IR spectrometer	spectroscopy of the liquid in the gut	laboratory tests: the spectra provide signals to sense a number of target analytes at the same time	Still requires higher sensitivity to differentiate important signatures of chemicals at low concentrations.	93
color sensing	simple version of spectroscopy for single peak detection	laboratory tests: simple method for sensing blood at low cost, can become very small in size	Only sensitive to blood leaving many limitations in operation.	94
fluorescence endoscopy	sensing fluorophores that are excited in the presence of target analytes	laboratory tests: can be very selective to trace concentrations of the target analytes	Chemical labeling inside the gut is challenging—accurate processes in labeling should be designed.	95
electrochemical sensing	sensing many important chemicals in the lumen liquid	laboratory tests: can be very selective, low cost and small size	Relies on the presence of specific enzymes or selective layers for ultimate selectivity needed in the devices. They can be noisy due to the nature of the electrochemical transducers. Stability remains an issue for these sensors as they are logarithmic due to the Nernst equation.	99
confocal microendoscopy and optical coherence tomography	imaging based on confocal techniques	laboratory tests: for sensing disorders such as esophagitis that are related to the quality of tissues along the esophagus walls	Large data sets need to be processed and transmitted at high speed. Therefore, the systems are quasi capsules with fiber optic connection. It is a quasi-capsule as it is tethered. Still the quality of the data should be improved and physician should become familiar with the meaning of the output data. It requires expert users which is costly.	97, 98, 101
ultrasound imaging	imaging based on ultrasonic transducers	laboratory tests: can image and give information about the quality of the lumen walls; can also penetrate further into the tissue depending on the operation frequency and power	The number of elements in the array needs to increase to give enough resolution. Still in early tests with advanced processing algorithms needed to understand the meaning of the obtained images. The usage will require expert training and will be expensive.	100
pyroelectric systems for chromatography	measuring gases or liquid signatures by using pyroelectric sensors with incorporated filters for spectrometry	not tested yet: spectrometers such as those by Pyreos Inc. is within the size that can be incorporated in capsule sensors; it is a possibility for the near future	Devices are still too large to be ingestible. They are still expensive.	NA
raman spectroscopy	creating raman spectra to sense the presence of chemical with vibrational raman signatures	only concept based according to ref96: can potentially differentiate between many chemicals with high sensitivity	The report is only a nonproven claim. Requires sophisticated and often bulky, accurate optical equipment for low detection sensing limits.	NA

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Table 2. continued

type of sensor in capsule	what it does	progress: advantage	technical issues	major manufacturer or references
physisorption sensors	can be surface treated for sensing a variety of chemicals	not tested yet: they have been successfully used for assessing organic vapors from fecal samples for diagnostics	The selectivity can be a problem and they will need complex mathematical algorithms to extract the data.	NA
surface acoustic wave	measuring concentrations based on piezoelectric transducers	not tested yet: they can sense materials of interest based on mass sensing at very low detection limits	The vibration noise should be considered. Signal-to-noise ratio can be a problem in actual measurements in the gut.	NA

eventually lead to the concept of monitoring the impact of food on an individual level and realize the concept of "individualized diet". This will revolutionize our understanding about food and how food affects our body, and also open the door to new market opportunities that are far larger than clinical diagnostics and monitoring markets.

Despite the early predictions that the field of ingestible sensors would experience a revolution after the emergence of the camera capsules in early 2000s, progress in the field has been surprisingly slow. The field has seen some serious movement after 2010, but as yet not many of the ideas have materialized commercially.

The unnecessary barriers by the United States Food and Drug Administration (FDA) that classify ingestible capsules as class II medical devices have been a significant obstacle, imposing costly processes for obtaining approval for usage. It is envisaged that advanced ingestible sensing capsules can go beyond standard diagnostic techniques by offering sampling, biopsy, tissue penetration, drug release, and specific actuations on demand. Ultimately, a new paradigm of doctor−patient care can be implemented with remote monitoring and administration. The possibilities are seemingly endless if the regulatory bodies can alter the traditional thinking on diagnostic technologies.

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Notes

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VOCABULARY

ingestible, material that can be taken into the body through the mouth; wireless transmission, transfer of information through electromagnetic waves between points that are not physically connected; gastrointestinal tract, system of organs that takes in food and transforms it into energy and nutrients through the process of digestion,and the byproducts are then expelled as waste; gut microbiome, microorganisms that reside in the gut; gut mucosa, innermost layer of the gastrointestinal tract forming a barrier between the luminal content and the human body

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