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On-demand electrically controlled drug release from resorbable nanocomposite films†

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Electroresponsive materials are promising carriers for developing drug delivery systems (DDSs) with excellent spatial, temporal, and dosage control over drug release. Current electroresponsive systems use high voltages (2–25 V), are not bioresorbable, or use materials with unknown long-term biocompatibility. We report here a nanocomposite film that is resorbable, electroresponsive at low voltages (<–2 V), and composed of entirely FDA-approved materials. Our DDS is based on poly(methyl methacrylate-*co*-methacrylic acid), commercially marketed as Eudragit S100 (EGT), which has pH-dependent aqueous solubility. Nanometric films of drug-loaded EGT were designed, synthesized, and coated with a protective layer of chitosan. We hypothesized that electric stimuli would cause local pH changes on the working electrode, leading to pH-responsive dissolution of EGT with concomitant drug release. Our results confirm that local pH changes impart electroresponsive release behavior to the films. Furthermore, drug release scales linearly with voltage, current, and time. The generalizability of the system is shown through the release of several molecules of varying hydrophobicity, pK_a, and size, including fluorescein (free acid and sodium salt), curcumin, meloxicam, and glucagon. The ability to modulate drug release with the applied stimulus can be utilized to design minimally invasive drug delivery devices based on bioresorbable electronics. Such devices would allow for personalized medicine in the treatment of chronic diseases.

Introduction

Conventional oral and intravenous methods of drug delivery distribute drugs systemically, which can result in low drug efficacy and side effects. To circumvent such issues, a new class of DDS's based on nanocarriers composed of stimuli-responsive polymers has received considerable attention.[1] The stimuli-responsive properties of nanocarriers provide an avenue for releasing drugs with spatial and temporal precision in response to patient needs. In addition, DDS's based on such nanocarriers can efficiently target the release of drugs to specific affected areas in the body. Thus, these types of systems are most suitable for treatment of localized chronic diseases like cancer, diabetes, pain, neurodegeneration, *etc*., all of which require repeated medication. Several DDS's that respond to light,[2,3] pH change,[4] ultrasound,[5] temperature change,[4] *etc*. have been developed.

An exciting burgeoning area of research is the use of electricity as the stimulus to trigger drug release.[6,7] Electricity possesses several advantages over other types of stimuli for drug delivery: (i) complex instrumentation is not required to generate electric signals, (ii) electronic devices can be easily miniaturized, and (iii) electric signals can be finely tuned with regard to the magnitude of voltage or current, duration of pulse, *etc*.

Over the past three decades, three primary classes of electroresponsive DDSs have been developed: electroresponsive hydrogels,[7] conducting polymers,[8] and electroresponsive layer-by-layer (LbL) films.[9] Hydrogels are prepared from polyelectrolytes and generally de-swell or erode in response to electric stimulation, releasing drugs.[7,10] Conducting polymers can release charged drugs by undergoing partial oxidation or reduction when electrically stimulated.[8] LbL films undergo induced dissolution or destabilization upon stimulation with concomitant drug release.[11,12]

Despite the significant progress in electroresponsive drug delivery (summarized briefly in Table S1†), each primary DDS class has certain disadvantages that hinder its potential for clinical translation. Hydrogels typically require relatively high voltages, of 2 to 25 V, to trigger drug release.[7] Conducting polymers are not biodegradable, can therefore trigger long-term adverse effects in the body (*e.g.*, local inflammation), and require surgery to remove after use.[13] Recently, aniline-based

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biodegradable conducting polymers with degradable ester linkages were synthesized for drug delivery.[14] However, the toxicity of the degradation products is not well-studied, and aniline is known to be toxic[15,16] and has not been approved by the FDA. LbL films overcome several of the aforementioned issues, but are not suitable platforms for general DDSs. In LbL films, drug molecules constitute layers of the films, so drug incorporation relies on specific electrostatic properties of the drug itself.[11,12]

To bypass the aforementioned issues with current electroresponsive drug delivery systems, we have developed a nanocomposite film composed of drug-loaded poly(methyl methacrylate-*co*-methacrylic acid) coated with a protective layer of chitosan (Fig. 1 and 2a). Both polymers have been FDA-approved for biomedical applications and are resorbable.[17–19] The selected drug-carrying copolymer has a methyl methacrylate to methacrylic acid ratio of 2 : 1 and is commercially marketed as Eudragit S100 (EGT).[19] EGT is insoluble in water with a pH below 7, and soluble in pH 7 and above.[19] EGT has been previously studied and commercially developed for enteric coatings for oral DDS,[18,20] but has not been investigated for electroresponsive drug delivery. We hypothesized that the application of weak negative electric stimuli would reduce water at the working electrode, thereby increasing the local pH, and inducing dissolution of EGT with concomitant drug release (Fig. 2b). We studied our system with five model compounds with varying hydrophilicity, size, and pK_a, namely, fluorescein (FL), fluorescein disodium salt (FL-Na), curcumin (CM), meloxicam (MX), and glucagon (GLU).

