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IMPLANTABLE DRUG DELIVERY SYSTEM IN CHRONOTHERAUPTICS

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ABSTRACT

In mammalian physiology, diurnal fluctuation in enzymes, hormones, and other biological mediators has long been recognised. Pharmacobiology advances in the last few decades have demonstrated that timing drug delivery can improve treatment efficacy. We present the creation of a battery-free, refillable, subcutaneous, and trocar-compatible implanted system that enables tight control over medication administration time in response to external mechanical actuation. The external wearable system is linked to a mobile app to allow for dosage timing control. We demonstrate the efficacy of bromocriptine on glucose control in a diabetic rat model using this technique. We also show that anti-hypertensive medications may be supplied using this device, which could have practical implications given the known diurnal variation of hypertension-related problems. We think that chronotherapy-capable implants will have a significant influence on our ability to improve treatment effectiveness for a wide spectrum of chronic illnesses.

KEYWORDS: Controlled release, Drug delivery System, Implants, Nano technology and extended drug release.

INTRODUCTION

Chronotherapy is the strategy of optimizing drug effectiveness by understanding the impact of delivery time.[1] Taking drugs at certain times of the day may also help to reduce hazardous side effects. Chronotherapy considers the circadian clock, which drives the biological cycle of behaviour and physiology with a 24-hour regularity. A phenomena characterised by the discovery of underlying biological processes that regulate circadian rhythms. In clinical medicine, chronotherapy has the potential to significantly improve treatment outcomes; yet, providing medications at precise and regular times of the day remains a significant difficulty. To begin with, it is difficult for patients to stick to a recommended schedule; according to the WHO, only around 50% of individuals with chronic conditions adhere to their treatment regimen(s). Taking the drug at a predetermined time complicates adherence even more. Second, extended-release systems such as implantable devices, Nano-/micro particles, hydrogels, and microneedle patch systems can enhance medication adherence; however, surgically implanted systems cannot administer medications at the same time during the drug delivery interval. These delivery techniques primarily allow for diffusion-based continuous drug release, which cannot be used in chronotherapy. Examples are the Nexplanon etonogestrel implant and the exenatide implantable mini-pump ITCA650, which only allow for a predefined, continuous medication release. Similarly, while modifying the pharmacokinetic features of biologics, such as fatty acid acylation, PEGylation, Fc-fusion, and so on, offers increased half-life and hence enhanced convenience and therapeutic efficacy, these treatments do not address factors linked to circadian activity.

We hypothesised that a medication delivery system that uses chronotherapy to administer pharmaceuticals with precision timing while reducing the patient's adherence burden by providing extended drug delivery could improve therapeutic effectiveness. To address this, we created an implanted pump capable of extended medication administration and releasing discrete doses at predetermined times. Our wirelessly controlled battery-free implanted system (WCBIS)[3] is intended to improve patient acceptability. Most active implantable drug delivery pumps are rather large to accommodate the mechanical component and/or driven by an electronic circuit and battery, which occupy a minimum volume of

2.57 to 67.5 ml and necessitate lengthier recovery times and/or surgery to replace the battery.[4] Implantable devices would necessitate the use of a trained professional for implantation, and the procedure itself would be quite simple. Previously, the only way to eliminate the peak and trough plasma levels of drug medical assistance was too continuously IV infuse a patient at a pace that supported the material medica of the drug. To address this issue, it was necessary to replace the method for obtaining regulated drug delivery. Danckwerts et al. began researching sustained release implantable drug delivery systems by hypodermic method in the late 1930s.

It is expected that demand for parenteral and implanted structures will increase 14% year on year through 1998, reaching $59 billion. Because the device will be implanted, it must be biocompatible with the human body. Certain characteristics must be met for a substance to be biocompatible. Historically, implantable drug delivery mechanisms were classified into two categories: drug implants and implanted pumps holding the medicine. The primary elegance regulates the release kinetics of medication from the shipping device by utilising various types of polymers and polymeric membranes. This initial classification of implants can be further classified into biodegradable and non-biodegradable. IDDS has evolved as a clinical achievement that aims to maximise the medication's useful high-satisfaction, so lowering the risk of life-threatening conditions such as cancer, ischemic coronary heart disease, brain stroke, and aids. Implantable drug delivery systems are placed beneath the skin and are designed to release pills into the bloodstream without the need for repeated needle insertion. A sterile drug transport tool for hypodermic implantation that supplies medicine at a controlled price over a lengthy period of time, consisting of a rod-formed polymeric internal matrix with a long frame and ends.[5]

METHODS

HPLC-UV Analysis

To evaluate the pump performance under in vitro environments, the concentration of bromocriptine mesylate (Medchem Express, NJ, USA) and Lisinopril (Sigma-Aldrich, MO, USA) in PBS (Gibco) was measured by high-performance liquid chromatography (HPLC) m, 4.6 mm by 150 mm; with an Eclipse XDB C18 column (5 Agilent Technology) and a Zorbax Eclipse XDB C18 column (4.6 mm m; Agilent Technology), respectively by 150 mm.

