Editorial

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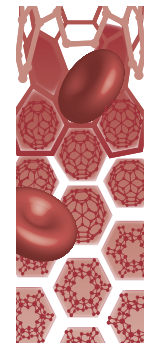

Elastic drug delivery: could treatments be triggered by patient movement?

"The research and development of patients' movement-controlled drug delivery systems hold promise in improving patients' compliance by providing a self-directed and on-demand treatment."

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Nanoparticle-based drug delivery systems have drawn extensive attention for treating a broad range of diseases during the last few decades [1,2]. In order to enhance therapeutic efficacy, reduce side effects and prolong action time, vast efforts have been dedicated to the development of on-demand, precise drug release. In light of this, numerous stimuli-responsive designs have been exploited, including external triggers like mechanical force, temperature, light, ultrasound, electric current and magnetic field as well as internal factors like pH, redox, enzymes, ATP and hypoxia [3–8]. Compared with other stimuli-responsive designs, the macroscopic mechanical force-mediated approach, as one of the most promising strategies, possesses several advantages. It can be generated on-demand during the patients' daily movement, such as tension in bone joints, tendons and muscles, or compression in cartilage and bones. Therefore, a self-administrated therapy can be readily achieved without requirement of additional instrumentations. In addition, in contrast to the inaccurate internal factors due to the complicated physiological environment, the degree of stretch or compression is more conveniently controlled by the patient themselves, leading to a precise dosage-, spatial- and temporal-controllable administration of drug release.

Physical deformation of drug carriers supported on an elastomer substrate caused by stretch or compression is one of the most important strategies for mechanical force-triggered release. Mooney group designed a compression-responsive system for controlled release of growth factor [9]. Inspired by the natural extracellular matrices, they developed a hydrogel with reversible binding of drug as synthetic extracelluar matrices. The physical-loaded hydrogel could respond to repeated compression stimulus and as a result released free drug. Afterward, the matrices could be refilled by free drug during relaxation via dissociation of previously bound drug. Using VEGF as a model drug in *in vivo* studies, they demonstrated that the implanted hydrogels allowed an increase in VEGF concentration near implantation site as applying mechanical signals, subsequently leading to a local enhanced vascularization. In another case, Jeong group developed a strain-sensitive patch consisting of arrays of microcapsules onto a rubbery substrate for drug release [10]. When stretch was applied to the elastomer substrate, the volume of the stretchable microcapsules encapsulating cargoes decreased accordingly with the substrate, then pumping out the preloaded molecules. Under different degrees of mechanical stretching, the release rate and amount of cargoes could be adjusted. This patch has the potential to respond to body motions, even to the mechanical stretching of organs, muscles and tendons when it is implanted into body.

We have recently developed a multipurpose wearable, tensile strain-triggered

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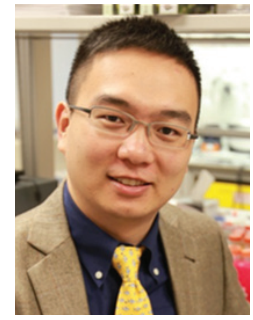

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drug delivery device, which comprised of a stretchable elastomer and microgel depots containing drug-loaded nanoparticles [11]. The drugs can be continuously released from the nanoparticles and temporarily stored in the microgels. When applying a tensile strain, the drugs were released from microdepots due to the enlarged surface area for diffusion and Poisson's ratio-induced compression toward the microgels. Therefore, a sustained drug release can be conveniently achieved by daily body motion, while a pulsatile release is able to be controlled through intentional administration. We demonstrated that this device could be simply attached to a finger joint, and stretched to trigger the drug release when the finger is flexed for multiple cycles, which allowed patients to control the dose and release timing of antibacterial drug on their own.

Furthermore, we integrated this stretch-sensitive device with a microneedle array patch for on-demand transcutaneous insulin delivery [3], which allowed the blood glucose level of mice to decline quickly to a normoglycemic range within 0.5 h. Meanwhile, the obvious pulsatile and continuous reduction in blood glucose level were observed when applying a strain with an interval of 4 h. Based on this technology, the diabetic patients can easily maintain normoglycemia through simple joint movement instead of a traditional painful insulin injection. This skin-mountable device can be further extended for anti-inflammatory, anti-infective drug or painkiller delivery. More importantly, this facile strategy allows immediate medical treatment in emergency situation by patient's simple body movement.

Besides the direct drug release via changing diffusion area or pumping out caused by physical deformation, tension or compression can also generate energy to change the physical properties of drug carriers. For example, Pioletti group exploited dissipation properties of hydrogel as an internal heat source to trigger the thermal-sensitive drug release instead of additional external heat source [12]. Self heating was quickly produced after 5 min cyclic mechanical loading. The increased temperature further caused the shrinkage of thermal-responsive nanoparticles entrapped in the hydrogel and subsequent drug release.

In addition, mechanical stretch or compression is able to tune the molecular conformation and intermolecular interaction between host molecule and guest molecule, resulting in a force-triggered drug release [13,14]. Based on this phenomenon, Ariga group reported a mechanically controlled monolayer formed by a steroid cyclophane molecule with a cyclic core linked to four steroid moieties via the flexible L-lysine spacer [13]. The applied compression could lead to a cavity-forming conformation of the cyclophane. Therefore, the hydrophobic model drug was easily trapped in this hydrophobic cavity. In contrast, expansion of the monolayer could release the encapsulated drug through the molecular transformation from cavity to planarity. Similarly, they developed a mechanical stimulus-activated β-cyclodextrin (CyD)-crosslinked alginate gel [15]. As applying mild mechanical compression, the model drug ondansetron, the entrapped guest, could be released from the host CyD moieties, due to the change in inclusion ability of CyD. The host–guest interactions dominated by van der Waals interactions and hydrogen bonds in a gel matrix can be more easily broken than covalent bonds, which provide a convenient on-demand administration of medicines operated intentionally by the patient.

The research and development of patients' movement-controlled drug delivery systems hold promise in improving patients' compliance by providing a self-directed and on-demand treatment. Nonetheless, there are still many remaining challenges for clinical development. For example, the current systems cannot precisely control the release dose of therapeutics. A fundamental study on the dynamic relationships between the phase transitions of materials and the relevant release profile should be closely investigated. Moreover, regarding the different movement extent and ability for different individuals, how to generate a personalized platform and consistently apply the mechanical trigger signal are difficult tasks ahead that need to be addressed. Integration of this device with other wearable modalities to monitor the real-time physiological signals (e.g., electrocardiograph, blood glucose levels or body temperature [16,17]) and motion signals [18,19] might be able to provide feedback to guide the precise, personalized drug delivery. Last but not least, good biocompatibility and biodegradability for materials is extremely important for further translation of the elastic drug delivery system. Tailoring materials mimicking the structures and composites of natural systems offer a promising strategy [5,20].

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