This work is the first report of low-voltage electrically triggered release from a drug delivery nanocarrier that is resorbable, composed solely of FDA-approved materials, and versatile for the incorporation of drugs of varying properties. This work also represents a generic platform for a new class of electroresponsive drug delivery systems based on any resorbable polymer that deforms, dissolves, or degrades in response to electrically induced local pH changes, releasing the drug payload.

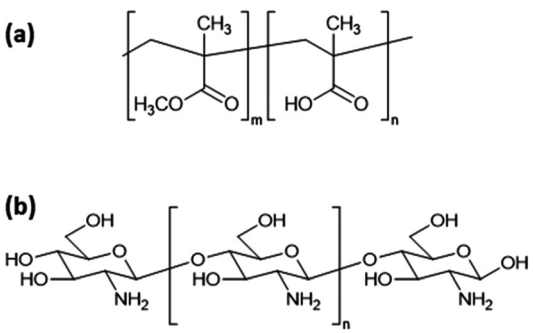

Fig. 1 Chemical structures of (a) poly(methyl methacrylate-*co*-methacrylic acid) and (b) chitosan. The ratio of $m:n$ in (a) is 2 : 1 for Eudragit S100.

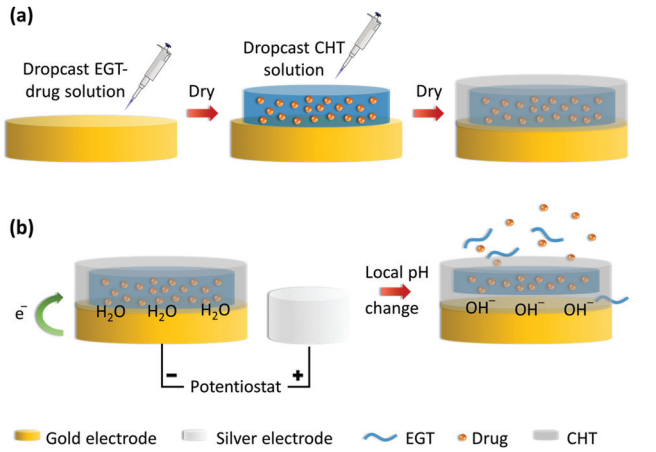

Fig. 2 Schematic representation of (a) preparation of EGT–CHT nanofilms and (b) electroresponsive drug release from them.

Materials

Eudragit S100 was received as a gift from Evonik Industries. Fluorescein free acid and disodium salt, sodium hydroxide, Greiner 96-well plates, chitosan (low molecular weight, molecular weight 50 000–190 000 Da), curcumin, human serum, and dimethylsulfoxide (DMSO) were purchased from Sigma-Aldrich. Meloxicam was obtained from TCI America and fluorescently tagged (FAM-labeled) glucagon was obtained from AnaSpec, Inc. Screen-printed electrodes (SPEs) with gold (Au) working (WE) and silver (Ag) counter and reference (CE/RE) electrodes were acquired from Metrohm and were used for all stimulation experiments.

Methods

All experiments and measurements were performed at room temperature in triplicate, unless otherwise mentioned.

Preparation of drug-loaded Eudragit® S100 (EGT) nanofilms

EGT was dissolved in DMSO at a concentration of 20 mg mL^{-1}. The incorporated molecules tested, fluorescein free acid (FL), fluorescein disodium salt (FL-Na), curcumin (CM), and meloxicam (MX) were separately dissolved in DMSO at concentrations of 10 mg mL^{-1}. Glucagon (GLU) was dissolved in DMSO at a concentration of 5 mg mL^{-1}. For the preparation of drug-loaded EGT films, the drug and EGT solutions were mixed at a ratio of 1 : 1 (9 : 1 in the case of FL) and 2 μL (1 μL in the case of FL) of the resultant solution were dropcast onto an Au SPE. The SPE was placed in a 65 °C oven for 20–30 min to ensure complete evaporation of DMSO. Thereafter, 10 μL of 0.01% (w/v) chitosan (CHT) in 0.1 M HCl were dropcast onto the WE and dried. The drug loading was approximately 32% (w/w, with respect to the carrier material) for FL-Na, CM and MX, 19% for GLU, and 6.4% for FL.