In the case of bromocriptine, the optimized mobile phase consisted of 10 mM ammonium acetate at a pH of 4.00 in water and methanol (30:70, v v−1) at a flow rate of 1.5 ml min−1 over a 10 min l, and the bromocriptine run time. The injection volume was 10 concentrations were measured at 240 nm.

For Lisinopril, the mobile phase consisted of a mixture of 20 mM dipotassium phosphate at a pH of 3.00 in water and acetonitrile (55:45, v v−1) and was forced at 1 ml min−1 for an HPLC run time of l sample was injected into the column, 5 min. For each analysis, a 5- max = 210 nm and ultraviolet (UV) absorbance was monitored at max = 210 nm.

Pharmacokinetics of Lisinopril delivered from pump

For the pharmacokinetic evaluation, 0.2 ml of blood was obtained at g). 0, 15, 30, 60, 90, and 180 min after Lisinopril administration. The collected samples were centrifuged at 5000 rpm for 15 min to separate the plasma and stored at −20°C. For the pharmacokinetic analysis, the area under the blood concentration versus time curve (AUC) was calculated by the trapezoidal rule.[6]

Histology

At the end point of the experiments, the ZDF rats were anesthetized with isoflurane, and a terminal cardiac blood collection was per formed. Here, the tissues surrounding the device were biopsied from three distinct locations to investigate the biocompatibility of the implanted device, as depicted in Fig. 4. Each tissue sample was then prepared into slides, which were stained with MT and H&E to measure the fibrous capsule thickness around the implanted device and to assess the number of polymorph nuclear cells, respectively. The stained slides were analyzed using an optical microscope at ×200 magnification.[7]

Design and operated features of WCBIS (wirelessly controlled battery-free implantable system)

The system combines a battery-free, manually actuated pump, a wearable controller, and a mobile app. The small, cylindrically shaped pump consists of a drug reservoir with a refill septum and an actuator that is assembled with an inlet valve, a fluid chamber, a button magnet, and an outlet valve in series. Notably, the pump does not need a battery since there are no electronic circuits inside the device and thus can be designed with a small volume for minimally invasive implantation. The pump is similar in size to the abovementioned passive sub dermal implants, but drug release can still be controlled at specific times from outside the body.

To prevent an accidental or unwanted actuation, the button magnet in the actuator is designed to be small so that the pump cannot be driven even when pressed with a baby's small finger. To extend the pump's life span, it has a flexible drug reservoir with a high volumetric loading efficiency and a protruding septum for easy refilling via 30-G syringe needle injections after implantation. The pump prototype measures 4 mm in diameter and 46 mm in length. The wearable controller is designed to be located outside the skin and mainly consists of the solenoid motor, FSR (force sensitive resistor), Hall Effect sensor, accelerometer, PPG (photo plethysmography), and control circuit.[8]

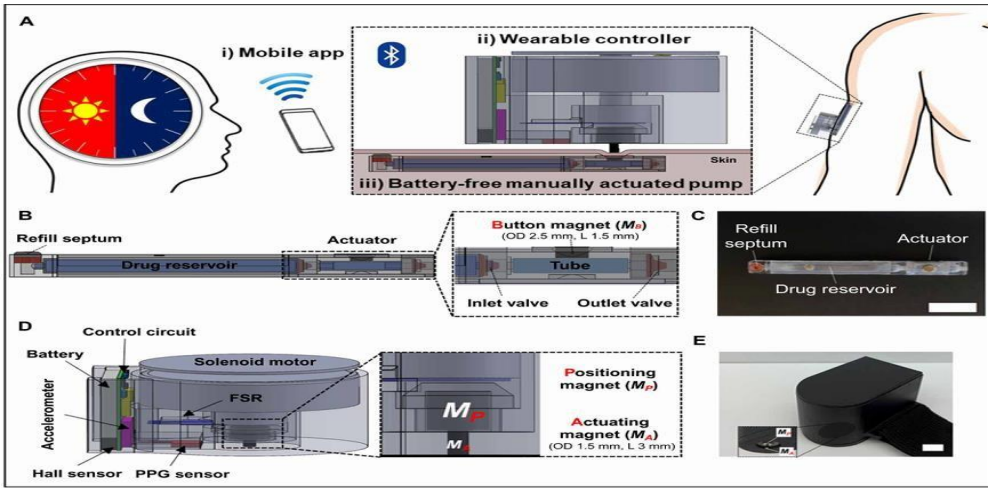

Fig 1: Descriptive illustrations and images of wirelessly controlled battery-free implantable system (WCBIS) for chronotherapy.

