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Special Focus on Materials

Review

Materials Advances for Next-Generation Ingestible Electronic Medical Devices

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Electronic medical implants have collectively transformed the diagnosis and treatment of many diseases, but have many inherent limitations. Electronic implants require invasive surgeries, operate in challenging microenvironments, and are susceptible to bacterial infection and persistent inflammation. Novel materials and nonconventional device fabrication strategies may revolutionize the way electronic devices are integrated with the body. Ingestible electronic devices offer many advantages compared with implantable counterparts that may improve the diagnosis and treatment of pathologies ranging from gastrointestinal infections to diabetes. This review summarizes current technologies and highlights recent materials advances. Specific focus is dedicated to next-generation materials for packaging, circuit design, and on-board power supplies that are benign, nontoxic, and even biodegradable. Future challenges and opportunities are also highlighted.

Trends

Microelectronic device miniaturization. There is a continuous trend in the miniaturization and reduced power consumption of many electronic components including transistors and logic elements, optoelectronics, and biosensors.

Bioresorbable electronics. Imparting novel properties of transience and biodegradability to functional electronics has the potential to reduce the intrinsic risk of many types of ingestible electronic devices.

Biologically derived energy storage materials. Naturally occurring endogenous compounds can serve as nontoxic electrochemical energy storage materials when combined with benign minerals and aqueous electrolytes. This materials framework could serve as on-board energy storage systems to power next-generation ingestible electronic devices.

The Promise of Next-Generation Electronic Medical Devices

Emerging healthcare strategies of the 21st century will be informed by datasets that are generated from continuous physiological monitoring of the human body. Comprehensive biosensor networks and modalities for therapeutic intervention can be established by connecting wearable electronics, implantable devices, and other sensing hardware to create a mobile health technology ecosystem [1,2]. Wearable electronics are advantageous because they are minimally invasive while implantable devices can measure biomarkers and monitor *in vivo* physiology with increased specificity. Implantable electronic devices also offer efficient channels for therapeutic delivery as evidenced by the clinical success of pacemakers, cochlear implants, continuous glucose monitors, and deep brain stimulators [3,4]. Next-generation implantable devices may include brain–machine interfaces, neurostimulators for 'electroceuticals' [5], and smart-controlled release systems [6]. Rapid advances in implantable electronic devices are enabled in part by miniaturized low-power microelectronics, improved packaging, and increased battery performance. Unfortunately, implantable medical devices are highly invasive and subject to manufacturing challenges and economic constraints. Chronic implants evoke complex biological responses that impact device performance [7,8] and increase the risk of complications such as fibrosis and infection [9]. Novel materials that may address these technical challenges are subject to strict regulatory standards because of the nature of the implant.

Alternative channels for biosensing and therapeutic intervention utilize semi-invasive modalities such as electronic contact lenses and ingestible electronics [10,11]. This complementary class of medical devices could feed additional data into biosensor networks and provide new avenues

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for therapeutic delivery. Semi-invasive electronic devices harness the advantages of electronic implants (e.g., active electronics, on-board sensors, actuators, telemetry) while obviating many of the challenges. Ingestible electronics, in particular, could transform many aspects of monitoring and treating diseases because of the wide range of biomarkers and therapeutic targets in the gut. Although the prospect of ingestible electronics is intriguing, many challenges remain. Progress in ingestible electronics may benefit from recent advances in materials including flexible electronics, biologically derived energy storage materials, and biomaterials-based circuits. This review summarizes recent advances in ingestible electronics and highlights several recent clinical successes. Anticipated challenges and future opportunities in next-generation devices are also outlined with a focus on the need for novel materials. Specific focus is granted to new materials for energy storage, flexible electronic components, and biodegradable circuitry for potential use in edible electronic devices.

Current Technologies for Ingestible Electronics

One of the first applications of ingestible electronic devices was *in vivo* measuring of physiological biomarkers in ambulatory human subjects. Continuous monitoring of core body temperature, oxygen tension, and gastrointestinal (GI) pH provides valuable insight into real-time human performance [12] (Figure 1). Early devices leveraged silicon-based microelectronics for *in vivo* sensing and communication. Advances in microelectronic fabrication have enabled miniaturization and increased the sophistication of devices. Form factors with smaller dimensions increase the probability of free gastric transit while limiting the risk of device retention [13–15]. For example, the Discover by Proteus is a personalized digital medicine system that consists of a small ingestible sensor and an external transceiver to monitor patient compliance when taking oral medications (Proteus Digital Health, Redwood City, CA, USA) [16]. The ingestible component consists of a millimetric scale device ($W \times L \times t = 1 \times 1 \times 0.3\ mm^3$) that contains an integrated circuit (IC) powered by an Mg–Cu electrochemical couple. The IC contains nonvolatile memory and a circuit to modulate the current of a dipole within the sensor. The sensor modulates the current in the dipole to produce data that is then transmitted to the external receiver via an electric field. The device contains structures to increase the amplitude of the E-field and an adhesive to affix the device on oral tablets. The device remains dormant until the electrochemical cell is formed upon contact with gastric fluid (Figure 1B). The device transmits data with 99.1% positive detection accuracy despite significant variations in externally

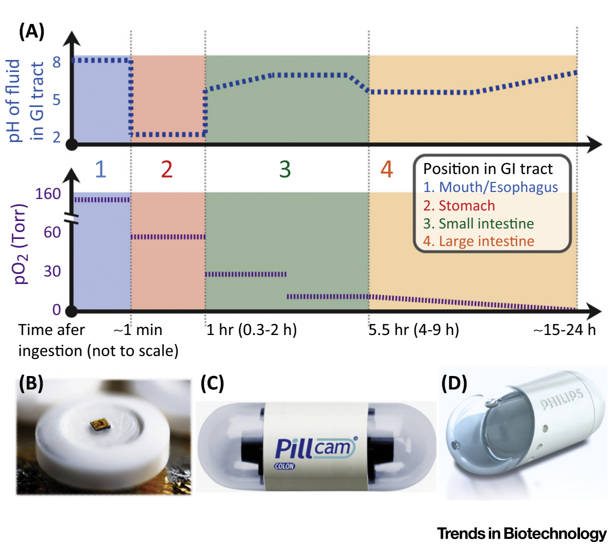

Figure 1. Gastrointestinal Tract Physiology and Recent Examples of Ingestible Electronics. (A) Spatially-dependent physiological parameters within the gastrointestinal (GI) tract. Gastric transit times approximate values for foodstuffs and strongly depend on the size and geometry of the device along with the physiological state. The transit times for the stomach and small intestine represent median (min–max) times for a device ($D \times L$ = 6 mm × 15 mm) [66]. The transit time for the large intestine represents a range that is estimated from that of nondisintegrable tablets in the fasted state. Representative examples of ingestible medical devices including the (B) ingestible component of the Discover by Proteus Digital Health (affixed to pill, $W \times L$ = 2 mm × 2 mm), (C) PillCam by Given Imaging ($D \times L$ = 11 mm × 26 mm), (D) IntelliCap by Philips ($D \times L$ = 11 mm × 26 mm). Images reproduced with permission.