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2017

Cheng, T., O'Rorke, R., Ortiz, R. F., Yan, T. Y., Hemmer, E., Vetrone, F., et al. (2017).
Self-assembled photoadditives in polyester films allow stop and go chemical release. *Acta
Biomaterialia*, in press.

<https://hdl.handle.net/10356/80664>

<https://doi.org/10.1016/j.actbio.2017.03.021>

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[<http://dx.doi.org/10.1016/j.actbio.2017.03.021>].

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Self-assembled photoadditives in polyester films allow stop and go chemical release

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ABSTRACT

Near-infrared (NIR) triggered chemical delivery allows on-demand release with the advantage of external tissue stimulation. Bioresorbable polyester poly-L-lactic acid (PLLA) was compounded with photoadditives of neat zinc oxide (ZnO) nanoparticles and 980 $\rightarrow$ 365 nm LiYF₄:Tm³⁺, Yb³⁺ upconverting nanoparticles (UCNP). Subsequently, neat ZnO and UCNPs blended PLLA films of sub-50 μ m thickness were knife casted with a hydrophobic small molecule drug mimic, fluorescein diacetate. The PLLA films displayed a 500 times increase in fluorescein diacetate release from the 50 mW NIR irradiated PLLA/photoadditive film compared to non-irradiated PLLA control films. Larger ratios of UCNPs/neat ZnO increased photocatalysis efficiency at low NIR duty cycles. The synergistic increase results from the self-assembled photoadditives of neat zinc oxide and upconverting nanoparticles (UCNPs), as seen in transmission electron microscopy. Colloidal ZnO, which does not self-assemble with UCNPs, had less than half the release kinetics of the self-assembled PLLA films under similar conditions, advocating Förster resonance energy transfer as the mechanism responsible for the synergistic increase. Alternative to intensity modulation, pulse width modulation (duty cycles from 0.1 to 1) of the low intensity 50 mW NIR laser diode allowed tailorable release rates from 0.01 to 1.4 % per day. With the low intensity NIR activation, tailorable release rates, and favourable biocompatibility of the constituents, implanted PLLA photoadditive thin films could allow feedback mediated chemical delivery.

KEYWORDS: PLLA; controlled release; FRET; chemical delivery; photocatalysis; upconversion emission

INTRODUCTION

Compared with other stimulation methods such as pH, temperature, voltage, or mechanical stimuli, [1-3] near-infrared (NIR) light has the advantage of requiring no implantable actuators; irradiation can be applied externally as long as the tissue is transparent at the given wavelengths and scattering is accounted for. Light activated release mechanisms rely on photoactive functional groups that undergo either conformation changes (*i.e.* *trans*→*cis* azobenzenes), or photochemical reactions. Azobenzene derivatives in *trans* form have been immobilized within pores of mesoporous silica nanoparticles to act as gate keepers. *Trans*→*cis* transitions upon exposure to UV light (365 nm) leads to gate opening and increased diffusion across the mesoporous silica pores and the subsequent release of the encapsulated contents. This technology allows high ratios of drug loading, but suffer from drug selection limited by pore size, non-linear release kinetics, and high background rates of release. [4-6] An example of photochemical activated delivery is UV sensitive *O*-nitrobenzyl (ONB) functional groups, which can be incorporated into particles, hydrogels, and adhesives. [7-9] ONB hydrogels can encapsulate small molecule drugs up to large biomacromolecules, but drug flux in the UV ‘ON’ is only 2-3 times larger than diffusional rates.[9] Anticancer drug release is demonstrated with 5-fluorouracil conjugated to the surface of gold nanoparticles through ONB linkage. Upon UV irradiation, 5-fluorouracil is released from the gold surface into tumor tissues, but this elegant technology comes at the cost of a low yield complex synthesis that only allows limited amount of drug loading. [7]

UV light is commonly employed for photocatalysis and cleavage of light sensitive functional groups, but is highly absorbed and scattered by biomacromolecules, limiting its penetration depth within tissues. [10] To overcome these limitations, NIR light that falls in the limited optical window of tissue transparency, also known as *biological window*, allows for larger penetration depths in the order of centimeters. [11] Ideally, if NIR light is used to generate UV

light *in situ*, then UV-mediated photocatalysis can be activated in normally UV opaque materials. Moreover, the local generation of UV light, spatially limited to the proximity of the NIR-to-UV converting agent, reduces the risk of UV-induced effects such as phototoxicity or photodegradation in areas where these effects are undesired. Upconverting nanoparticles (UCNPs) allow luminescence from NIR to visible and UV wavelengths, creating varied methods of upconversion-mediated drug delivery. [12] Drugs have been conjugated onto the surface of silica coated UCNPs or directly on the surface of UCNPs with photocleavable linkers of coumarin [13] and *O*-nitrobenzyl derivatives. [14-16] Upon NIR irradiation, the drugs are cleaved off the surface and released. The above mentioned release systems show advantages in controllable kinetics by tuning the implemented power density of the applied NIR light and with regards to on-demand release by on-off-switching of the NIR light. However, to date, the reported periods of drug release are within 24 hours. Long term on-demand release systems are required for many applications, such as for the treatment of refractory cancer pain [17] or for neurodegenerative disorder diseases (Alzheimers, Parkinsons). [18] These pathologies would benefit from chemical depots that allow dynamic treatments requiring specific doses and long term drug release. [19-22]

Polyester materials, such as poly (D,L-lactic-co-glycolic acid) (PLGA) and poly (lactic acid) (PLLA), have been developed for extended chemical release as they have predictable degradation rates, are environmentally inert, and have been approved in several medical devices. [22, 23] Previously, we have used NIR light to tune chemical release from composite films consisting of PLGA, neat zinc oxide (ZnO) nanoparticles and lanthanide-doped LiYF₄ UCNPs. [24] PLGA is found to have several disadvantages as a matrix, as it shows high rates of background chemical release (0.1 %.d⁻¹ or 1 µg.cm⁻².d⁻¹) and NIR mediated release (1 %.d⁻¹ or 10 µg.cm⁻².d⁻¹) is due to the early onset of autocatalysis. [25] This could be an advantage if the purpose of the system is to release chemical encapsulants with minimal additives present,

but an order of magnitude difference in chemical release rates limits tailorability and restricts applications in on-demand release, such as that presented in **Figure 1**. Considering that 1) the glass transition (T_g) of PLGA (36-40 °C) is in the range of physiological temperatures, and 2) NIR light of 980 nm can induce heating of entrapped water in porous PLGA nanoparticles *via* vibrational transitions in water molecules; [26-28] it was speculated that photothermal effects may cause shifts in the matrix temperature and be partly responsible for PLGA's NIR sensitivity. We hypothesized that the sensitivity towards NIR light can be reduced by using materials with T_g well outside the physiological temperature range. Addressing these considerations, PLLA has been chosen as the matrix for NIR-controlled release studies due to the slow autocatalysis, minimal diffusion release, and excellent UV to NIR light transparency. [29] Light-triggered release kinetics of fluorescein diacetate (FDAC) are reported herein to be over two orders-of-magnitude faster compared with diffusion-based release. Chemical release was found to increase synergistically by an order of magnitude with the combination of neat zinc oxide (ZnO) and upconverting nanoparticles (UCNP) vs either photoadditive irradiated alone. Furthermore, we show for the first time that the release kinetics can be decreased by a factor of 20 when the NIR irradiation is removed. We hypothesized the synergistic release is a result of the self-assembly of photoadditives ZnO (neat) and UCNPs, which ultimately heightens the NIR sensitivity. This hypothesis was challenged with a null hypothesis experiment designed to incorporate both additives, but prevent self-assembly with ZnO (colloidal) and UCNPs that are homogenously distributed.

