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Towards soft robotic devices for site-specific drug delivery

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Towards soft robotic devices for site-specific drug delivery

Abstract

Considerable research efforts have recently been dedicated to the establishment of various drug delivery systems (DDS) that are mechanical/physical, chemical and biological/molecular DDS. In this paper, we report on the recent advances in site-specific drug delivery (site-specific, controlled, targeted or smart drug delivery are terms used interchangeably in the literature, to mean to transport a drug or a therapeutic agent to a desired location within the body and release it as desired with negligibly small toxicity and side effect compared to classical drug administration means such as peroral, parenteral, transmucosal, topical and inhalation) based on mechanical/physical systems consisting of implantable and robotic drug delivery systems. While we specifically focus on the robotic or autonomous DDS, which can be reprogrammable and provide multiple doses of a drug at a required time and rate, we briefly cover the implanted DDS, which are well-developed relative to the robotic DDS, to highlight the design and performance requirements, and investigate issues associated with the robotic DDS. Critical research issues associated with both DDSs are presented to describe the research challenges ahead of us in order to establish soft robotic devices for clinical and biomedical applications.

Keywords

delivery, towards, soft, robotic, devices, site, specific, drug

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Towards soft robotic devices for site-specific drug delivery

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Towards soft robotic devices for site-specific drug delivery

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Abstract

Considerable research efforts have recently been dedicated to the establishment of various drug delivery systems (DDS) which are mechanical / physical, chemical and biological/molecular DDS. In this paper, we report on recent advances in site-specific drug delivery¹ based on mechanical / physical systems consisting of implantable and robotic drug delivery systems. While we specifically focus on the robotic or autonomous DDS, which can be reprogrammable and provide multiple doses of a drug at a required time and rate, we briefly cover the implanted DDS, which are well-developed relative to the robotic DDS, to highlight the design and performance requirements, and investigate issues associated with the robotic DDS. Critical research issues associated with both DDSs are presented to describe the research challenges ahead of us in order to establish ~~really~~ soft robotic devices for clinical and biomedical applications.

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Keywords: soft robotics, site-specific drug delivery, robotic drug delivery systems, capsule endoscope, magnetic drug carriers, gastrointestinal tract, robotic capsules

1. Introduction

In parallel to recent developments in soft smart materials and additive manufacturing (aka 3D printing), the field of soft robotics has recently been gathering significant momentum to bring a new dimension to the establishment of new robotic concepts leading to the design and manufacture of soft robots which will safely interact with (or operate within) the natural world better than their predecessors. As a sub-class of biologically inspired engineering, it is a new paradigm to establish innovative robotic systems made of soft materials, components, and active monolithic structures [1-4]. The progress in soft robotics will have a significant impact on medical applications including prosthetic devices, assistive devices, and rehabilitation devices which require human-machine interaction. The new generation of robots must have adaptive elasticity and the ability to interact with humans and to operate within the human body and they must be sufficiently miniaturised. For applications in medicine, they must have compliance matching with human tissues and organs, and

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¹ Site-specific, controlled, targeted or smart drug delivery are terms used interchangeably in the literature, to mean to transport a drug or a therapeutic agent to a desired location within the body and release it as desired with negligibly small toxicity and side effect compared to classical drug administration means such as peroral, parenteral, transmucosal, topical, and inhalation.

biocompatibility. Pipe inspection is another important area which will benefit from the progress in soft robotics. Prosthetic limbs or wearable robots are other areas which will significantly benefit from the developments in soft robotics. The progress in soft robotics will have a significant effect on other fields such as stretchable electronics, microfluidic systems (lab on chip systems) and in-body drug delivery systems.

Site-specific drug delivery systems consist of mechanical/physical, chemical and biological/molecular delivery systems, as shown in Figure 1. In this paper, we focus on the mechanical/physical delivery systems, especially robotic or autonomous drug delivery systems. We exclude (i) classical drug delivery, which refers to the development of drugs and nano-medicine formulations based on nano-materials and how they can be implemented in real day-to-day clinical practice, (ii) functional polymers, which store a drug, and are responsive to internal and external stimuli in order to release the drug, and diffusion-controlled hydrogels and other hydrophilic systems and (iii) biodegradable and biocompatible bioactive molecules such as food proteins (e.g., casein) and the like, which are used to encapsulate various drugs so that their release can be controlled [5]. This review is limited to untethered robotic devices, excluding, for example, a flexible cable colonoscopy and its robotic versions with automated locomotion, where a computer controls the movement of a colonoscopy. A robotic colonoscopy that carries a light source, a camera, biopsy channel, and air/water tubing can move from the anus to the cecum with no damage to surrounding tissue [6]. Robotic DDS carry a drug or drugs or direct a swarm of a drug or drugs or drug containers to a specific location within the body where they can be released at relevant sites so that they can have optimal efficacy with no side effects [7].

Figure 1: Classification of site-specific drug delivery systems.