Calibration curves for FL, FL-Na, CM, and MX

For FL, a 2.5 μg mL^{-1} solution was prepared in water. 20, 40, 60, 80 and 100 μL of this solution were placed in 5 wells of a 96-well plate. The volume of each well was adjusted to 100 μL. 100 μL of 0.1 N NaOH were subsequently added to each well. The absorbance was recorded between 400–700 nm using a TECAN infinite M1000 plate reader. As the addition of NaOH converts FL to FL-Na, the same calibration curve could be used for both the molecules. For CM, MX, and GLU, 1 μL of the drug solution in DMSO (10 mg mL^{-1} for CM and MX, 5 mg mL^{-1} for GLU) were diluted to 200 μL with 0.9% (w/v) saline solution in a well of a 96-well plate. 100 μL of the resultant solution was added to an adjoining well containing 100 μL saline solution. In this way, several serial half-dilutions were performed. At the end, 100 μL 0.1 N NaOH were added to each well. The absorbance of the wells, each containing 200 μL (100 μL saline and 100 μL NaOH) of solution of varying drug concentrations were read using the plate reader. The absorbance ranges recorded were 350–650 nm for CM and 230–550 nm for MX. For GLU, the fluorescence spectra were recorded between 510–700 nm using an excitation wavelength of 494 nm. It should be noted that the GLU used was fluorescently tagged with FAM.

Effect of voltage, current, and time on FL release

Electric stimuli were applied to the drug-loaded Au SPEs using a Pine WaveNow potentiostat. Initially, 200 μL of an isotonic 0.9% (w/v) saline solution was pipetted onto the drug-loaded Au SPEs, covering both the WE and the RE. After 2 min, the solution was mixed and 100 μL of it were retrieved and placed in the well of a 96-well plate. 100 μL fresh saline solution were added. Thereafter, fixed voltages (0 V, −0.5 V, −0.8 V, −1 V or +1 V) were applied for 20 s at 3 min, 6 min, 9 min, 12 min and 15 min to different sets of electrodes. At time-points of 2 min, 5 min, 8 min, 11 min, 14 min and 17 min, the solutions were mixed; 100 μL of the samples were retrieved and mixed with 100 μL 0.1 N NaOH for absorbance measurements, and 100 μL fresh saline solution were added.

A similar procedure was followed for application of current to the SPEs. However, in this case, only one time-point was used. At 2 min, 0 μA, 50 μA, 100 μA, 200 μA or 400 μA for 20 s were applied to different sets of electrodes (direction of electron flow was from WE to CE). The sampling was done at 5 min.

Pulsed release of FL-Na, CM, MX, and GLU

200 μL of an isotonic 0.9% (w/v) saline solution was pipetted onto the drug-loaded Au SPEs, covering both the WE and the RE. After 2 min, the solution was mixed and 100 μL of it were retrieved and placed in the well of a 96-well plate. 100 μL fresh saline solution were added. Alternate pulses of −1 V for 20 s and 0 V were applied at 3 min, 6 min, 9 min, 12 min and 15 min to the SPEs. At time-points of 2 min, 5 min, 8 min, 11 min, 14 min and 17 min, the solutions were mixed; 100 μL of the samples were retrieved and mixed with 100 μL 0.1 N NaOH for absorbance measurements, and 100 μL fresh saline solution were added. Absorbances of the samples retrieved at 5 min, 11 min, and 17 min correspond to drug release after stimulation while those of the samples retrieved at 2 min, 8 min, and 14 min correspond to free diffusion of the drugs.

To confirm electroresponsive release is maintained in biological fluid, pulsed release experiments were performed using CM-loaded EGT–CHT films in human serum. The procedure remained similar to the one before, except the volume of serum initially used and the volume of aliquots sampled were reduced by half. 150 μL 0.1 N NaOH was added to 50 μL of the aliquots for absorbance measurements. Also, −1.5 V for 20 s was used as electric stimuli as opposed to −1 V for 20 s. The pH of the serum was measured before and after application of 5 pulses of −1.5 V for 20 s using pH paper.