Figure 1. Schematic of on-demand photo-stimulated release kinetics: the release of encapsulated chemicals starts with NIR stimulation and release stops with removal of external stimulation. Duty cycle (DC, also known as pulse width modulation) is employed

to tailor the release kinetics (K_{release}). A high K_{release} is required to overcome local clearance kinetics ($K_{\text{clearance}}$) to attain a therapeutic concentration. Duty cycle is then mediated to maintain the concentration until a local response has been met, wherein the NIR stimulation is removed and $K_{\text{clearance}}$ allows the chemical concentration to dissipate. Thus, a chemical depot system requires 1) the K_{release} to be tailorable such that it exceeds the $K_{\text{clearance}}$ under NIR stimulation, 2) can be fine-tuned to match $K_{\text{clearance}}$ to maintain a preset dose, and 3) have $K_{\text{clearance}}$ exceed K_{release} when the NIR stimulation is removed.

MATERIALS AND METHODS

Materials

Poly (lactide-acid) (PLLA, $M_w = 128\text{kDa}$, $M_n = 72\text{kDa}$, methyl end-capped, 30.3% crystallinity) was purchased from Dongguan Pioneer (China). Chloroform [HPLC grade, cat# CS1332] and dichloromethane (DCM) [cat# DS1432] were purchased from Tedia (USA). Fluorescein diacetate (FDAC) [cat# F7378], neat ZnO nanoparticles [cat# 544906, nanopowder, particle size: $<100\text{ nm}$ (average)] and organic solvent colloidal ZnO [cat# 721085, nanoparticles, 40 wt. % in ethanol, particle size: $<130\text{ nm}$ (DLS)/ $<35\text{ nm}$ (average)], were purchased from Sigma-Aldrich (Singapore). Other nanoparticles of TiO_2 [cat# 791326, nanopowder, particle size: $<100\text{ nm}$ (average)], Fe_2O_3 [cat# 544884, nanopowder, particle size: $<50\text{ nm}$ (average)] and ZnFe_2O_4 [cat#633844, nanopowder, particle size: $<100\text{ nm}$ (average)] were purchased from Sigma-Aldrich (Singapore) as well. Lanthanide oxides (Y_2O_3 , REacton®, 99.999 %, powder; Yb_2O_3 , REacton, 99.998%, powder; Tm_2O_3 , REacton, 99.997%, powder), trifluoroacetic acid (CF_3COOH , 99%), 1-octadecene ($\text{CH}_3(\text{CH}_2)_{15}\text{CH}=\text{CH}_2$, tech. 90%), and oleic acid ($\text{CH}_3(\text{CH}_2)_7\text{CH}=\text{CH}(\text{CH}_2)_7\text{COOH}$, tech. 90%) were purchased from Alfa Aesar (Ward Hill, USA). Lithium trifluoroacetate (CF_3COOLi , 98 %) was obtained from Sigma Aldrich (St. Louis, USA). Hydrochloric acid

(HCl, Reagent A.C.S.) was purchased from Fisher Scientific (Nepean, Canada). All chemicals were used without further purification.

Synthesis of Tm³⁺/Yb³⁺ doped LiYF₄ UCNPs

The preparation of solvent-dispersible Tm³⁺ (0.5% mol%) and Yb³⁺ (25% mol%) co-doped LiYF₄ UCNPs is reported in supporting information, and is a modified version of the thermal decomposition synthesis reported previously. [30]

PLLA thin film preparation

Composite films were prepared as reported previously.[24, 31-34] Briefly, 1:10:100 mass ratio of FDAC:PLLA:dichloromethane (DCM) with or without ZnO (1% w/w), UCNPs (1 or 5% w/w), or a combination of both photoadditives were vortexed and knife casted with a wet thickness of 500 μm on sheets of clear polyethylene terephthalate (50 μm thick) to yield PLLA or PLGA (Mw = 103 kDa, methyl end-capped) thicknesses of 20 to 40 μm. ZnO refers either to neat ZnO nanoparticles or organic solvent colloidal ZnO (solZnO).

High-throughput *in-vitro* FDAC release study and microplate NIR activation

High-throughput quantification of FDAC was carried out as previously reported. [32] Briefly, 20 μL FDAC was drawn out of the release microplate plate and diluted with 180 μL of 100 mM NaOH in the read plate. The amount of FDAC released was quantitated from fluorescent signal (ex/em: 490/520) using prepared calibration curves. Two arrays of NIR laser diodes, with excitation density of $110 \pm 3 \text{ mW.cm}^{-2}$ (50 mW optical power) and $15 \pm 3 \text{ mW.cm}^{-2}$ (10 mW optical power) respectively, were mounted to two microplates accordingly, as previously described.[24] **Table S1** displays the duty cycle dependent intensity and fluence averages. PLLA films described above were punched into 6 mm round disks, incubated in 200 μL of PBS release buffer, and sampled for FDAC release every 48 h in 37 °C. Samples were irradiated with NIR laser diodes for 17 days at duty cycles of 0.1, 0.3, 0.7 and 1.0 (at 50 mW) and at duty cycles of 0.5 and 1.0 (at 10 mW). Laser diodes were pulsed at 1.7 ms (586 Hz).

The laser diode beam illuminated 90% of the film disks by area. **Tables S2-S8** display the raw kinetic values for all the duty cycle dependent FDAC release investigations.

Quantitative analysis of PLLA mixtures by size exclusion chromatography (SEC)

Both pristine films not subjected to the release study and films that remained after the 30 day release study were dissolved in chloroform at concentration of 2.5 mg mL⁻¹. To remove nanoparticles, polymer solutions were centrifuged at 17,000xG for 15 min and filtered through a 0.2 µm PTFE filter. An Agilent 1100 series high-performance liquid chromatography pump complete with degasser and PLGel mixed C (Polymer Standards Service, Mainz, Germany) in a 35 °C temperature-controlled oven was connected in-line with a Wyatt MiniDawn 3-angle light scattering detector and an Agilent 1100 refractive index detector (Agilent Technologies, Santa Clara, CA, USA). The elution buffer was chloroform at a flow rate of 1.0 mL min⁻¹. The injection volumes were typically 50 µL.

TEM imaging of polymer films

PLLA films were embedded in Araldite epoxy microtomed into 100 nm cross-sections (Ultracut UCT Microtome, Leica, Singapore), placed on a 300 mesh copper grid with supportive amorphous carbon (cat#01883-F, Ted Pella, USA), and imaged with a transmission electron microscope (TEM, Carl Zeiss Libra 120 Plus, Carl Zeiss) with a LaB₆ filament. The operating voltage was 120 kV and the emission current was adjusted to 4 µA, slightly undersaturated to produce a more coherent electron beam. For elemental mapping of the ZnO and UCNP nanoparticles distribution in the PLLA, a JEOL 2100F with a Schottky Field Emission Gun was used in STEM mode equipped with a EDAX EDX detector.

Statistical analysis

All thin films were measured for FDAC release in quadruplicate (n = 4) and sampled for FDAC concentration every 48 h. A one-way ANOVA test (OriginPro 2015) was used to

identify significance between FDAC release kinetics, duty cycle and photoadditive composition. A value of $P < 0.05$ (*) or $P < 0.01$ (**) was considered statistically significant.