By site-specific drug delivery we mean physically carrying or transporting a drug to a specific location in or out of body, and discharging or releasing it at an appropriate (optimal) dose and rate at the appropriate time with negligibly small toxicity compared to the classical

drug administration routes. It must be noted that the drug release is a part of the drug delivery once the drug is at the relevant site. There is a growing need to establish such drug delivery systems. Classical medications such as orally taken drugs require much higher doses to obtain the necessary effect with a cost of systemic side-effects, especially when treating a serious disease such as cancer. Advantages of site-specific drug delivery are (i) a reduced dose of a drug, (ii) increased and stabilized drug concentration at the targeted tissue, (iii) minimized trauma, inflammation and side-effects, and (iv) releasing a drug according to a patient's need while providing continuous therapy. The concept of site-specific drug delivery will help to effectively attain precision or personalized medicine.

While the implantable DDS are internally and externally placed around the treatment area through a minimally invasive surgical operation, the robotic DDS use –a mobile system carrying the drug to various locations within the body to release them as programmed. The implantable DDS [8-11] can be in the form of biodegradable drug implants such as a polymer matrix filled with a drug which cannot be refilled and the drug release is not quite controllable as the drug diffuses out of the reservoir. It must be noted that depending on the polymer used, a polymer-based DDS can release the drug following a specific controlled release profile over a predetermined period of time, but not in real time as desired with a variable dose or timing. These DDS are known as encapsulated drug delivery systems. On the other hand, microchip-based DDS and micropump-based DDS release a drug in a controlled manner in real time.

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Robotic DDS can carry encapsulated drug containers and other formulations to the desired location for effective drug release but one problem associated with the robotic DDS is being able to anchor them before releasing the –drug and making sure that their location is accurately controlled so that they release the drug at the desired location [12-15]. In this regard, the implantable drug delivery systems are less problematic and more reliable than the robotic drug delivery systems for site-specific drug delivery but they have to be removed from the body once they complete their mission if they contain non-biodegradable components, or they must be left at the implantation location in order to have them disposed of naturally if they are made of biodegradable components. Further, specific ligands such as polysaccharides [69, 70] can be used for anchoring the drugs at specific locations providing specificity (active targeting) and more precision once the drug is delivered to a specific site. Usually, active implantable drug delivery systems require an on-board power source and a wireless communication module. This –imposes limits on the drug implantation and delivery period. Unless they are externally implanted and are the only choice, active implantable DDS, and implantable DDS made of non-biodegradable components are –generally to be preferred.

We believe that the topic of site-specific drug delivery requires a multi-disciplinary approach. To this aim, collaboration among researchers in various disciplines such as engineering, and physical, chemical, biological, mathematical, and biomedical sciences would be useful in order to solve the fundamental and applied research problems of establishing innovative, low-cost and effective DDS, drug design including drug design parameters such as the rate

and dose of the drug to be delivered to relevant areas, and the way a drug will be released in order to attain optimal efficacy with enhanced permeability and retention. An integrated approach needs to be followed in order to shorten the path between the research outcomes in the laboratory environment and their translation into day-to-day clinical practice in order to make a significant impact on medical treatment, resulting in improved health care for the community.

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2. Implantable Drug Delivery Systems

The implantable DDS consist of microchip-based, encapsulated and micropump-based DDS. Microchip-based DDS, also called 'pharmacy-on-a-chip' [9, 16], which are fabricated using microtechnology and hard substrates such as silicon, glass and metallic thin films do not have moving parts such as pumps to release the drug [66, 67]. The drug, which is stored in multiple reservoirs in liquid, gel or solid form, can be discharged by applying a potential difference between an anode membrane covering a reservoir and a cathode. How to fill their reservoirs aseptically, how to seal the reservoirs hermetically, how to achieve biocompatibility, and how to implant them through non-invasive surgery are some of the current difficulties associated with this class of implantable DDS [9, 16, 66, 67]. Another important problem is that a membrane grows around the device once it is implanted in the body. The membrane slows down the drug release and lessens the efficacy of these site-specific drug delivery systems. If space is not a constraint, implantable micropump-based systems can be more effective in satisfying the requirements of site-specific drug delivery.

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Encapsulated DDS can be in the form of micro/nano-sized drug containers made of polymers, gels, liposomes, micelles, proteins and antibodies, and relatively new and not clinically fully established peptides, viruses, cells, gold, iron oxide, carbon and silica nanoparticles, nanospheres, shells, sheets, diamonds, cubes, tubes, microcapsules and similar drug-containing molecules [7, 17]. To accumulate them in tumours and at relevant sites for enhanced permeability and retention and to prevent their aggregation before achieving their desired effects, the size of these drug containers must be much less than 100 nm [7]. Smart soft materials such as electroactive polymers can be engineered as a drug container with a large amount of a drug to be released over a long period of time. They are encapsulated DDS implanted at a certain location inside or outside of the body so that they function to conceal the bad taste of a drug and improve drug stability and drug release characteristics.

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A telemetric technique has been proposed to govern an insulin pump for drug release [18]. This technique is used to remotely control the time and rate of the drug. It is an implantable DDS like an electroactive polymer container releasing a drug over a long period of time, when it is remotely activated. The pump-based DDS can be placed externally and operated outside the body for drug delivery to transfer the drug in the liquid form from the drug reservoir to the blood vessel or tissue accurately and reliably, compared to conventional routes [19]. A typical drug delivery system based on a micropump is shown in Figure 2. Such devices usually need an on-board power source (e.g. a battery), which significantly affects the overall size of the device and where it can be implanted in and around the body [20]. On the other hand, an osmotic micropump [21] does not require energy and this means that a drug

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delivery system based on an osmotic pump is much smaller and simpler than the actively operated mechanical displacement micropumps and electro and magneto-kinetic micropumps [22]. Their main disadvantages are that their operation is temperature dependent, and this can be problematic if the DDS is implanted externally, it does not allow refilling or multiple uses, and its release rate is constant and cannot be modified once it is set for use.