Scanning electron microscopy (SEM) imaging

To measure the film thickness, the SPEs were broken into two pieces across the center of the films, and the broken edges were sputter-coated with Au/Pd and imaged using a Zeiss Sigma FESEM. To image film morphology, EGT–CHT films were prepared without drugs. 1 μL of 20 mg mL^{-1} EGT was dropcasted onto the Au WE of the SPE. However, care was taken not to cover all of the Au surface so that a contrast would be visible between the gold layer and the EGT layer. To avoid imaging artifacts from inhomogeneous drying of the protective CHT layer, a 1% (w/v) CHT solution in 0.1 M HCl was spin-coated on top of the EGT-film. Either 0 V or 5 pulses of −1.5 V for 20 s (with 40 s delay time) were applied to the Au SPE coated with EGT and CHT. The nanofilms on the Au SPEs were mounted onto aluminum stubs, sputter-coated, and imaged.

pH dependent release of FL from EGT–CHT films

2 μL of DMSO containing 10 μg FL and 20 μg of EGT were dropcast onto the Au WE of three SPE. After evaporating the DMSO by drying in an oven at 65 °C, 10 μL of 0.01% (w/v) chitosan were added to the electrode. After drying, 200 μL of buffer solution at pH 6, 7, and 8 were added to the three electrodes (covering the WE) respectively. After 10 s, the solutions were mixed and after 5 s more, 50 μL of each solution were retrieved and added to 150 μL 0.1 N NaOH for absorbance measurements and subsequent quantification.

Results and discussion

Fabrication and characterization of EGT–CHT films

EGT–CHT films were prepared on screen-printed electrodes (SPEs) with a gold working electrode (WE) and a silver counter/reference electrode (CE/RE) (Fig. S1a†). First, a solution of EGT in DMSO containing the drug was dropcast onto the WE. The DMSO was evaporated by drying the SPE in a 65 °C oven. Thereafter, a 0.01 wt% CHT solution was dropcast on top of the drug-loaded EGT film, and dried. The thickness of the nanocomposite film was measured by scanning electron microscope (SEM) imaging. The SPE was fractured at the

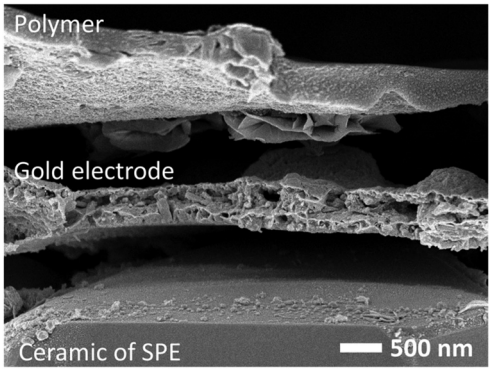

Fig. 3 SEM image of the transverse cross-section of the EGT–CHT films. Three distinct layers corresponding to the ceramic of the SPE, the gold electrode and the EGT–CHT polymeric film can be seen. The separation in the layers arises from mechanical stress during fracturing of the electrodes for imaging.

center of the WE and the transverse cross-section was imaged. From Fig. 3 it can be seen that the film was smooth and homogeneous, with a thickness of ~400 nm near the center of the film. However, toward the edges, a coffee ring effect[21] was observed leading to micron-sized film thicknesses (Fig. S2†).

Effect of voltage, time, and current on drug release

To study electroresponsive drug release, initial tests were performed using fluorescein free acid form (FL) as a hydrophobic drug surrogate for ease of visualization. Release experiments were carried out in an isotonic 0.9 wt% saline solution. EGT–CHT films with ~6.4 wt% FL loading were electrically stimulated using a potentiostat. Fig. 4(a–d) demonstrates that by applying −1.5 V for 20 s, FL release can be easily observed owing to its characteristic green color.

To determine the effect of voltage on FL release, fixed voltages (0, −0.5 V, −0.8 V, −1 V, −1.5 V and +1 V) were applied for 20 s to the nanocomposite films every 3 min. As EGT dissolution and consequent FL release is expected upon reduction of water, negative voltages were applied to the WE. Less than 3% of the incorporated FL was released by passive diffusion. When −0.5 V was applied, statistically significant differences in FL concentrations between the control and the stimulated sample were not observed until later time points (~5% released after 5 stimulations). This behavior could be explained by taking into account that the electrochemical water window is typically reported to be −0.6 to 0.8 V,[22,23] implying that a threshold of −0.6 V is necessary to initiate the reduction of water. Therefore, at −0.5 V, the small increase in release is possibly caused by electrophoresis of negatively charged FL molecules as opposed to dissolution of the polymer.

