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On-Demand Drug Delivery from Local Depots

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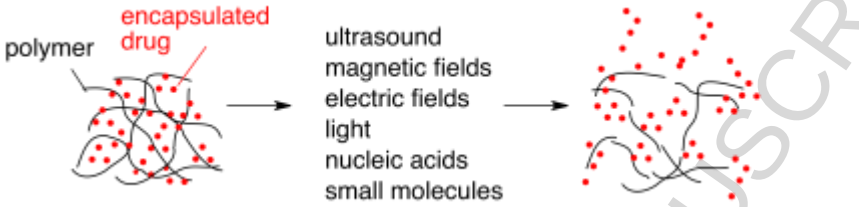
Graphical Abstract:



Abstract
Stimuli-responsive polymeric depots capable of on-demand release of therapeutics promise a substantial improvement in the treatment of many local diseases. These systems have the advantage of controlling local dosing so that payload is released at a time and with a dose chosen by a physician or patient, and the dose can be varied as disease progresses or healing occurs. Macroscale drug depot can be induced to release therapeutics through the action of physical stimuli such as ultrasound, electric and magnetic fields and light as well as through the addition of pharmacological stimuli such as nucleic acids and small molecules. In this review, we highlight recent advances in the development of polymeric systems engineered for releasing therapeutic molecules through physical and pharmacological stimulation.

Keywords
drug delivery; depot, polymer, therapeutic, on-demand, ultrasound, magnetic, electric, light, pharmaceutical, nucleic acid, stimulated

Introduction

Regulated drug presentation made possible through on-demand control over drug release could substantially improve current methods to deliver drugs from local depots. Macroscale drug-delivery devices are gaining attention in medicine due to their ability to exert spatiotemporal control over drug availability locally at a disease site. These drug-releasing depots usually take the form of a polymer or device implanted at a site of need, and release drugs locally. Local, controlled release technology presents a number of advantages over traditional drug administration. The first advantage is finer control over drug concentration at disease sites than is typically possible through oral or intravenous drug dosing. The second advantage is that peripheral, off-target side effects can potentially be avoided because drugs are presented locally. Drug depots can also release drugs for long periods of time (weeks to months), obviating the need for patients to repeatedly dose themselves or come in for a doctor's visit, thereby helping to improve patient compliance. Examples of currently employed drug delivering depots include drug-eluting stents for the treatment of cardiovascular disease (e.g., the Cypher® stent), Gliadel™, an implantable wafer capable of controlled release of chemotherapeutics, the INFUSE® bone graft, which releases growth factors to stimulate bone growth, and various vaginal and subcutaneous implants for stable, long-term contraception release. The clinical and commercial success of controlled-release devices now opens the opportunity for the next step in controlled drug delivery, the ability for real time control over the timing and dosing of a locally-released therapeutic molecule.

The vast majority of drug-releasing depots that are commercially available or currently in development rely on the intrinsic physical and biological environments surrounding the depot to control drug release, but this may not always be appropriate. Most drug-releasing depots rely either on the diffusion of drug out of the depot or the use of local pH, hydrolysis, and enzymatic cleavage to degrade the depot and release the drug. However, the local environment of the disease may dramatically impact these processes, and