RESULTS

Isolation of release kinetics by quantitation of NIR-mediated photocatalysis

Five different mechanisms, (1)NIROFF, (2)NIROX, (3)NIRZO, (4)NIRUV and (5)NIRPH (illustrated in Figure 2A and described below), are responsible for the majority of chemical release in polyester films with UCNP and ZnO photoadditives under NIR illumination. Figure 2B displays the overlap of UCNP UV luminescence and ZnO absorbance. (1) NIROFF, no NIR exposure, light OFF) correlates to the surface diffusion of FDAC from PLLA matrix under 0.0 DC. Four additional mechanisms are introduced to the system as exposed to NIR light: (2) NIROX (NIR-mediated Oxidation) light photooxidation or NIR induced thermal effects on the PLLA matrix; note that there are no photoadditives present. (3) NIRZO (NIR activation of Zinc Oxide), NIR-mediated photooxidation, photocatalysis, or other unknown NIR-ZnO induced mechanisms. (4) NIRUV (NIR conversion to UV) *in situ* UV generation by UCNPs that activates UV-induced polyester photooxidation. (5) NIRPH (NIR activation of PHotocatalysis) *in situ* UV generation by UCNPs that induces UV-mediated ZnO photocatalysis. To isolate each mechanism, PLLA thin films (sub-50 μm thickness) with dispersed prodrug fluorescein diacetate (FDAC) are prepared neat (for NIROFF & NIROX), with photoadditives of photocatalytic ZnO nanoparticles (NIRZO), UCNPs (NIRUV), and a combination thereof (ZnO + UCNPs, towards NIRPH). UCNPs convert NIR light to UV light, which is required for the ZnO photocatalysis reaction. Adding ZnO in polyester thin film, higher release kinetics can be achieved under identical UV irradiation compared with other photocatalytic nanoparticles (TiO_2 , Fe_2O_3 , ZnFe_2O_4 , **Figure S1**). The controlled release of FDAC by NIR irradiation (980 nm) is investigated with FDAC, which is a colorless, non-fluorescent hydrophobic pro-drug of fluorescein. As this study studied the effect of six parameters on drug

release (polyester matrix, diode intensity, duty cycle, type of ZnO, conc. of UCNP, and ZnO + UCNP photoadditives), a high-throughput strategy is needed to handle the thousands of film samples. Previously published FDAC protocols allow high-throughput quantitation over 5 orders of magnitude ($0.001\text{-}10\ \mu\text{g.mL}^{-1}$). [24, 31, 32, 35-38] FDAC is required in many biological applications, including to track groundwater bacteria, [39, 40] and has been used to mimic hydrophobic release kinetics from polyester matrices. [24, 31, 36] Thus, FDAC has been chosen as model compound in our system in order to study the effect of NIR activated UCNPs on the release kinetics from PLLA films. Note that if encapsulated FDAC (colorless) is prematurely converted to fluorescein (bright orange) within the PLLA films, it can be visually identified. All films remained colorless before and after exposure to irradiation and release medium.

The NIR dose is controlled both by laser diode excitation density and duty cycle ($0.1 - 1.0$) using pulse width modulation. Laser diodes with power ratings of 10 mW and 50 mW are used, both of which have been shown to activate UCNPs. [41] FDAC release is monitored during 17 days of NIR irradiation and a further 14 days under dark conditions to investigate the responsiveness to NIR irradiation. Release kinetics K_{light} (NIR irradiation, day 2 to 15) and K_{dark} (dark conditions, day 18 to 31) are evaluated for the four NIR-mediated release mechanism described above (NIROX, NIRZO, NIRUV, and NIRPH), and are reported as percent per day. The 100 % value was calculated by dissolving the remaining film. Day 1 release kinetics are attributed to surface burst release.

FDAC release from PLGA films containing ZnO photoadditives has been shown to correlate with UV dose. [24] Under NIR irradiation, UCNPs act as point sources of UV light for ZnO photocatalysis. As such, we hypothesized that FDAC release could be controlled by the UCNP concentration as well as the NIR dose. Two UCNP formulations are investigated; equal mass ratios of UCNPs to ZnO (both 1% w/w PLLA) and an excess of UCNPs (5% w/w PLLA).

Figure 2. A) Probable release mechanisms in PLLA films with photoadditives of upconverting nanoparticles (UCNPs) and zinc oxide (ZnO) under NIR irradiation. 1) NIROFF, surface diffusion with no NIR irradiation; 2) NIROX, NIR mediated photooxidation and photothermal effects; 3) NIRZO, NIR-mediated photooxidation, photocatalysis, or other unknown NIR-ZnO induced mechanisms; 4) NIRUV, in situ UV irradiation and subsequent UV-mediated photooxidation; 5) ZnO mediated photocatalysis by in situ UV generated from UCNP. B) overlap of the emission spectrum of UCNPs at 980 nm excitation with the absorbance spectrum of ZnO nanoparticles. Redrawn from reference [24].

NIR dose dominates FDAC release from PLGA, but PLLA matrix is 580x less sensitive.

FDAC release from PLGA and PLLA matrices is compared as a function of NIR dose (Watt * duty cycle * time = Joule, J) in **Figure 3**. The NIR dose is dependent on the NIR LED lasers' power (10 or 50 mW) and duty cycle (0.1 to 1.0). The cumulative FDAC release is evaluated against the NIR dose at day 5 without additives (Figure 3A) as well as with UCNP and ZnO additives (Figure 3B). In the absence of additives, PLGA released 58 % FDAC in 5 days at 4 kJ of 980 nm NIR. In contrast, only 0.1 % FDAC (580x difference) is released from PLLA under similar conditions. As the NIR dose increased to 13 kJ, less than 1.5 % FDAC was released from PLLA. With addition of UCNP and ZnO additives, PLGA displays greater than 95 % FDAC release at 4 kJ compared to PLLA's 15 % FDAC release NIR dose of 13 kJ. This suggests that PLGA films have a higher sensitivity to NIR irradiation than PLLA even without photoadditives. We speculate that the NIR dose sensitivity is attributed to the PLGA glass transition temperature. The incubation temperature was 37 °C in release study, which lays in the glass transition zone of PLGA but below that of PLLA (See **Figure S2** for Tg analysis

comparing PLGA and PLLA). Thus, PLGA release kinetics are likely to be more sensitive to minute shifts in medium or thin film temperature and were not further investigated herein. **Figure 3A** and **3B** demonstrate that PLLA had little to no increase in release kinetics over 0.0 DC at NIR doses of <2 kJ, regardless of NIR intensity applied. Size exclusion chromatography also showed no significant change in PLLA bulk molecular mass, as assessed by elution volume on thin films irradiated over 17 days (data not shown).

Figure 3. Cumulative FDAC released at day 5 as a function of NIR dosage from A) PLGA, PLLA matrix and B) PLGA, PLLA matrix with addition of UCNP and ZnO inside. Two NIR laser diodes were applied as the light source, 10 and 50 mW. Standard deviation is smaller than symbol, unless indicated.

Laser diode with higher optical power (50 mW) provides duty cycle dependence

Temporal release of PLLA/FDAC matrices exposed to 10 mW and 50 mW NIR laser diodes is plotted in Figure 4 and 5, respectively. Both laser diodes had a positive effect on release kinetics (*e.g.* formulations in **Figure 4A,C** vs. **5A,C**). Only samples irradiated with 50 mW source display a predictable reduction in release kinetics when NIR irradiation is discontinued, as compared in **Figure 4D,E,F** vs. **Figure 5D,E,F**. The formulations at 50 mW NIR PLLA/FDAC release display a higher positive Pearson's R correlation (Pearson's R = 0.95, see **Table S9**) with duty cycle and FDAC, up to day 17, highlighting the responsiveness of the PLLA formulations after an unknown (between 10 and 50 mW) threshold of NIR intensity is crossed.

Figure 4 FDAC release profiles under 10mW NIR activation from PLLA thin films containing A) 1% w/w UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w neat ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP. Films

exposed of NIR light of 0.5 DC (triangles) and 1.0 DC (squares), or not exposed to NIR (0.0 DC, circles) as control. Samples exposed to NIR light were irradiated 0 to 17 days, thereafter dark (0.0 DC) conditions to day 31.