Stimuli of −0.8 V, −1.0 V, and −1.5 V resulted in markedly enhanced FL release from films as compared to the control. FL release scaled linearly with both the applied potential as well as the number of stimulations corresponding to increased stimulation time (Fig. 4e). More than 98% of FL was discharged within 5 stimulations of −1.5 V for 20 s. Negligible FL release was observed on application of +1 V, confirming that reduction of water to generate hydroxyl ions is essential for drug release.

The effect of current on FL release was studied by applying a fixed current for 20 s. It can be seen from Fig. 4f that FL release scales linearly with the applied current, and currents as low as 100 μA can trigger release. Our results indicate that by choosing appropriate parameters for electrical stimulation, it is possible to finely tune the drug release quantity from EGT–CHT films. The current, voltage, and duration of electrical stimulation are three degrees of freedom that can be varied, allowing control not only over the amount of drug release but also over the rate.

Pulsed release of drugs in saline solution

An important characteristic of a stimuli-responsive drug delivery system is the ability to release precise amounts of drugs with repeated stimuli. Such a feature will enable the development of programmable drug delivery devices with potential applications in the treatment of chronic diseases. To ensure pulsed release of drugs is possible from EGT–CHT films, experiments were first performed with fluorescein disodium salt (FL-Na), a hydrophilic colored drug surrogate.[24] An intermediate voltage of −1 V for 20 s was chosen as an electric pulse. No stimulus and the electric pulse were applied alternately every 3 min. From Fig. 5a, it is apparent that when voltage is applied (indicated by red arrows), FL-Na release is elevated compared to release in the absence of voltage. To examine the versatility of our nanocomposite film, we also

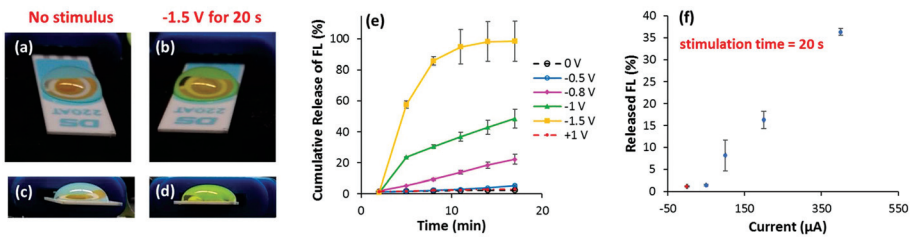

Fig. 4 FL release from EGT–CHT films. (a, b) Top and (c, d) side view of FL release without and with electrical stimulation, (e) effect of voltage and time on FL release, and (f) effect of current on FL release. Red data point in (e) corresponds to FL release in the absence of any applied current. FL release increases with increasing voltage, time and current.

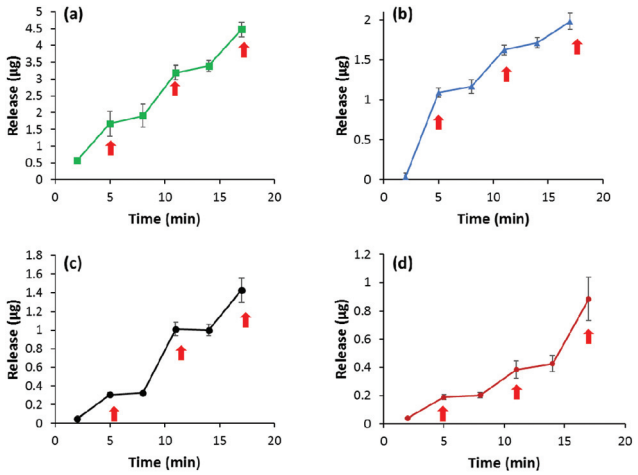

Fig. 5 Pulsed release of (a) FL-Na, (b) MX, (c) CM, and (d) GLU. 0 V and −1 V for 20 s were applied alternately to the drug-loaded EGT–CHT films. The red arrows indicate drug release corresponding to application of electrical stimuli.

examined the pulsed release of three other molecules with differing physicochemical properties. We tested meloxicam (MX),[25] a hydrophobic non-steroidal anti-inflammatory drug used in the treatment of rheumatoid arthritis, curcumin (CM),[26] a potential therapeutic lead being investigated for use in the treatment of various chronic illnesses, and glucagon (GLU),[27] a polypeptide used in the treatment of hypoglycemia. FL-Na, MX and CM molecules were loaded onto the films at 32 wt%, while GLU was loaded at 19 wt%. The release of all molecules was carried out under identical conditions in 0.9 wt% saline solution. It should be noted that although the compounds studied here are starkly different in terms of their hydrophobicity, pK_a, molecular weight, and function, electro-responsive release is possible for all of them (Fig. 5).