Micro-electromechanical systems (MEMS) technology is used to establish implanted drug delivery devices which are assembled or implanted at an appropriate place in and around the body for controlled drug release [66, 67]. The drug sealed with a thin film is released at the desired time and rate by rupturing the thin film using electrochemical and electro-thermal means [16, 18, 23-26].

Figure 2: Elements of an implanted DDS based on a micropump concept.

Figure 3: A practical drug release concept based on magnetic actuation, adapted from [24].

Magnetic actuation has been proposed to minimize the overall size of the micropumps, which are activated by applying a magnetic field to a flexible magnetic reservoir containing a drug. The operation principle of such a magnetic drug delivery system is illustrated in Figure 3 [23, 24]. This basic drug release concept is suitable for the robotic capsules [14, 15, 29, 30] for drug delivery in the gastrointestinal (GI) tract. The duration and magnitude of the magnetic ~~field-flux density~~ determine the rate and amount of drug to be released. For example, a

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compact magnetic drug release concept has been proposed to release a drug near the surface of the sclera (white part of the eye) to treat proliferative retinopathy in the eye [24]. It is implanted in the space surrounding the eye, towards the back of the eye. This is proposed as an alternative to a manually operated drug release system to treat chronic ocular diseases [27].

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In addition to the external and implantable drug release systems based on the micropump concept, bioadhesives, polymer implants, transdermal patches, microencapsulation, microchip drug reservoirs, immuno-isolating capsules and diffusion chambers are other examples of implantable drug release/delivery systems [28]. Powering the implantable active DDS such as micropumps and associated wiring are two main challenges which must ~~be~~ overcome before they can be used *in vivo* and subsequently in clinical applications. Wireless power transfer [72] is one option to consider though it is not easy because extra hardware must be brought in for energy generation and usage at the site.

3. Soft Robotics for Drug Delivery

Although there is no agreed definition of the term ‘robotics’, we define robotics as the science and engineering of robots which are reprogrammable, multi-functional, multi-purpose and versatile systems and devices intelligently linking sensing to action. This definition can be extended to soft robotics as the science and engineering of the robots primarily made of soft materials, components and monolithic active structures so that they can safely interact with the natural world better than their predecessors (i.e. robots made of hard components).

A robotic drug delivery system must have a minimum size as large as a vitamin pill, like a typical endoscopic capsule [15, 29, 30] (if it is operating within the digestive tract, which is the largest opening within the human body), a minimum drug release time (<1 second), a large enough volume of the drug reservoir (at least 30% its overall volume, storing not less than 0.3 mL of a drug), a high drug release rate and multiple doses. As it operates within the body, it is essential to have a soft robotic device in order to ensure that it does not apply excessive pressure on the tissues or organs and that it makes a soft-on-soft contact with an adaptable mechanical compliance matching with the tissues or organs along its path.

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A soft robotic system for drug delivery must meet the following requirements:

- It must be biocompatible (biodegradable with no toxicity or harmful by-products, or not generating any harmful by-products if not biodegradable).
- It must be mechanically and chemically strong against loads or pressure and harmful body fluids.
- It must have adaptable compliance and shape match with organs, tissues and the like. It must be programmable, reliable and have localized drug delivery (dose, rate, timing).
- There must be no drug degradation in the reservoir during the delivery period.
- It must be economically viable for the patient, preferably re-usable for ~~long-term~~ operation.
- It must have wireless actuation, anchoring, localisation and control.

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- It must be small enough to be operated within the body.
- It must be simple to fabricate, sterilise, implement and remove.
- It must be robust against accidental delivery.
- It must meet –Food and Drug Administration (FDA) and European Medicine Evaluation Agency (EMA) and similar agencies’ approval requirements.

Current research issues in soft robotic devices for site-specific drug delivery centre on developing actuation, localisation, anchoring and drug release concepts satisfying these requirements, (see the expert Commentary Section).

A soft robotic system needs energy. For an in-body robotic system, it is extremely difficult to store enough energy to activate any possible actuator (e.g. an overly miniaturised electric motor) for a long time (typically less than 10 minutes). While on-board batteries can be used for very short operations, other means such as electromagnetic induction, ionic signals, organic energy harvesting need to be considered.

Recently, a starfish-like biocompatible, biodegradable and soft microgripper responsive to temperature change and a magnetic field [31, 32] has been –proposed for medical applications including drug delivery within the human body. Swelling and photo-cross-linked soft hydrogel containing iron oxide particles were blended with a non-swelling and stiff segmented polymer to establish the gripper which opened and closed upon heating and cooling above and below 36°C, respectively. Although this concept has been used for cell gripping and excision, it can also be used for drug release within the body, assuming that it will be loaded with a drug which can be released upon activation. This is a good example of synthesising new soft and biocompatible materials which can be used to establish functional actuation concepts with a low foot-print (no batteries, power source, wires, tethers etc), amenable to remote actuation upon change in a remotely generated field or stimuli such as magnetic field and heat. Progress in soft robotics for medical applications within the human body depends on –progress in soft, biocompatible, and printable materials amenable to remote stimuli such as a magnetic field or a heat field, not requiring any on-board energy source.