Figure 5 FDAC release profile under 50mW NIR light from PLLA thin films containing A) 1% w/w UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w neat ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP. Films exposed NIR duty cycles of 0.1 (triangles), 0.3 (diamonds), 0.7 (stars) and 1.0 DC (squares) or not exposed to NIR (0.0 DC, circles) as control. Samples exposed to NIR light were irradiated 0 to 17 days, thereafter dark (0.0 DC) conditions to day 31.

Reduced chemical release when NIR irradiation is removed

Release kinetics K_{light} and K_{dark} are plotted as a function of duty cycle for all the formulations illuminated with the 50 mW laser diode in **Figure 6**. The ratios of release kinetics ($K_{\text{light}}/K_{\text{dark}}$) are given in the table inserts. This ratio indicates the ability of the release system to respond to an “on demand off” order as turning off of the NIR light. A higher value indicates a better responsiveness towards reducing release kinetics when the triggering event (*i.e.*, NIR light) is removed. To account for the burst release, diffusion, autocatalysis, or combination thereof, the ratio of release kinetics is evaluated for days 2 to 15 and days 18 to 31 for control samples not exposed to NIR light (0.0 DC). Non-irradiated films are also listed in the $K_{\text{light}}/K_{\text{dark}}$ 0 duty cycle, **Figure 6, inset** for convenient comparison to NIR irradiated samples. For each sample formulation, an increase in the $K_{\text{light}}/K_{\text{dark}}$ ratio relative to 0.0 duty cycle indicates a controlled on/off-demand release kinetics. $K_{\text{light}}/K_{\text{dark}}$ values at 0 DC (**Figure 6**) are approximately 2.6 (with the exception of 5/1 PLLA/UCNP, which is 3.9), suggesting that there is no appreciable

autocatalysis in the measured time period, and diffusion kinetics are a constant 2.6 times faster in the first two weeks than the following two weeks. Although there is no linear correlation between the $K_{\text{light}}/K_{\text{dark}}$ ratio and duty cycle (with the exception of PLLA/UCNP/ZnO, see **Table S2**), samples exposed to NIR light with 0.7/1.0 duty cycle show higher K_{light} and higher $K_{\text{light}}/K_{\text{dark}}$ values compared with irradiation under 0.1/0.3 duty cycle. The highest $K_{\text{light}}/K_{\text{dark}}$ value of 21.4 was obtained from PLLA/UCNP/ZnO (100/1/1) films exposed to NIR light with 1.0 duty cycle, as observed in **Figure 6A**. In other words, up to 26.1 % of loaded chemical (FDAC) was released during 17 days of NIR irradiation of 1.0 duty cycle, compared to 1.24 % release during the following 14 days without NIR irradiation.

Figure 6. FDAC release kinetics of PLLA thin films containing A) 1% w/w UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w neat ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP in control group (0 DC). NIR laser diodes of 50mW irradiated at duty cycles of 0.1, 0.3, 0.7 and 1.0 DC. The kinetics was calculated based on release profile from day 2-15 (K_{light}) and from day 18-31 (K_{dark}). $K_{\text{light}}/K_{\text{dark}}$, the ratio of the two kinetics, for each formulation is listed in the insert (see **Table S2** for raw values). For samples that not exposed to NIR irradiation (0 DC), two release kinetics were calculated from day 2 to day 15 and from day 18 to day 31 respectively, the ratio of these two kinetics accounts for the burst/diffusional release of the film. NIR Release kinetics (K_{light}) showed significant difference (*, $P<0.05$) compared with PLLA film not exposed to NIR; For the same sample, significant difference (**, $P<0.01$) is found between K_{light} and K_{dark} .

Synergism of ZnO/UCNP increased release kinetics over 2 orders of magnitude

Four possible release pathways arise from NIR irradiation, in addition to diffusion as illustrated in Figure 2. NIROFF is from diffusion only. For each duty cycle, release kinetics arising from NIROX is calculated by subtracting NIROFF from the total release kinetics (K).

NIRZO and NIRUV is calculated by subtracting NIROX from the total release kinetics. With FDAC release kinetics accounted for by the as-mentioned mechanisms, any excess release from films containing both ZnO and UCNP is attributed to synergistic NIRPH.

Total K_{light} contributions for the 5 mechanisms listed above are compared under different NIR duty cycles in Figure 7. FDAC release kinetics from PLLA with 1/1 or 5/1 UCNP/ZnO w/w is compared in Figure 7A and 7B, respectively. In both ratios, the release mechanism is dominated *via* NIRPH mechanism. An observed 304x increase in kinetics (compared to 0.0 DC) is achievable under 1.0 DC NIR irradiation with photoadditives of 1/1 UCNP/ZnO, as seen in Figure 7A. Raising the ZnO/UCNP ratio to 5 increased NIR sensitivity at lower duty cycles of 0.1 to 0.7, but the 1.0 DC K_{light} is approximately 20% reduced compared to 1/1 ratio (see Figure 7B and Table S2). When considering PLLA films with only UCNP as photoadditives, a higher additive content increased K_{light} across all duty cycles, as illustrated in Figure 7E and 7F, suggesting higher intensity *in situ* UV emission. To investigate the cause of the 20 % difference of 1.0 DC K_{light} kinetics, transmission electron microscopy is employed to analyze cross-sections on the thickness scale of the photoadditive diameter (PLLA ultramicrotomed to ~100 nm slices). These nano-thin cross-sections are then analyzed for bulk photoadditive phase separation and homogenous PLLA matrix distribution.

Figure 7. Release kinetics is plotted into portions with different colors, illustrating FDAC released via different pathways as summarized in Figure 2. FDAC release kinetics (K_{light}) from PLLA thin films containing A) 1% w/w UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP in control group (0.0 DC) and under 50mW NIR duty cycles of 0.1, 0.3, 0.7 and 1.0 DC. NSD: no statistical difference.

TEM displays self-assembled photoadditive aggregates, responsible for increasing K_{light}

ZnO nanoparticles can be visually distinguished by their aggregated, columnar-like morphology as magnified in neat ZnO in **Figures 8A, 8B**, and organic solvent colloidal ZnO (solZnO) in **Figure S3A**. The ZnO volume concentration couldn't be significantly assessed for neat ZnO/PLLA film but is subjectively estimated to be $\sim 1 \text{ cluster} \cdot \mu\text{m}^{-3}$ versus $128 \pm 8 \text{ particles} \cdot \mu\text{m}^{-3}$ for the solZnO. In contrast, the UCNPs have an easily recognizable rhomboid diamond shape ($\sim 50 \text{ nm}$ width) with homogenous matrix distribution, as seen in **Figures 8A, 8C (1%), and 8D (5%)**. The 1 and 5% UCNP/PLLA films have a volume distribution of 14 ± 4 and $60 \pm 10 \text{ particles} \cdot \mu\text{m}^{-3}$. However, UCNPs are found to self-assemble and co-aggregate with the neat ZnO clusters when the photoadditives are combined, as seen in the highlighted **Figures 8E to H**. Supporting the self-assembly of the dual photoadditives is the notable reduction of homogenous distribution of UCNPs when comparing similarly magnified cross-sections of **Figures 8C vs. 8E and 8D vs. 8G**. In contrast, the UCNPs and solZnO nanoparticles remain well separated and show no such trend to form UCNP-ZnO aggregates, as seen in **Figure S3B**. Visual differentiation of neat ZnO and UCNPs is further aided through Zn and F (UCNPs consist of LiYF_4) elemental mapping *via* TEM energy-dispersive X-ray microanalysis (EDXMA). **Figure 9** illustrates the distribution of Zn (cyan) and F (red) elements, displaying that UCNPs and neat ZnO are overlapping for both ratios 1/1 and 5/1 UCNP/ZnO, whereas no overlap exists for solZnO (see **Figure S4**). We speculate that the photoadditives co-aggregate and self-assemble during the knife casting or drying, where dispersion forces are no longer present.