Ideally, the molecule incorporated in the film should be released only when electric stimuli are applied. Under such conditions, a staircase graph would be obtained in which each step has zero slope (corresponding to no stimuli) and a positive step height (corresponding to electro-stimulated drug release). However, we note that some steps (Fig. 5) have slightly positive slope, indicating minor passive diffusion of the compound into the surrounding solution. This behavior arises from the hydrophilicity of the molecule. For example, we note that in case of CM (water solubility = 6 μg mL^{-1}),[26] the slope of step is closer to zero than that in case of FL-Na (water solubility = 500 mg mL^{-1})[24] which is substantially more hydrophilic. The total amount of drug released within the experimental timescale is also reflective of the solubility of the molecules in saline. It should be noted that the drug-loading and stimulation parameters were not optimized for release of specific quantities of each drug over a given period of time. Rather, our focus was on examining the feasibility of releasing various compounds from the EGT–CHT nanocomposite films. Our results demonstrate the versatility of our system for the delivery of drugs of varying properties. It possible to easily fine tune the system for a particular drug by adjusting drug loading, film composition, film thickness, or the applied electrical stimulus.

Mechanism of drug release

Poly(methyl methacrylate-*co*-methacrylic acid) has a pH-dependent solubility[19] in water, which can be altered by changing the ratio of methyl methacrylate to methacrylic acid. In case of EGT, the ratio is 2 : 1, rendering the polymer soluble at pH 7 and above. The rate of dissolution is also pH-dependent and is enhanced at higher pH. Solubility tests confirmed that EGT is soluble in the pH 7 and pH 8 buffers and insoluble at pH 6, in agreement with the reported dissolution profile of EGT.

Using FL as a model compound, we quantified the amount of drug released from EGT dissolution at pH 6, 7, and 8 (Fig. 6a–g). Fluorescein release from the films was significantly enhanced at pH 7 and 8 as compared to pH 6, confirming that pH can be used as a trigger for drug release.

We hypothesized that application of electric stimuli would cause an increase in the local pH due to water reduction at the WE, initiating partial dissolution of EGT with concomitant drug release. The window for water electrolysis is −0.6 V to 0.8 V *vs.* Ag/AgCl, as previously reported. At negative voltages greater than −0.6 V, water is reduced at the WE in the reaction:

$$4H_2O\ (l) + 4e^- \rightarrow 2H_2\ (g) + 4OH^-(aq)$$

The production of OH^- ions at the WE increases the local pH at the electrode surface. This local pH increase was con-

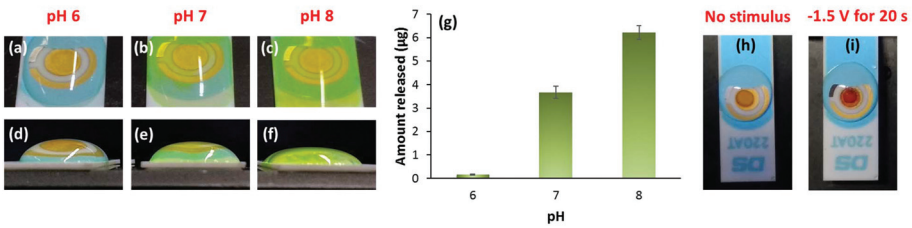

Fig. 6 (a–c) Top and (d–f) side views of pH dependent FL release from EGT–CHT films and (g) quantification of FL release at different pH. FL release is negligible at pH 6 and is significant at pH 7 and 8, consistent with EGT dissolution at pH 7 and above. (h) and (i) show the pH at the WE before and after electrical stimulation, respectively, as evidenced by the color change of CM. CM is a well-known indicator that changes color from yellow to red around its pK_a (~7.8).

firmed through the use of curcumin (CM), an established indicator molecule.[28] CM changes color from yellow to red at its first pK_a of 7.8.[29] When a voltage of −1.5 V was applied for 20 s to a CM-loaded EGT–CHT film, CM clearly changed from yellow to red (Fig. 6h and i), indicating a pH change. The pH of our saline solution was measured to be 5.7; thus, the pH increased from 5.7 to above 7.8 upon application of −1.5 V for 20 s in the saline solution.