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3.1. Robotic Drug Delivery Systems

It is now unlikely that an autonomous robotic system with an on-board energy source could be devised for operation or drug delivery within the body especially in the GI tract. One possible robotic approach would be –to employ a robotic magnetic navigation system in the form of a robot manipulator carrying the magnetic source which externally navigates the target device in the body. Another one is a commercial magnetic navigation system [33], which carries a magnetic source to steer cardiovascular interventional devices [33, 34, 35], or gastrointestinal (GI) devices such as endoscopic capsules within the body [36, 65]. The commercial magnetic navigation system equipped with a fluoroscopic detector provides x-ray images and feedback data to the surgeon to update the location of the medical device within the body for any medical purpose such as screening, diagnostic or therapeutic purposes. The target device within the body has magnetic features interacting with the external navigation system. One of the disadvantages of these systems is that the magnetic ~~field-flux density~~

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applied on the target robotic device containing a magnetic element is a nonlinear function of the distance between the magnetic source and the target points. When such systems operate under a magnetic field gradient, they generate a magnetic force to pull or push the medical device within the body. In addition to the disadvantage associated with the distance between the magnetic source and the target point, another disadvantage associated with this is the problem of safety. How to limit the magnetic field gradient in order to prevent any damage to the contacting tissue and patient is a challenging problem. The magnetic field gradient must generate a stress (through the target device within the body) less than the maximum stress ($<5\text{--}6\text{ kPa}$) the surrounding tissue can withstand [34]. It must be noted that magnetic gradients provided by the imaging coils of an magnetic resonance imaging (MRI) scanner generated body depth-independent navigation forces on drug-loaded nanorobotic agents [57, 71]—thanks to the high magnetic flux densities (at least 1.5 Tesla) provided by the scanner.

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Devising a truly soft robotic system to operate within the human body for drug delivery is challenging. One recent proposal is a soft capsule robot for drug delivery in the stomach [37–39]. It is a magnetically actuated soft capsule robot with a diameter of 15 mm and a length of 40 mm consisting of a camera module, two heads with internal magnets, a drug chamber, and side links connected between the two heads. It is activated externally with a pulse type magnetic field in the range of 0.01–0.07 T and with a frequency in the range of 1.2 – 2 Hz to bring the heads closer in order to squeeze the drug out of the chamber. When squeezed, its diameter increases to 20 mm and its length decreases to 30 mm; 10 mm of the original length being the stroke needed for drug delivery. With these dimensions, it is suitable for operation in the stomach but not beyond, for drug delivery only, not for other functions such as biopsy or biosensing yet. Another problem is that it does not deliver the drug at the target, but at four separate areas around the target.

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A remote controlled capsule [40] has been proposed for site-specific drug delivery within the GI tract. It has a diameter of 10.4 mm and a length of 30 mm and consists of a shell, a piston, an embedded magnetic marker, a tele-control unit, a drug release mechanism, and a magnetic switch. An external 330 MHz radio frequency signal is used to activate the drug release mechanism which consists of a micro-thruster, a sliding protective shell and a piston. The ignited propellant pushes the piston forward with enough force to discharge the full amount (0.6 mL) of the drug from the drug reservoir. Although the size of the capsule may be acceptable, the problems associated with this device are its small drug reservoir, the impossibility of multiple dose drug delivery and safety concerns due to using propellants and a thruster. Not having a dedicated anchoring mechanism when the thruster is ignited is a serious problem with this capsule.

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Woods and Constandinou [41] proposed a robotic capsule equipped with an anchoring mechanism and a drug release mechanism for site-specific drug delivery within the GI tract. It has a size of 32 mm in length and 11 mm in diameter, and contains micromotors to drive the anchoring and release mechanisms which occupy 60 % of the capsule volume. It was designed to deliver 1 ml of drug. No *in vivo* or *in vitro* drug delivery results have been

presented, however, in order to demonstrate whether this capsule is up to its task (i.e. drug delivery) specifications.