(A) Three-dimensional schematic of the WCBIS. (B and C) CAD drawing and image of the battery-free manually actuated pump (scale bar, 10 mm). (D and E) Computer-Aided Design (CAD) drawing and image of the wearable controller (scale bar, 10 mm). FSR, force sensitive resistor.

In-Vitro performance test

To evaluate long-term feasibility, the pump was immersed in phosphate-buffered saline (PBS) for 28 days. After immersion, the l, similar m average infused fluid volume per actuation was 1.96 ± 0.14 to the pre immersion volumes, again showing high reproducibility; also, no drug was detected during no actuation periods. Enabled the pump to infuse m. The flexible drug reservoir (i.e., 150 l with up to 60 ma reproducible volume per actuation of 1.93 ± 0.12 consecutive actuations until approximately 89.1% of the total solution volume in the drug reservoir was consumed, the drug infusion profile was not affected by the refilling procedure. Each Bromocriptine and Lisinopril formulation loaded into the device was stable without apparent degradation when stored at 37°C for 2 or 4 weeks.[9]

In-Vivo evaluation

To demonstrate the effect of chronotherapy, we evaluated the WCBIS for two different applications. One was for treating type 2 diabetes using bromocriptine, which is a sympatholytic D2 dopa mine agonist and has inhibitory effects on serotonin turnover within the central nervous system. The other was for treating hyper tension using a Lisinopril, which is an angiotensin-converting enzyme (ACE) inhibitor. To demonstrate the feasibility of chronotherapy of hypertension, we evaluated the pharmacokinetic profiles of Lisinopril with the pump and the subcutaneous injection groups. As shown in Fig. 3F, the peak plasma concentrations of Lisinopril (Cmax) for both the pump and injection groups were similar: 394.2 ± 83.2 ng ml−1 and 322.7 ± 64.7 ng ml−1, respectively. The time of maximum concentration observed (Tmax) for both groups was 30 min. Here, the AUC for plasma Lisinopril concentration for both the pump and subcutaneous injection groups was 25,335.5 ± 7640.9 ng ml−1 min and 24,484.5 ± 5643.8 ng ml−1 min, respectively, which were not significantly different ($P > 0.05$). Over a 28-day period, there was no drug leakage detected from the implanted pump during the no actuation periods. Also, the plasma concentrations of Lisinopril at 30 min, Cmax, were not significantly different, indicating that the in vivo pump's performance was not affected by the refilling procedure.[10]

DISCUSSION

Chronotherapy is the timing of drug delivery that considers the patient's circadian rhythm to attain optimal efficacy. Although it can effectively improve drug efficacy and reduce toxic side effects, taking a medication at a specified time contributes to an additional level of medication adherence complexity. In particular, most current extended-release systems that allow only diffusion-based continuous drug release are incompatible with chronotherapy. Therefore, an active implantable device capable of on-demand/ programmable delivery of a therapeutic agent at a specified time holds great promise for chronotherapeutic approaches. However, many such devices require electronic circuit components and batteries, which make them relatively large for implantation; they also require additional surgery for battery replacement. Since patient acceptance is the key to the success of implantable systems, the complexity and limitations of surgical procedures for implantation and explanation can have a considerable impact on the device acceptance in patients.

To address these challenges, in this work, we developed a WCBIS capable of an on-demand/programmable drug delivery by enabling the synchronization of drug administration with the time of delivery. Previously, several battery-free implantable devices have been

proposed, for example, a soft implantable drug delivery device using a wireless power transmission and, in another instance, a wirelessly controlled, bioresorbable drug delivery device that combines biocompatible wireless power- harvesting function. These devices rely on electronics, do not have refill features, and require an incision for implantation, which can limit subject acceptability. In contrast, the WCBIS represents a mechanically driven, refillable system that is compatible with trocar implantation to help maximize translatability.

CONCLUSION

Diurnal variation in enzymes, hormones, and other biological mediators has long been recognized in mammalian physiology. Developments in pharmacobiology over the past few decades have shown that timing drug delivery can enhance drug efficacy. Here, we report the development of a battery-free, refillable, subcutaneous, and trocar-compatible implantable system that facilitates chronotherapy by enabling tight control over the timing of drug administration in response to external mechanical actuation. The external wearable system is coupled to a mobile app to facilitate control over dosing time. Using this system, we show the efficacy of bromocriptine on glycemic control in a diabetic rat model. We also demonstrate that anti-hypertensive can be delivered through this device, which could have clinical applications given the recognized diurnal variation of hypertension-related complications. We anticipate that implants capable of chronotherapywill have a substantial impact on our capacity to enhance treatment effectiveness for a broad range of chronic conditions.

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