Figure 8 TEM micrographs of 100 nm cross-section PLLA thin films. A) Morphology of neat ZnO at 63kX magnification, UCNPs at 125,000X magnification; and distribution of nanoparticles inside PLLA matrix for formulations of B) PLLA/ZnO (100/1), C) PLLA/UCNP (100/1), D) PLLA/UCNP (100/5), E) PLLA/UCNP/ZnO(100/1/1), G)

PLLA/UCNP/ZnO(100/5/1) at 4,000X magnification, 16,000X magnification of sample E) and G) is presented in panel F) and H) respectively. Note, samples are supported on amorphous carbon substrates, which is shown in the grey/white honeycomb structure. PLLA film itself is transparent at the applied voltages.

Figure 9 TEM images show A) is the morphology for PLLA/UCNP/ZnO(100/1/1) at 20,000X magnification, B) shows the distribution for element fluorine and zinc in that area obtained from EDXMA and C) is the overlay of A) and B); D) is the morphology for PLLA/UCNP/ZnO(100/5/1) at 20,000X magnification, E) shows the distribution for element fluorine and zinc in red framed area obtained from EDXMA and F) is the overlay of D) and E). Fluorine (red pixels) was from UCNP (LiYF_4) zinc (cyan pixels) was from neat ZnO.

DISCUSSION

PLLA matrices display low diffusional release, allowing NIRPH dominant kinetics.

A current unmet need exists for chemical depot systems that allow tailored kinetics in dynamic environments (e.g. adhesive films and implants [42-47]), such as the simplified scheme in **Figure 1**. An ideal chemical depot would allow for tailorable K_{release} to be chosen that exceeds a local (and often dynamic) $K_{\text{clearance}}$ (clearance rate), thus allowing a buildup to a preset concentration. K_{release} is then relaxed to maintain the preset until depot exhaustion or a physiological response is met (*i.e.* analgesia). In terms of localized drug delivery, this would allow for most efficient kinetics in order to maintain the pharmaceuticals' therapeutic range. PLGA and PLLA chemical-depot matrices have been presented based on NIR-mediated release activation mechanism, each offering NIR duty cycle dependent kinetics, allowing a range of K_{release} . PLGA matrices have an elevated NIR sensitivity, leading to higher kinetics per joule of 980 nm irradiation applied as seen in Figure 3. However, our previous investigation with

PLGA displayed sigmoidal release kinetics, suggesting NIRPH was not the dominate release mechanism, ultimately limiting the control and reduction in kinetics after NIR irradiation was removed. [24] Following the PLGA investigation, other matrices were attempted, including poly-ketals, -anhydrides, and –amides, but were quickly abandoned due to NIR insensitive kinetics; release was found to be independent of NIR duty cycle. [48] PLLA matrices offer an extended matrix biodegradability, transparency, and were previously seen to have little to no FDAC diffusional release within 30 days (data not shown), making it a good candidate for NIR activated materials. Room temperature knife casting retained crystallinity of PLLA (30.3%) (**Figure S5**) which may further modify the drug release. Besides diffusional release (NIROFF) four other mechanisms (see **Figure 2**) NIROX, NIRUV, NIRZO, and NIRPH contribute to NIR-mediated chemical release and must be quantitatively assessed with a high-throughput strategy. **Figure 7** displays these duty cycle-dependent distributions for six PLLA formulations with various photoadditives (ZnO and UCNP) as well as two UCNP ratios. When both photoadditives are present, NIRPH dominates (> 90 % contribution) at 0.7 and 1.0 DC at the 1/1 UCNP/ZnO ratio (**Table S7**). At the 5/1 UCNP/ZnO ratio, *all* duty cycles are NIRPH dominate, likely due to the saturation of neat ZnO aggregates with UCNP (**Table S8**). While the 5/1 UCNP/ZnO ratio does not give the highest release rate, it did prove highly NIR sensitive with a 60x and 35x increase in drug release compared to 1/1 UCNP/ZnO ratio at 0.1 and 0.3 duty cycles, respectively with the 50 mW diode. Even at 10 mW, a 5x increase in drug release is seen at 0.5 duty cycle across the two formulations. For applications where less NIR irradiation is best (e.g. subocular implant) and high release kinetics aren't required, the more NIR sensitive 5/1 UCNP/ZnO formulation may be the most applicable.

Self-assembled UCNP/ZnO aggregates have the greatest efficiency of NIR-mediated chemical release kinetics

369 Three photoadditives were tested individually in PLLA matrices and are listed in order of
370 NIR efficiency: 1) organic solvent colloidal ZnO (solZnO, 0.20 %. d^{-1}), 2) neat ZnO (0.09 %. d^{-1}),
371 and 3) UCNPs (0.07 %. d^{-1}) with 1% w/w particle/PLLA loading at 1.0 DC NIR activation.
372 Despite solZnO having the highest efficiency in terms of single photoadditives, UCNP
373 mixtures with neat ZnO have a 220 % increase in kinetics over UCNP mixtures with solZnO
374 (at 1.0 DC, see **Figure S6**). The TEM images in **Figures 8E** and **S4B** exemplify the contrast
375 in both ZnO and UCNP distribution between the two ZnO formulations. Neat ZnO causes a
376 favorable phase separation or self-assembly of UCNPs onto the surface and interior of neat
377 ZnO aggregates as seen in **Figures 9C** and **9F**, versus no co-aggregation is displayed in
378 UCNP/solZnO films (as seen in **Figures S3B** and **S4**). The UCNP/ZnO phase separation is
379 likely driven by the reduced entropy of minimizing organic solvent shells around both ZnO
380 and UCNP. The distance between the UCNPs and ZnO nanoparticles strongly affects the
381 energy transfer between the energy donor UCNPs and the energy acceptor ZnO. More
382 precisely, UV light transits from the donor UCNPs to the acceptor ZnO through photon
383 reabsorption or Förster resonance energy transfer (FRET) mechanism, or a combination
384 thereof. FRET processes typically require an interparticle distance of less than 10 nm, but is
385 more efficient towards ZnO-mediated photocatalysis. [49, 50] We speculate that this is
386 responsible for the 220% increase in kinetics in the self-assembled UCNP/ZnO aggregates. For
387 the UCNP/solZnO formulations, UV emission and photon reabsorption is likely to be the main
388 mechanism of energy transfer and subsequent ZnO photocatalysis—distances between the
389 donor and acceptor unit are exceeding the 10 nm range for efficient Förster resonance energy
390 transfer as seen in **Figures S3B** and **S4B**. Another benefit of co-aggregation is their larger
391 diameter, which will lower the probability of diffusional particle release from the PLLA film.
392 Thus, photocatalysis is at its zenith with UCNP and neat ZnO photoadditives compared with
393 homogeneously distributed UCNP and colloidal ZnO. However, without UCNP, colloidal ZnO

is more efficient in increasing release kinetics compared with neat ZnO because of more exposed surface area, as seen in Figures 8E and S3A.

Photoadditives of UCNP/ZnO (solZnO) dispersion show potential in formulation optimization

The co-aggregation and self-assembly of neat ZnO and UCNP displays more efficient NIR-mediated chemical release but at the scientific cost of forming submicron-sized clusters with untestable structure activity relationships. The concentration of UCNPs in PLLA is calculated to be 14 ± 4 and 60 ± 10 nanoparticles/ μm^3 at 1 wt% and 5 wt% loading respectively. However, from **Figure 9B** and **Figure 9E**, concentration of primary UCNPs in clusters is 154 nanoparticles/ μm^3 and 77 nanoparticles/ μm^3 , shows no correlation with its original percent dosing. Indicating the co-aggregation of ZnO and UCNP is a non-linear process that requires a trial and error approach. As a result, optimization of FRET efficiency will be likely dependent on ZnO and UCNP mass ratios, rate of solvent evaporation, polyester matrix, and solvent polarity.