The IntelliSite® Capsule (Innovative Devices, Raleigh, US), which is an FDA approved cylindrical capsule with the dimensions of 10 mm in diameter, 35 mm in length with a drug reservoir of 0.8 ml, is radio frequency activated to deliver a drug within the GI tract. Gamma scintigraphy is used to localise the capsule within the GI tract and then the drug is remotely released. One important problem associated with this device is that there is no anchoring mechanism to ensure that the capsule does not move during the release period [123, 42, 43], and this is an essential feature of a robotic DDS. Other technical problems are drug leakage, the heat generating shape memory alloy actuators are used to activate the capsule, and activation times are greater than 2 minutes. The Enterion capsule (Phaeton Research Pharmaceutical Profiles) which has the dimensions of 9 mm in diameter, 32 mm in length with a drug reservoir of 1 ml of powder or liquid drug, was developed to overcome some of the disadvantages of the Intelisite capsule [43]. An external magnetic field is applied to the capsule to increase the temperature of a heater element in the capsule in order to trigger the opening of the capsule and release the drug. Compared to the Intelisite capsule, the release time is much quicker and it can deliver a wide range of drugs, however, in addition to its complex release mechanism, it does not have an anchoring mechanism to ensure that capsule is stopped at the delivery site during the release period. A new capsule or container-based DDS would need to have two essential features: (i) an anchoring mechanism to ensure that the device is stationed at the site of delivery and, (ii) a drug release mechanism to regulate the drug dose, release rate, and number of doses to be released. In general, there needs to be four modules in a soft robotic DDS: actuation, localisation, anchoring and drug release. The release mechanism or technique used in the implantable DDS can be incorporated in the soft robotic DDS to expedite the progress in the robotic site-specific DDS.

We have recently proposed a new magneto-mechanical robotic drug delivery system to be incorporated into the next generation wireless capsule endoscope (WCE), as illustrated in Figure 4 [44, 45]. It is based on a miniaturized slider-crank mechanism articulated with an externally induced magnetic torque. This system consists of three main components: the external magnetic system made of permanent magnets or an electromagnetic system (A) that surrounds the patient, the drug release module (B) embedded in the robotic capsule (C) and three complementary modules (D) integrated in the robotic capsule. The components of the drug release module are: an internal permanent magnet (IPM), a slider crank mechanism that is connected to the IPM, a drug reservoir to store the drug to be released and an orifice through which the drug is expelled as per the stroke of the slider-crank mechanism. We are in the process of testing this drug delivery system in a model of the GI tract.

Figure 4. The main components of a drug delivery system for WCE. A: ring-shaped external magnetic system, B: drug release module, C: the robotic capsule, D: complementary modules within the capsule (anchoring mechanism, active locomotion system and localization and orientation detection module), E: patient bed, F: surgeon, G: joystick, H: Human Capsule Interface.

3.2. Swarm-based DDS: Bacterial microsystems and microrobots

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In proportion to efforts to establish self-powered microrobots [46, 47], the propulsion mechanism of microorganisms such as flagellar bacteria has been used as a model to design biomimetic microrobots to be operated within narrow spaces inside the human body. Most of the established systems have been built as a macrorobot to validate the bio-inspired robotic concept. Another popular microrobotic model is flagellated magnetotactic bacteria (MTB) which are proposed as microcarriers for drug delivery within the circulatory system of human body where the hydrodynamics are described by a low Reynolds number. Both of these biologically inspired microrobotic concepts are magnetically actuated remotely. The latter, bacterial microrobot MTB, requires less power to operate. Of these bacteria, the rounded cell of the MC-1 magnetotactic bacterium with a diameter of 1-2 μm which has a large enough surface to hold a therapeutic agent (e.g. anti-cancer drug) had been proposed in order to move through the tiniest passages in humans to deliver the drug to specific points such as tumors [48, 49]. This is a computer-controlled therapeutic microrobot, which can move with and against blood flow with an accurate directional control, for example, using MRI-based actuation to magnetically guide these bacterial microrobots to a target [46, 71]. Detailed reviews of -microrobots and their applications are provided in [46, 47, 71].

Sperm-inspired microrobots that consist of a magnetic head and soft body have been developed for drug delivery applications [50]. An oscillating magnetic field as small as 5 mT is applied to the head to generate the torque needed to oscillate the soft body and hence steer a supposedly drug loaded sperm-like microrobot to the drug delivery site. The potential medical uses include in vitro fertilization (IVF), cell sorting and opening clogged arteries.

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A corkscrew structure made of plants is coated with titanium and magnetic nickel in order to build a microswimmer which is propelled via a rotational magnetic field in a wet environment [51]. This biodegradable microswimmer and other similar microswimmers [52] can be moved forward or backward and side-to-side in order to direct it to a desired location for drug delivery or to dig into blood clots in order to open obstructions in arteries and the like. Almost all microswimmers rely on a rotational or an oscillating body articulated through a magnetic field. Helical or oscillating magnetic structures can be fabricated using 3D fabrication techniques. These structures can be loaded with drug, chemical, biological sensing molecules and the like.

3.2.1. Magnetic Drug Carriers for Swarm-based DDS

Intravenously administered drugs affect the whole body and can cause undesired side-effects as the drug diffuses not only into the target tumor/cells/organ, but also into healthy ones. This means that site-specific drug delivery is essential in order to minimize any side effects. To this aim, many externally regulated stimuli-responsive drug delivery systems such as photo-responsive, magnetic field responsive, ultrasound-responsive, thermo-responsive and ultrasound-responsive systems have been proposed. Of these, the magnetic field responsive drug delivery systems are the most well studied and effective systems and they have a high potential for use in clinical applications as they guide a swarm of drug containers to the desired site using an external magnetic field. Magnetic drug carriers containing, for example, an anti-cancer agent such as doxorubicin, are guided to cancerous tumors within the body, and the drug is released using various mechanisms [53, 65]. A biocompatible magnetic nano/microparticle carrier loaded with a drug which is prepared as a biocompatible ferrofluid is dispensed into the circulatory system of a patient. An external magnetic field (~ 0.2 T) with a high enough gradient (~ 0.08 - 0.1 T/m) is applied to the target point in order to concentrate and keep the desired dose of the carriers there. Using release mechanisms such as an enzymatic activity or a change in pH, osmosis, temperature, among others, the drug is released at the target point *in vivo* in order to obtain the maximum possible efficacy with little or no side effects [53]. Hydrodynamics parameters such as blood flow rate, drug concentration, infusion route and circulation time and physiological parameters such as the distance from the magnetic field to the target site, reversibility and strength of the drug/carrier binding, and volume of the targeted tissue or tumor affect the success of such a typical site-specific drug delivery system based on magnetic drug carriers [53].