The dissolution of EGT was further verified using SEM imaging. In this case, an EGT solution in DMSO was dropcast onto the WE and dried. Care was taken not to completely cover the gold WE so that on imaging, the gold and EGT layers could be distinguished by contrast. To avoid observing artifacts from inhomogeneous drying of the CHT coating film, instead of dropcasting, an acidic solution of CHT was spin-coated on top of the EGT layer. From Fig. 7a, it can be seen that the EGT appears as a dark layer on the brighter gold electrode of the SPE. After applying 5 pulses of −1.5 V for 20 s (1 pulse every minute), the contrast between the gold and EGT layers was diminished (Fig. 7b). A faint boundary is discernible corresponding to the edge of the EGT film (indicated by white arrows). As mentioned before, due to the coffee ring effect, the EGT films were thicker toward the edges compared to the center of the films. Therefore, it is possible that the EGT at the edges was not fully dissolved by five −1.5 V pulses.

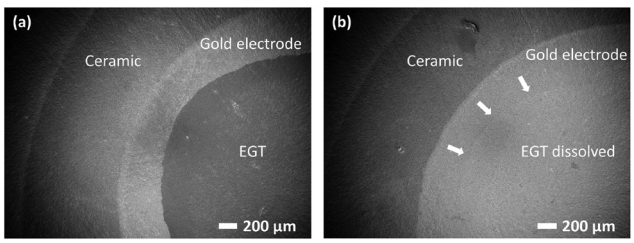

Fig. 7 SEM image of EGT–CHT nanocomposite films (a) before and (b) after electrical stimulation. 5 pulses of –1.5 V for 20 (1 pulse applied every minute) were used as electric stimuli. The EGT layer appears as a dark layer on the brighter gold electrode in (a). The contrast is diminished in (b) indicating dissolution of EGT. The white arrows in point to a faint discernible boundary corresponding to the edge of the EGT film.

Pulsed release of CM in human serum

After performing release experiments in isotonic 0.9 wt% saline solution, we wanted to confirm that our system can electroresponsively release drugs in human serum, which mimics physiological conditions in the human body. Human serum is buffered at pH 7.4.

We first confirmed that local pH changes still occur in buffered solution. CM-loaded nanocomposite films were subjected to −1.5 V for 20 s. CM changed color from yellow to red, confirming that the local pH does increase even in buffered solution (Fig. 8a and b). The buffering of the release solution should in general have a minimal effect on the pH changes used in our system as the release mechanism depends on local pH changes at the electrode surface rather than global pH changes to the whole solution.

A concern for the clinical application of pH-dependent electroresponsive systems is that pH changes in the body could cause tissue damage. We ascertained that the global pH of the serum solution remains at 7.4 before and after 5 stimulations of −1.5 V for 20 s each (Fig. S3†), confirming that the pH increase is only local at the electrode surface and would likely not change body pH *in vivo*.

CM was successfully released in an electroresponsive manner from our EGT–CHT films in human serum. In Fig. 8c, the cumulative amount of CM released when alternate pulses of no stimulus and −1.5 V for 20 s were applied is plotted as a step graph. For clarity, the cumulative amounts of the drug released for the both the application and lack of stimuli have been separated and individually plotted in Fig. 8d. The CM release was consistently elevated when the voltage was applied. Drug leakage in the absence of electrical stimuli was higher from the films in serum compared to saline solution. This behavior is expected, as EGT is soluble in human serum (pH 7.4), while it is insoluble in saline solution (pH 5.7). However, local pH changes can still be harnessed to release drugs electroresponsively, as EGT dissolution is accelerated at higher pH values.

An improvement to our current system would be decreasing the free leakage of drug from the films in pH 7.4 solution. The ratio of methyl methacrylate to methacrylic acid in EGT is 2 : 1, and this ratio governs the pH at which the polymer becomes soluble. Increasing the proportion of methyl methacrylate

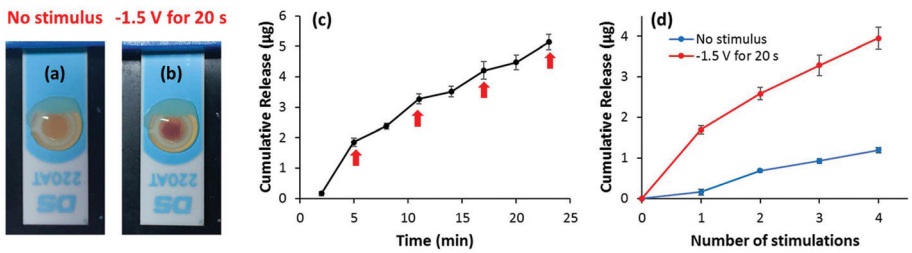

Fig. 8 Release of CM in human serum. Local pH change upon electrical stimulation evidenced by change in CM color from (a) yellow to (b) red. (c) Pulsed release of CM when no stimulus and –1.5 V for 20 s are applied alternately. The red arrows indicate elevated drug release corresponding to application of electrical stimuli. (d) Cumulative release of CM with and without stimulus, derived from (c).