We are left with the lingering resentment that there remains no practical method of cluster elucidation, and even if there was, the knife casting method of film synthesis (practical for mg-g film production) is too unsophisticated for reproducible cluster/particle ratio exploration. Thin film production methods of calendaring or extrusion are required, where shear stress and shear rates can be tightly controlled—however these methods required 10s of grams to kilograms of expensive polymer matrix and photoadditive. Limited by the fabrication process, we speculate that in situ co-aggregation may not be the best approach. We are currently exploring composite structures of neat ZnO/UCNP and physical mixtures of colloidal ZnO/UCNP that allow predictable interparticle distances where FRET would predominate. Formulations with colloidal ZnO that homogeneously disperse in polyester films will allow predictable distances between ZnO and UCNP, but FRET-like distances will require higher

concentrations of colloidal ZnO, UCNP, or both. In this manner, a system with lowest loading of photoadditives yet optimal photocatalysis efficiency would be preferred for nominal NIR-mediated chemical release and biocompatibility.

Advantages of PLLA photoadditive matrices versus other chemical depot formulations

Several investigators have designed NIR triggered release strategies through variants of UCNP/polymer matrices requiring NIR doses of 10 to 200 J within minutes to hours, as summarized in Table 1. [11, 41, 51-53] Compared with other chemical depots, we demonstrated a release system capable of tailoring release over weeks using NIR intensities at the mW scale. The formulations in Table 1 display a NIR-sensitive ‘all or none’ release mechanism that is capable of complete drug release with 20 min or ~24 h after activation. These formulations required less NIR dosage to release more encapsulation drug compared with the PLLA formulations presented herein. Previously reported innovations have the advantage of high drug flux rates ($> 100 \mu\text{g}\cdot\text{d}^{-1}$) in short time periods (hours to days) where in PLLA photoadditive formulations should be applied at timescales of weeks or longer. To avoid side effect caused by long time NIR irradiation (e.g. overheating of tissue) in future clinic application, [54] NIR irradiation intensity limited to known threshold values ($0.726 \text{ W}\cdot\text{cm}^{-2}$) for continuous human skin exposure. [55] However, higher intensities may be required towards attenuation of medium scattering—thus optimization of duty cycle will be required to limit exposure but allow high enough intensity towards photocatalysis activation.

Considering mass delivery, we have compared our PLLA/PLGA thin film formulations to a range of polyester matrix thin films in Figure 10. [24, 31, 35, 56, 57] Matrices in columns (1) to (16) are static formulations - once implanted, their delivery profile cannot be tailored. Most thin films are designed to have a chemical flux of 0.1 to $10 \mu\text{g}\cdot\text{cm}^{-2}\cdot\text{d}^{-1}$. The tailorable PLGA/PLLA photoadditives matrices of (17) to (19) have chemical fluxes that exceed this normal range and cover fluxes over four orders of magnitude, from 0.02 to $20 \mu\text{g}\cdot\text{cm}^{-2}\cdot\text{d}^{-1}$. Drug

flux could be extended with increased drug loading or higher surface area geometries (e.g. rods, microparticles) at the cost of considerable burst release or shorter time intervals respectively[58]. Concerning matrix mechanical properties, ultrafine particles less than 1 micron act as toughening agents for PLA matrices, even at 1 to 10 % particle loading. Thus the photoadditives may increase the robustness of PLLA as a biomaterial or medical implant[59]. Another advantage of this technology is its ease of scalability compared to chemical synthesis dependent drug depot systems. The photoadditives can be easily be compounded and concentrated into the polyester of choice to make a masterbatch resin, like other nanoadditives[60]. The photoadditive masterbatch would then allow photoadditives to be incorporated in calendaring, extrusion, or injection molding manufacturing of polyester thermoplastic biomaterials, such films, rods, screws, and buttress plates[61-63]. In terms of bioresorbility and biocompatibility, ZnO nanorod (dia. = 21nm, L = 50 nm) has in vitro biocompatibility towards Hela cells at 10 $\mu\text{g/mL}$ while silica and chitosan coated UCNP (LiYF_4 doped with Tm, Yb) had little toxicity to bovine nucleus pulposus cells at 500 $\mu\text{g/mL}$ [11, 64]. However, the oleic acid-capped UCNP employed herein are not aqueous soluble. If by some means all ZnO were instantly dissolved (1% ZnO formulation has 35 $\mu\text{g.cm}^{-2}$ ZnO surface conc.) potential levels of ZnO could develop, especially in strongly acidic environments (e.g. stomach acid). In neutral pH environments we were unable to detect ZnO and UCNP elements during the normal course of drug release using inductively coupled plasma atomic emission spectroscopy. For example, concentration of Zn^{2+} and Y^{3+} was below the instrument detection limit (0.1ppm).

Figure 10 A comparison of mass release kinetics from static and dynamic polyester thin films (<200 μm). Release kinetics is calculated by dividing the total release through day 15.

CONCLUSION

We have demonstrated a tailorable chemical release system based on the synergistic effect of UV-emitting UCNPs and ZnO photoadditives. The PLLA matrices were activated by low intensity 50 mW NIR laser diodes at a wavelength of 980 nm. The release kinetics response was tailorable from 0.02 to 8.0 $\mu\text{g}\cdot\text{cm}^{-2}\cdot\text{d}^{-1}$ or 0.01 to 1.4 $\%\cdot\text{d}^{-1}$, demonstrated with the model prodrug fluorescein diacetate. The PLLA/photoadditive formulations highlighted the responsiveness towards NIR irradiation with release kinetics nearly halting after removal of illumination. Transmission electron microscopy cross-sectioned micrographs suggest that the photoadditives of neat ZnO and UCNPs are self-assembling into clusters of sub-micrometer diameter, while self-assembly was prevented by organic solvent colloidal ZnO. The self-assembled photoadditives may benefit from their close association with a higher rate of *in situ* UV energy transfer, ultimately resulting in higher rates of ZnO-mediated photocatalysis.

Released chemicals	Photosensitive formulation	Matrix	% release vs. time	NIR light dosage (kJ)	NIR intensity (W/cm ²)	NIR power output (W)	Ref.
FTIC-BSA	O-nitrobenzyl	Polyacrylamide–poly(ethylene glycol)	67% in 50 min	15	-	5.0	[41]
FTIC-BSA	Succinimidyl and acetylene group	UCNPs@SiO ₂ @GPS@CH/PhL/F ITC-	100% in 12 min	0.24	1.8	0.33	[10]
β-gal	Spiropyran dye	Hollow structured UCNP	70% in 20 min	0.60	-	0.50	[42]
DOX	Stilbene	Core-shell UCNP-MSN	100% in 17 h	198	8.9	0.69	[43]
5-FU	O-nitrobenzyl	UCNP	100% in 20 min	0.10	-	0.08	[37]
FDAC	ZnO	PLLA	24% in 17 days	38	0.1	0.05	Fig. 5

Table 1. Comparison of UCNP and NIR-mediated chemical depot release systems, FTIC-BSA: Fluorescein isothiocyanate labelled bovine serum albumin; β-gal. β-galactosidase; DOX, doxorubicin; 5-FU, 5-Fluorouracil; FDAC, fluorescein diacetate; GPS, (3-glycidyloxypropyl) trimethoxysilane; CH, chitosan; PhL, photosensitive formulation; PEGBA, polyethylene glycol-bis(azide); min, minutes; h, hours.