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Figure 5: A typical magnetic drug carrier with a ferrite core encapsulated with a biocompatible polymer shell in order to attach various drug formulations [53].

As shown in Figure 5, magnetic nano/microparticle carriers can be in the form of a ferromagnetic sphere (e.g., Fe_3O_4 , or maghemite, $\gamma\text{-Fe}_2\text{O}_3$, cobalt, iron, nickel and similar). They are coated with a biocompatible polymer such as polyvinyl acetate (PVA) or dextran, or inorganic materials such as silica or a noble metal such as gold to protect them from the surrounding environment and attach them to functional groups such as carboxyl groups, biotin, avidin, carbodi-imide and other molecules holding the drugs or target antibodies [53].

Swarm based DDS are also known as magnetically targeted DDS. A swarm of magnetic microspheres is targeted to relevant sites or cells under an externally applied magnetic field, as demonstrated in Figure 6. Organic sheaths (as shown in Figure 5) are used to encapsulate the magnetic core so that a drug can be attached to microspheres and prevent the aggregation of the magnetic microspheres. Magnetic navigation system is used to guide a swarm of the microspheres to the relevant sites [48, 49]. For example, the Stereotaxis robotic navigation system [33, 54] which is an FDA approved system can be used to navigate a swarm of micro-particles to the desired site within the body, especially in the cardiovascular system. It generates a controlled magnetic field via two large coaxial permanent magnets assembled on automatically operated arms. It guides a magnetic catheter through the arterial system. Much research has been done into magnetic drug delivery systems [53, 55, 59, 61, 67], but for the sake of brevity, we are not including them.

Figure 6: Illustration of how magnetic drug carriers (MDC) in the circulatory system can be attracted to a relevant site using an external magnetic field, adapted from [56].

There are some research problems associated with site-specific drug delivery based on magnetic drug carriers [48, 49, 53, 57-61]: (i) occlusion of a blood vessel due to the high concentration of the carriers just before release, (ii) the distance from the magnetic field source to the target point--there is a non-linear relationship between the magnetic field and distance to the target point, (iii) once the drug is released, the blood flow reduces its efficacy, no retention of the drug under the magnetic field, and (iv) toxicity due to the magnetic core of the drug carrier. While the first two problems can be solved using practical measures, the last two must be solved in order to pave the way for using this promising site-specific drug delivery technique in clinical applications.

Expert Commentary

Compared to the swarm-based robotic DDS, the container-based robotic DDS are autonomous robotic systems, which carry a drug to various relevant locations within the body in order to release it as required multiple times. With this in mind, an actively operated capsule endoscopy for operation within the GI tract is a very good example of the container-based robotic DDS. A comprehensive review of the diagnostic and therapeutic capabilities of

the actively navigated capsule endoscopy has recently been published [63]. Interested readers are encouraged to read that review paper to complement what is presented in this paper. Some critical research issues which need to be addressed for soft robotic systems for site-specific drug delivery include:

1. The progress in soft robotics strongly depends on the progress in materials science and technology. There is a need to establish materials the actuation and sensing properties of which can be programmed or varied using remotely applied fields such as a magnetic field or temperature change so they can be fabricated using additive manufacturing technologies to establish low footprint soft robotic systems. In general, there is an ongoing need for smart materials amenable to additive manufacturing and responsive to various stimuli such as electric, stress/pressure, light, heat, magnetic field, water/moisture, pH and the like, which change their various properties in a reproducible and predictable manner so that they can be used to establish actuators and sensors with a small footprint, meeting a strict space requirement for soft robotic devices for medical applications.
2. As a soft robotic device needs to be actively navigated and there is a very limited space on board to store enough energy (i.e. battery), magnetic actuation appears to be the most ~~viable technique~~ viable technique to use. To this end, a user- friendly hybrid magnetic system consisting of a permanent magnetic system and an electro-magnetic system is needed to navigate and anchor a soft robotic device and then release the drug in the chamber of the device. If a robotic DDS needs an on-board power source, the energy density of the current batteries will likely be insufficient, for example, for device propulsion, anchoring and drug release. For drug release only, the disk batteries in the current endoscopic capsules (3V, 55mAh $\cong$ 20 mW) will be sufficient as they last 8-9 hours for powering a number of LEDs, taking images and sending them wirelessly to an external data recorder. A detailed review of ~~endoscopic~~ capsules is presented elsewhere [12, 13, 62, 63, 68].
3. We need to follow an integrated or mechatronic design approach when establishing a soft robotic system for drug delivery. To this aim, we propose to follow a top-down approach: (i) understand the task or application requirements (e.g., site-specific drug delivery), (ii) develop design concepts for actuation, sensing, motion transmission, energy conversion and creation at the system level and component level, (iii) assuming that the actuators and sensors cannot be sourced from existing ones, determine material properties, and synthesise materials which can easily be processed and 3D printable, to establish a monolithic device compactly hiding actuation, sensing, mechanical mechanism and control topology in its monolithic topology, and (iv) model, analyse, design optimise the device in the light of operation and fabrication constraints, and fabricate its prototype and finally test it under near-real conditions to verify the task and application requirements.

