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PATENT WATCH

Microscale implantable drug delivery systems: emerging IP strategies

Microscale implantable drug delivery systems (IDDSs) have advanced the control of drug delivery parameters, providing better disease control through more accurate, targeted and less painful drug delivery. Numerous physical designs, actuation and control techniques for microscale IDDSs are being explored. Microscale IDDSs have been effective in treating diseases and improving patient compliance and quality of life for osteoporosis and have the potential to reach other disease areas such as diabetes, neurological disorders and contraception (*Sci. Transl Med.* **4**, 122ra21; 2012) (see Further information).

Successful commercial development of microscale IDDSs will rely on strategic partnerships and cooperation between pharmaceutical and medical device companies to leverage resources and implement therapeutic improvements. Developers must not only demonstrate the clinical safety and efficacy of their technologies, but also successfully grow and protect their intellectual property (IP) within the competitive landscape through strategic IP decisions.

To examine the IP surrounding microscale IDDSs, we reviewed English-language US, European Patent (EP) and Patent Cooperation Treaty (PCT) patents and applications published in the past 10 years in the International Patent Classification/ Cooperative Patent Classification (IPC/CPC) subclasses A61M5/14276 (which covers devices specially adapted for implantation) and A61K9/097 (which covers micro-machined devices). Documents that described an IDDS of nano- or micro- scale or with nano- or microscale features were included in the analysis. The documents were classified by therapeutic area, internal or external control mechanism, and drug delivery parameters (FIG. 1).

IP filings surrounding microscale IDDSs have been relatively steady at approximately 60 documents per year over the past 10 years, evenly distributed between US granted patents, US applications and EP or PCT documents. Nearly 100 assignees are represented in this fragmented space: 85% of the assignees have fewer than 2% of the documents each. Approximately 25% of the filings were by large companies, 34% by small companies and 20% by academic institutions (FIG. 1). Philips is the most prolific assignee with 8% of the documents. Prolific small companies (such as Microchips Biotech and Minipumps) and academic institutions (such as the University of Southern California, Los Angeles, USA) have 4–5% of the documents per institution. Only about two-thirds of the documents disclosed specific therapeutic areas, most commonly diabetes management and neurological or nervous system disorders. The most commonly controlled drug delivery parameters were controlling the timing of drug release over time (57%) and controlling the specific flow and speed (35%). Approximately

Philips

Disclosed technical features

Therapeutic area		Control mechanism	
Diabetes	0	External	17
Cardiovascular	0	Internal	36
Infection	0	**Drug delivery parameters**	
Neurological	3	Flow/speed	11
Cancer	0	Temperature	1
Other	0	Mixing	1
General	44	Drug release	45

Technology summary

- Tiny capsule for targeted delivery to the GI tract
- Integrated cameras and sensors for controlled location specific drug release
- *In vivo* drug dilution and mixing

Microchips Biotech

Disclosed technical features

Therapeutic area		Control mechanism	
Diabetes	1	External	10
Cardiovascular	1	Internal	15
Infection	5	**Drug delivery parameters**	
Neurological	6	Flow/speed	0
Cancer	2	Temperature	0
Other	5	Mixing	1
General	17	Drug release	22

Technology summary

- Microchip drug delivery platform
- Controlled drug release
- PTH for osteoporosis treatment
- Diabetes, multiple sclerosis, contraception, cancer therapy and infections