483

484 **Supporting Information Available**

485 Supporting information includes the metal oxide dependent FDAC release kinetics,
 486 differential scanning calorimetry of PLGA and PLLA, TEM images of PLLA/solZnO films,
 487 and calculations of PLLA crystallinity.

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491 **ACKNOWLEDGEMENT**

492 Funding was greatly appreciated from the Ministry of Education Tier 1 Grant: Rapid
 493 Development of biocompatible surfaces through acrylate combinatorial libraries (RG 46/11)

and Ministry of Education Tier 2 Grant: Tailored soft-tissue bioadhesives for site-specific therapy (MOE2012-T2-2-046). This Research was also conducted by NTU-HUJ-BGU Nanomaterials for Energy and Water Management Programme under the Campus for Research Excellence and Technological Enterprise (CREATE), that is supported by the National Research Foundation, Prime Minister's Office, Singapore. The authors are also grateful for financial support from the Natural Sciences and Engineering Research Council (NSERC) of Canada, the Fonds de recherche du Québec – Nature et technologies (FRQNT), and the Alexander von Humboldt Foundation, Germany.

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Insert Table of Contents Graphic and Synopsis Here

Self-assembled photoadditives in polyester films

allow stop and go chemical release

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1 Table of Content

2 Figures

3

4 **Figure 1.** Schematic of on-demand photo-stimulated release kinetics: the release of encapsulated chemicals
5 starts with NIR stimulation and release stops with removal of external stimulation. Duty cycle (DC, also
6 known as pulse width modulation) is employed to tailor the release kinetics (K_{release}). A high K_{release} is
7 required to overcome local clearance kinetics ($K_{\text{clearance}}$) to attain a therapeutic concentration. Duty cycle is
8 then mediated to maintain the concentration until a local response has been met, wherein the NIR
9 stimulation is removed and $K_{\text{clearance}}$ allows the chemical concentration to dissipate. Thus, a chemical depot
10 system requires 1) the K_{release} to be tailorable such that it exceeds the $K_{\text{clearance}}$ under NIR stimulation, 2) can
11 be fine-tuned to match $K_{\text{clearance}}$ to maintain a preset dose, and 3) have $K_{\text{clearance}}$ exceed K_{release} when the NIR
12 stimulation is removed.

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Figure 2. A) Probable release mechanisms in PLLA films with photoadditives of upconverting nanoparticles (UCNPs) and zinc oxide (ZnO) under NIR irradiation. 1) NIROFF, surface diffusion with no NIR irradiation; 2) NIROX, NIR mediated photooxidation and photothermal effects; 3) NIRZO, NIR-mediated photooxidation, photocatalysis, or other unknown NIR-ZnO induced mechanisms; 4) NIRUV, in situ UV irradiation and subsequent UV-mediated

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19 photooxidation; 5) ZnO mediated photocatalysis by in situ UV generated from UCNP. B) overlap of the emission
20 spectrum of UCNPs at 980 nm excitation with the absorbance spectrum of ZnO nanoparticles. Redrawn from Ref. [24].

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Figure 3. Cumulative FDAC released at day 5 as a function of NIR dosage from A) PLGA, PLLA matrix and B) PLGA, PLLA matrix with addition of UCNPs and ZnO inside. Two NIR laser diodes were applied as the light source, 10 and 50 mW. Standard deviation is smaller than symbol, unless indicated.

43

44 **Figure 4** FdAc release profiles under 10mW NIR activation from PLLA thin films containing A) 1% w/w
 45 UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w neat
 46 ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP. Films exposed of NIR light of 0.5 DC (triangles) and 1.0 DC
 47 (squares), or not exposed to NIR (0.0 DC, circles) as control. Samples exposed to NIR light were irradiated
 48 0 to 17 days, thereafter dark (0.0 DC) conditions to day 31.

Figure 5 FDAc release profile under 50mW NIR light from PLLA thin films containing A) 1% w/w UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w neat ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP. Films exposed NIR duty cycles of 0.1 (triangles), 0.3 (diamonds), 0.7 (stars) and 1.0 DC (squares) or not exposed to NIR (0.0 DC, circles) as control. Samples exposed to NIR light were irradiated 0 to 17 days, thereafter dark (0.0 DC) conditions to day 31.

57

58 **Figure 6.** FDAC release kinetics of PLLA thin films containing A) 1% w/w UCNP and 1% w/w ZnO, B)
 59 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no additive, D) 1% w/w neat ZnO, E) 1% w/w UCNP, F)
 60 5% w/w UCNP in control group (0 DC). NIR laser diodes of 50mW irradiated at duty cycles of 0.1, 0.3, 0.7
 61 and 1.0 DC. The kinetics was calculated based on release profile from day 2-15 (K_{light}) and from day 18-31
 62 (K_{dark}). K_{light}/K_{dark} , the ratio of the two kinetics, for each formulation is listed in the insert (see **Table S2** for
 63 raw values). For samples that not exposed to NIR irradiation (0 DC), two release kinetics were calculated
 64 from day 2 to day 15 and from day 18 to day 31 respectively, the ratio of these two kinetics accounts for the
 65 burst/diffusional release of the film. NIR Release kinetics (K_{light}) showed significant difference (*, $P < 0.05$)

66 compared with PLLA film not exposed to NIR; For the same sample, significant difference (**, $P<0.01$) is
67 found between K_{light} and K_{dark} .

68
69 **Figure 7.** Release kinetics is plotted into portions with different colors, illustrating FDAC released via
70 different pathways as summarized in Figure 2. FDAC release kinetics (K_{light}) from PLLA thin films
71 containing A) 1% w/w UCNP and 1% w/w ZnO, B) 5% w/w UCNP and 1% w/w ZnO, C) neat PLLA, no
72 additive, D) 1% w/w ZnO, E) 1% w/w UCNP, F) 5% w/w UCNP in control group (0.0 DC) and under
73 50mW NIR duty cycles of 0.1, 0.3, 0.7 and 1.0 DC. NSD: no statistical difference.

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Nanoparticles

PLLA/ZnO

PLLA/UCNP

PLLA/UCNP/ZnO (100/1/1)

PLLA/UCNP/ZnO (100/5/1)

Figure 8 TEM micrographs of 100 nm cross-section PLLA thin films. A) Morphology of neat ZnO at 63kX magnification, UCNPs at 125,000X magnification; and distribution of nanoparticles inside PLLA matrix for formulations of B) PLLA/ZnO (100/1), C) PLLA/UCNP (100/1), D) PLLA/UCNP (100/5), E) PLLA/UCNP/ZnO(100/1/1), G) PLLA/UCNP/ZnO(100/5/1) at 4,000X magnification, 16,000X magnification of sample E) and G) is presented in panel F) and H) respectively. Note, samples are supported on amorphous carbon substrates, which is shown in the grey/white honeycomb structure. PLLA film itself is transparent at the applied voltages.

Figure 9 TEM images show A) is the morphology for PLLA/UCNP/ZnO(100/1/1) at 20,000X magnification, B) shows the distribution for element fluorine and zinc in that area obtained from EDXMA and C) is the overlay of A) and B); D) is the morphology for PLLA/UCNP/ZnO(100/5/1) at 20,000X magnification, E) shows the distribution for element fluorine and zinc in red framed area obtained from EDXMA and F) is the overlay of D) and E). Fluorine (red pixels) was from UCNP (LiYF_4) zinc (cyan pixels) was from neat ZnO.