4. Soft actuation with an energy or power source is the primary barrier to the construction of soft robotic systems. Flexible and compliant power sources incorporated into the monolithic topology containing the actuation system or externally induced into the topology are needed for soft robotic devices operating within the body.
5. Most of the current drug delivery systems, especially the implanted ones, are the drug release systems. It will be a pragmatic approach to incorporate these drug release mechanisms, especially the microchip-based and MEMS based release systems into the new robotic DDS.
6. There is a need for a low cost, low footprint localisation system (position and orientation relative to a reference coordinate frame) for robotic devices operating within the body. The recent innovative localisation method we proposed and the results we have presented to demonstrate its efficacy are the most accurate in the literature so far. The method, however, which is based on multiple (x3) positron emission markers requires a low cost gamma ray detection system [13-15], which is not currently available on the market as a stand-alone system. Therefore, this still remains as a challenging problem for in-body robotic systems including robotic DDS.
7. For anchoring, there is a need for an anchoring system based on soft-on-soft contact, rather than those, like most of the systems in the literature, which are based on the hard-on-soft contact, thus creating a safety concern. Recently, we have reported [64] on the fabrication of soft magnetic cilia and their assembly on the external surface of a typical capsule endoscope. An appropriately shaped magnetic field can be applied to the cilia to anchor the robotic capsule at the -desired location and then the drug is released using a drug release mechanism. Once the drug delivery and release is completed at a specified location, the magnetic field can be turned off in order to allow the capsule to travel along its path under natural peristalsis. In order to do this, this system requires only a -minimum modification to the existing capsule endoscopes. Once the magnetic field is turned off, the cilia can return to their collapsed neutral positions and do not create -any obstacle and/or hazard to the surrounding tissue.

We expect this review to stimulate more interaction between many disciplines including engineering, medicine, materials science, chemistry, physics and biology in order to facilitate collaboration -on the establishment of functional soft robotic systems for medical applications. This (i.e. functional soft robotic systems) has the potential to revolutionise medical diagnosis, procedures and treatment and subsequently provide unprecedented benefits to society. This collaboration will bring the necessary momentum and synergy to shorten the path from -laboratory-based research to clinical applications or devices which will be able to be approved by regulatory agencies such as the FDA and the EMEA.

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Five-year view

A typical robotic system consists of actuation, sensing, mechanical mechanism, control and communication interface elements. Such robotic systems are able to undertake intricate tasks requiring sophisticated positioning and force sensing abilities. Their control system is advanced enough to make contact with hard environments smoothly. On the other hand, soft robotic systems are made of (i) structural materials, making the skeleton of the robotic body, in the form of hard plastic or light metal alloys, which can tolerate some strain or deformation when under excessive load or stress, and (ii) soft smart materials which can be compactly hidden in and around the skeleton and overall topology of a soft robotic system to provide actuation, sensing, mechanical motion conversion and a control interface in order to facilitate a smooth human-machine interface. Softness and compliance matching are the important features of a soft robotic system, which need to be able to tolerate an unexpected contact with no damage to its environment. The concepts of embedded intelligence and morphological computation [1, 2] can be employed for the design of a soft robotic DDS so that it will have simple and compact propulsion, localization, anchoring and release mechanisms. Both concepts mean outsourcing some intelligence and computation in the morphology of the soft robot made of smart and structural materials. This means that we can expect significant progress in functional materials or what we call 'soft robotic materials' over the next five years. These materials are expected to be amenable to additive manufacturing so that the resulting multi-dimensional body can be programmed or allocated for actuation, sensing, control and communication interface and provide a mechanical structure or mechanism, all in a single monolithic body. Modelling, analyzing and subsequently designing such a soft robotic device the behavior of which is heavily affected by the properties of the materials it is made of will be challenging research areas over the next 5 years.

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Any autonomous drug delivery system must have propulsion, localization, and anchoring and release functions. There has been significant focus on their propulsion and drug release functions (which can be borrowed from the implantable DDS) as articulated in this paper and in recent reviews [12, 63]. We, therefore, believe that the primary focus over the next five years will be on the establishment of localizations and anchoring mechanisms. The anchoring mechanism needs to be compact and soft, and must not require too much power to activate. We expect significant progress in soft magnetic polymers fabricated as cilia, like actively controlled bristles, in the next 5 years to temporarily ground a robotic device (i.e. to anchor) to the drug delivery site. Most of the localization systems proposed for the container-based robotic drug delivery devices typified by an actively navigated capsule endoscope or robotic capsule are overly complex, requiring significant hardware and processing time to localize a device within the body, usually with limited accuracy. By localization, we mean to determine the position and orientation of the device relative to a reference coordinate frame. Some localization systems are based on magnetic sensing [13, 15]. Knowing that magnetic actuation is promising or currently the only practical one, there will be interference between magnetic actuation and sensing (i.e. localization). We expect to see significant progress towards establishing a localization system which is low cost, accurate, minimally invasive, and able to work with actuation, anchoring and drug release mechanisms, neither being affected by them nor affecting them. A system approach based on considering all of these functions simultaneously needs to be followed in order to establish a functional robotic drug

delivery system which can meet various operation, delivery and regulation requirements. Within five years, it will be possible to establish a magnetically controlled, autonomous soft robotic device for medical applications within the GI tract.