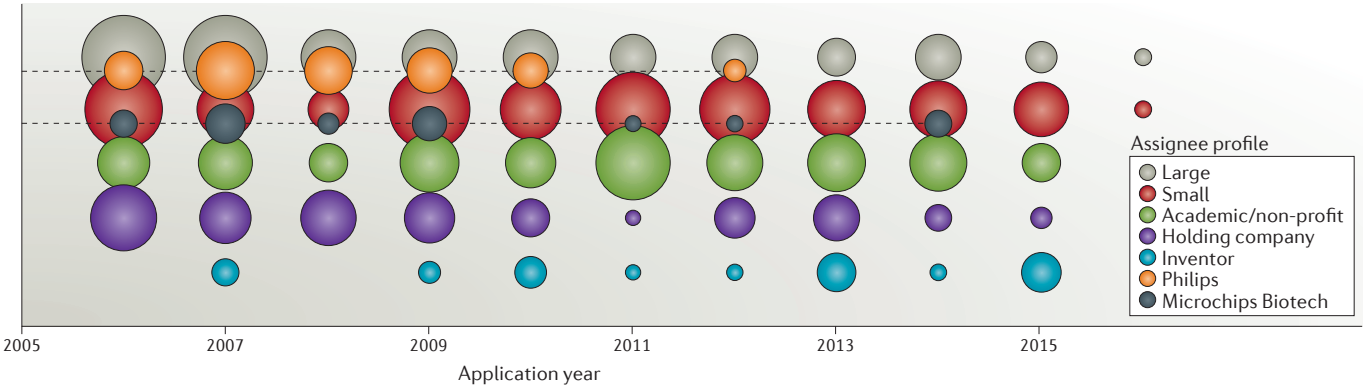

Figure 1 | **Intellectual property landscape surrounding micro- and nano- scale implantable drug delivery systems.** Patent documents collected for the landscape were organized by the assignee profile: large company, small company, academic institution, holding company or individual inventor. The filing activity was then plotted by application year. The size of the bubble represents the number of documents held by a company by application year (smallest bubble corresponds to one patent). Philips' documents are within the large company filing activity, and Microchips Biotech's are within the small company filing activity. Competitive analysis of Philips' and Microchips Biotech's portfolios is shown in scorecards. These scorecards highlight intellectual property strategy by breaking down the assignee's documents within the landscape, the technical features disclosed and a technology summary. GI, gastrointestinal; PTH, parathyroid hormone.

40% of the microscale IDDSs were externally controlled through wireless communication. About 60% of the microscale IDDSs were self-pumping (using an osmotic pump either preprogrammed or self-actuating via an internal sensor).

Examining the timing and technical content of a company's IP filings provides valuable insight into their strategy in microscale IDDSs. Academic institutions have varied positions within the IDDS space. Johns Hopkins University (Baltimore, Maryland, USA) has IP surrounding self-assembling microcapsules containing the drug that are programmed to release at specific times and locations (US8696740B2), including thrombolytic agents incorporated into stent grafts (US9005995B2). The University of Texas at Austin (USA) has IP focused on a device that contains micro- or nano-channels for a constant and controlled release of drug molecules for up to 1 year (WO2013063004A1). Although both institutions focus on self-pumping or internally actuated devices, Johns Hopkins focuses on targeted drug delivery in specific therapeutic areas whereas the University of Texas has a portfolio focused on a general platform with broader application across many therapeutic areas.

Large companies are also taking varied approaches. Philips' IP portfolio, which includes its affiliate Medimetrics, focuses on a tiny capsule with smart features that can be used to alter the drug release profile (for example, linear or pulsed) and delivers drugs to the gastrointestinal (GI) tract (*J. Control. Release*, **217**, 300–307; 2015). Two recently granted Medimetrics patents describe a battery-powered pill technology with low power consumption and integrated sensors. These sensors comprise a pH-sensitive hydrogel coating on the electrode surface to indicate position and circuitry to provide feedback to the mini-pump within the capsule. The microscale IDDS capsule also includes a wireless transceiver for external communication as an additional mechanism to control drug delivery and release. Drugs are released from multiple micro-reservoirs in response to temperature and sensed changes in GI tract conditions (US9227011B2 and US9067011B2). Philip's IP portfolio is summarized in FIG. 1.

Medtronic, which has been a leader in large devices, including implanted neuromodulation devices and more recently a capsule-sized leadless implanted pacemaker (see Further information), is also active in the IDDS space. Their IP portfolio focuses on smaller pumps with a shape memory diaphragm and a micro-machined flow restrictor consisting of tiny nano-sized channels for highly controlled drug flow (US7931643B2). Medtronic also has a controlled release platform targeting spinal therapies (US8642059B2) that includes wireless external control or an internal control of the delivery parameters based on data from incorporated sensors. Such technological capabilities transferred from larger pumps could be highly disruptive in the IDDS space and affect the treatment of many diseases.

Microchips Biotech, Inc. is a small company that focuses on implanted controlled release microchip devices. The chips contain hundreds of reservoirs that can be serially or independently actuated with caps that dissolve to release a specific drug upon exposure to an electric current. This novel approach exhibits enhanced delivery control for multiple therapeutics in a variety of body locations (US8403907B2). The microchip device can be preprogrammed to release a drug at a specific time or remotely controlled by the user (US8403915B2). The technology has been validated for the delivery of parathyroid hormone for treatment of osteoporosis (*Sci. Transl Med.* **4**, 122ra21; 2012). The general nature of the IP portfolio creates an opportunity to extend the delivery technology to other therapeutic areas. This technology has been leveraged in two recent partnerships, one with Teva Pharmaceuticals and the other with the Gates Foundation, which aims to develop a contraceptive delivery device using the platform (see Further information). Microchips Biotech's IP portfolio is summarized in FIG. 1.

The technologies addressed in the microscale IDDS IP promise major improvements to current standards of drug delivery and disease management in many areas. Several IP strategies are being used by academic institutions and companies, but it is yet to be seen which IP strategy has the most potential to be safely and effectively implemented in later stages of microscale IDDS product development.

Dana Daukss and Kennyn Statler are at Global Prior Art Inc., 21 Milk Street, Boston, Massachusetts 02109, USA.

Correspondence to K.S.
kstatler@globalpriorart.com

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FURTHER INFORMATION

Contraceptive microchip: http://www.medicalnewstoday.com/articles/279323.php
Medtronic's pacemaker: http://www.medtronic.com/us-en/healthcare-professionals/products/cardiac-rhythm/pacemakers/micra-pacing-system.html
Microchips Biotech partnering: http://microchipsbiotech.com/partnering.php
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