would increase this pH, while increasing the proportion of methacrylic acid would decrease this pH (for reference, Eudragit® L100, with a 1 : 1 ratio, becomes soluble at pH 5, while Eudragit® S100 with a 2 : 1 ratio, becomes soluble at pH 7 [19]). Synthesizing methyl methacrylate–methacrylic acid copolymers with different ratios would enable us to produce copolymers with virtually any dissolution pH. This would also allow us to synthesize a copolymer that minimizes leakage at pH 7.4 while still facilitating electroresponsive drug delivery.

Our EGT–CHT films have several properties that enhance their potential for clinical application and patient acceptability. The voltages used for drug release are low and do not pose risk of tissue damage. EGT and CHT are both resorbable polymers, avoiding the toxic effects of nondegradable implants, and eliminating the need for invasive surgery to remove the polymers after usage. Both EGT and CHT have also been approved by the FDA for biomedical applications. In particular, EGT, the drug carrier in our film, has already been used in pH-responsive coatings for oral drug delivery tablets (*e.g.*, Asacole®), improving the likelihood that our film will be safe and effective in the human body. Moreover, our DDS is versatile because any drug soluble in DMSO can be incorporated at high drug loading (>30%), and the leakage from the films is minimal. Many previously reported systems rely on drug properties (*e.g.*, hydrophobicity, size, charge, electrostatic properties, *etc.*) for drug release and loading, which is not ideal for a general DDS.

In the future, our EGT–CHT could be coupled with bio-electronics for *in vivo* studies and applications. If the disease site is near the skin, the nanofilm could be implanted at the target site, and an external electro-conducting skin patch could generate voltage to trigger drug release from the film.[30] If the diseased area is deeper in the body, the nanofilm could be coupled to one of several miniaturized implants that have been developed for generating electric stimuli *in vivo* by converting wireless energy sources into voltage. For example, electric stimuli-generating devices powered by ultrasound[31] and radiofrequency[32] have been developed for *in vivo* usage. In particular, Hwang *et al.* reported a radiofrequency-powered device for wireless stimulation composed completely of bio-resorbable materials.[32] We foresee that the integration of our films with such "transient" electronics[33] would facilitate the development of resorbable devices for localized, on-demand drug release *in vivo*, and would provide a realistic avenue for the translation of our films to the clinic.

Conclusions

We have developed an electroresponsive drug delivery system that is resorbable, electroresponsive at low voltages (<−2 V), and entirely composed of FDA-approved materials. Our system comprises nanometric films of a methyl methacrylate-*co*-methacrylic acid-based polymer, which has a pH-dependent solubility. Application of electrical stimuli causes local pH changes at the electrode surface owing to reduction of water, which in turn results in dissolution of the polymer with concomitant, "on-demand" drug release. The drug release dose can be controlled by several degrees of freedom including the current, voltage, and duration of electrical stimulation. The amount of drug discharged scales linearly with these parameters, implying the potential application of this system in the development of programmable drug delivery devices. Although we have used commercially available Eudragit S100, which is soluble at pH 7 and above, as a model polymer, it is possible to design other polymers that are soluble above specific pH values (*e.g.*, above 7.4) by altering the ratio of methyl methacrylate to methacrylic acid. Moreover, we have demonstrated the generality of this system in releasing several molecules with significantly different properties such as hydrophilicity, pK_a, size, and function. We have successfully released fluorescein free acid and fluorescein disodium salt (hydrophobic and hydrophilic drug surrogates), curcumin (a hydrophobic small molecule with therapeutic potential), meloxicam (a hydrophobic drug used in the treatment of rheumatoid arthritis), as well as glucagon (a polypeptide used as a hyperglycemic agent). Our drug delivery system could be coupled to bioresorbable electronics in the future for treatment of chronic diseases like cancer, neurological disorders, and chronic pain, each of which requires repeated drug doses.

Conflicts of interest

There are no conflicts to declare.

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