The progress in additive manufacturing has been significant over the last ten years. It will further advance in the synthesis of processable and printable soft materials. The mechanical, electrical, and chemical properties of these materials can be tailored to meet the application requirements. The materials can be polymeric and metallic. A drop in the cost of 3D printers which can accept a range of soft and hard polymeric materials and metallic materials is expected.

Magnetism appears to be the most suitable concept to remotely propel a robotic device, anchor it, release and do the site-specific drug delivery. Therefore, there is a need to develop a hybrid magnetic system consisting of a permanent magnetic system and a programmable or computer controlled electromagnetic system. Magnetic resonance imaging (MRI) systems [48, 49] have been re-engineered for the real-time control and navigation of untethered magnetic carriers, nanorobots, and/or magnetotactic bacteria (MTB) loaded with sensory or therapeutic agents in the blood vessels. This is an expensive alternative to consider unless the drug delivery needs to be done in a hospital environment. Therefore, there is a pressing need for a low cost, user-friendly, and compact magnetic actuation and navigation system for the propulsion, anchoring and drug release of a container-based robotic DDS. Such a magnetic system will also be needed for swarm-based DDS, as illustrated in Figure 6.

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Much research into magnetic nanoparticles or drug carriers has been done. New magnetic nanoparticles for drug delivery, contrast agents for MRI, magnetic hyperthermia treatment etc. are being synthesised every day. We believe the progress will be in making biodegradable magnetic carriers, which do not create toxicity once their function is completed in the body/tissue/organ, and synthesising new magnetic carriers with a higher magnetic moment such that they require a smaller magnetic field to guide a swarm of them through the blood stream.

Along with significant research progress in nanotechnology, microtechnology, smart materials, and intelligent mechatronic systems in the last decade, the field of site-specific DDS has been growing continuously to benefit from this progress in order to provide significant health benefits to society. We believe it is time to consider a simple and effective site-specific drug delivery application to demonstrate this progress. As far as the robotic or autonomous DDS are concerned, the field of soft robotics and its sub-fields of micro soft robotics or milli soft robotics are still in their infancy. We expect an exponential growth in them over the next five years, which will lead to functional, soft and biocompatible robotic devices for medical applications such as screening, minimally invasive surgery, diagnosis and drug delivery within the human body.

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Key issues

- Site-specific drug delivery refers to physically carrying or transporting a drug to a specific location within the body, and discharging –or releasing an appropriate (optimal) dose and rate of it when desired.
- Site-specific DDS are classified into mechanical/physical, chemical and biological/molecular DDS.
- Mechanical/physical DDS are further divided into implantable and robotic / autonomous DDS. We focus on the latter, which is still in its infancy, and raises significant research questions which must be answered before it can meet the strict application, technical and regulation requirements.
- Implantable DDS can be incorporated into the container-based robotic DDS as their drug release mechanism.
- Magnetic actuation acts remotely, negating the need for an on-board power source for implantable micropump DDS. This significantly decreases the size of the micropumps.
- If an implantable DDS requires on-board power, there is a need for high energy density batteries such as Li-ion batteries or the power must be induced wirelessly using a magnetic induction technique, which is complex to implement and operate. This applies to –container-based robotic DDS, too.
- A container-based robotic DDS needs a minimum size as large as a vitamin pill, like a typical endoscopic capsule.
- A container-based robotic DDS must have actuation, localisation, anchoring and drug release mechanisms intelligently hidden within its compact size.
- The progress in soft robotic devices for medical applications depends on the progress in soft, biocompatible, and printable materials amenable to remote stimuli such as magnetic field or –heat field, not requiring any on-board energy source.
- With current technology, it is not possible to have an autonomous robotic system with an on-board energy source, making magnetic actuation a strong candidate to articulate the robotic system.

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- An external magnetic system remotely navigates a target robotic device in the body, assuming that the anchoring and drug release mechanisms can be activated using an on-board power source, which will intermittently be used during the anchoring and drug release times only.
- Swarm-based DDS in the form of bacterial microsystems are inspired from the flagellar bacteria, usually requiring a remotely applied magnetic field.
- Swarm-based DDS responsive to a magnetic field are the most effective ones to guide the device to a desired site.
- The research challenges for the container-based robotic DDS are the same as the actively operated endoscopic capsules.

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**** A comprehensive review of existing DDS for capsule endoscopy is presented. The significance of anchoring and the release mechanisms for site-specific drug delivery is highlighted and various DDS systems in the literature are compared in order to identify critical research issues in drug delivery systems for capsule endoscopy.**

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