	Matrix:	M _w (kDa)	Additive:	Chemical Released:	Ref.
(1)	PLGA M	110	NA	PTX	[33]
(2)	PLGA M	110	PEG 400Da 20%	PTX	[33]
(3)	PLGA M	110	PEG 400Da 30%	PTX	[33]
(4)	PLGA M	110	PEG 10KDa 20%	PTX	[33]
(5)	PLGA M	110	PEG 10KDa 30%	PTX	[33]
(6)	PLGA M	110	NA	FDAC	[34]
(7)	PLGA M	20	NA	FDAC	[34]
(8)	PLGA A	40	NA	FDAC	[34]
(9)	PLGA A	15	NA	FDAC	[34]
(10)	PLGA M/A	Mix	NA	FDAC	[34]
(11)	PLGA M/A	Mix	NA	FDAC	[34]
(12)	PLA/EVA	121	NA	PTX	[56]
(13)	PLGA	56	NA	Ibuprofen	[57]
(14)	PLGA porous	56	NA	Ibuprofen	[57]
(15)	PLGA	56	PEG 3.3KDa 10%	Ibuprofen	[57]
(16)	PLGA porous	56	PEG 3.3KDa 10%	Ibuprofen	[57]
(17)	PLGA M	110	NA	FDAC	[24]
(18)	PLGA M	110	ZnO 1%	FDAC	[24]
(19)	PLLA	128	ZnO 1%; UCNP	FDAC	F7

EVA, polyethylene vinyl acetate; PLGA, poly(lactic-co-glycolic acid) with lactide/glycolide ratio 50/50; PLLA, poly-L-lactic acid; PLGA M, PLGA with methyl ester end group ; PLGA A, PLGA with carboxylic acid end group; PTX, paclitaxel; FDAC, fluorescein diacetate; NA, no additives; F7, reported in Figure 7.

Figure 10 A comparison of mass release kinetics from static and dynamic polyester thin films (<200µm). Release kinetics is calculated by dividing the total release through day 15.

Released chemicals	Photosensitive formulation	Matrix	% release vs. time	NIR light dosage (kJ)	NIR intensity (W/cm ²)	NIR power output (W)	Ref.
FTIC-BSA	O-nitrobenzyl	Polyacrylamide–poly(ethylene glycol)	67% in 50 min	15	-	5.0	[41]
FTIC-BSA	Succinimidyl and acetylene group	UCNPs@SiO ₂ @GPS@CH/PhL/FITC-	100% in 12 min	0.24	1.8	0.33	[10]
β-gal	Spiropyran dye	Hollow structured UCNP	70% in	0.60	-	0.50	[42]
DOX	Stilbene	Core-shell UCNP-MSN	100% in	198	8.9	0.69	[43]
5-FU	O-nitrobenzyl	UCNP	100% in	0.10	-	0.08	[37]
FDAC	ZnO	PLLA	24% in	38	0.1	0.05	Fig. 5

Table 1. Comparison of UCNP and NIR-mediated chemical depot release systems, FTIC-BSA: Fluorescein isothiocyanate labelled bovine serum albumin; β-gal. β-galactosidase; DOX, doxorubicin; 5-FU, 5-Fluorouracil; FDAC, fluorescein diacetate; GPS, (3-glycidyloxypropyl) trimethoxysilane; CH, chitosan; PhL, photosensitive formulation; PEGBA, polyethylene glycol-bis(azide); min, minutes; h, hours.

1 Supplementary Information

Duty cycle	Optical output (mW)	Excitation energy (mW.cm ⁻²)	Intensity peak (mW.cm ⁻²)	Fluence (J/day)
0.1	50	11±0.3	20±0.5	257±7
0.3	50	33±0.9	60±2	770±20
0.7	50	77±2	142±4	1800±50
1.0	50	110±3	202±5	2570±70
0.5	10	8±2	17±4	190±50
1.0	10	15±3	34±7	350±70
Table S1. NIR laser diode intensity and fluence with respect to duty cycle and optical output.				

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	Duty cycle	K_{light} , NIR on (day 2~15,%/d)	K_{dark} , NIR off (day 18~31,%/d)	$K_{\text{light}} / K_{\text{dark}}$ ratio	Pearson's R
PLLA	0	0.0028±0.0004	0.00103±0.00002	2.7	0.90
10 mW	0.5	0.0046±0.0005	0.0007±0.00002	6.6	
	1.0	0.0086±0.0007	0.00124±0.00007	6.9	
50 mW	0.1	0.0043±0.0004	0.00124±0.00007	3.5	0.83
	0.3	0.0070±0.0009	0.0007±0.00005	9.1	
	0.7	0.014±0.002	0.0020±0.0002	7.1	
	1	0.06±0.01	0.006±0.001	10.8	
PLLA/ZnO (100/1)	0	0.0071±0.0008	0.00295±0.00006	2.4	0.92
10 mW	0.5	0.010±0.002	0.0038±0.0002	2.6	
	1.0	0.008±0.001	0.00207±0.00003	3.9	
50 mW	0.1	0.0090±0.0007	0.0024±0.0001	3.7	0.40
	0.3	0.0158±0.002	0.0017±0.0001	9.5	
	0.7	0.052±0.005	0.0035±0.0006	14.9	
	1	0.09±0.01	0.019±0.003	4.5	
PLLA/UCNP (100/1)	0	0.0030±0.0005	0.00109±0.00002	2.7	-0.87
10 mW	0.5	0.0068±0.0005	0.0066±0.0008	1.0	
	1.0	0.0050±0.0003	0.0048±0.0008	1.0	
50 mW	0.1	0.0029±0.0002	0.0009±0.00004	3.1	0.58
	0.3	0.011±0.001	0.0110±0.0007	1.0	
	0.7	0.023±0.002	0.0074±0.0004	3.1	
	1	0.069±0.006	0.015±0.001	4.5	
PLLA/UCNP (100/5)	0	0.0062±0.0008	0.00160±0.00004	3.9	-0.68
10 mW	0.5	0.0099±0.0008	0.0053±0.0008	1.9	
	1.0	0.014±0.001	0.0057±0.0002	2.5	
50 mW	0.1	0.0099±0.0009	0.00161±0.00006	6.1	0.64
	0.3	0.013±0.001	0.0159±0.0004	0.8	
	0.7	0.059±0.004	0.027±0.003	2.2	
	1	0.14±0.02	0.008±0.001	18.0	
PLLA/UCNP/ZnO (100/1/1)	0	0.0046±0.0006	0.00179±0.00004	2.5	0.77
10 mW	0.5	0.0084±0.0007	0.0044±0.0002	1.9	
	1.0	0.0097±0.0004	0.00179±0.00002	5.4	
50 mW	0.1	0.00179±0.00004	0.0030±0.0002	0.6	0.96
	0.3	0.016±0.002	0.008±0.002	1.9	
	0.7	0.48±0.04	0.029±0.003	16.7	
	1	1.4±0.2	0.07±0.02	21.4	
PLLA/UCNP/ZnO (100/5/1)	0	0.024±0.0008	0.026±0.001	0.9	0.24
10 mW	0.5	0.038±0.002	0.029±0.002	1.3	
	1.0	0.029±0.001	0.029±0.0007	1	
50 mW	0.1	0.51±0.02	0.20±0.02	2.6	0.70
	0.3	0.56±0.03	0.15±0.009	3.7	
	0.7	0.75±0.02	0.15±0.01	5.0	
	1	1.09±0.03	0.31±0.03	3.5	

Table S2. Release kinetics (%.d⁻¹) for all formulations, $K_{\text{light}} / K_{\text{dark}}$ ratios, and Pearson R correlation between duty cycle and $K_{\text{light}} / K_{\text{dark}}$ ratios.

neat PLLA

Duty cycle (DC, NIR)	K^a (%.d ⁻¹)	K_{NIROX}^c (%.d ⁻¹)	K_{NIROX}/K^g (%)
K_{NIROFF}^b	0.0028±0.0004	-	-
10mW			
0.5	0.0046±0.0003	0.0018±0.0006	40±10
1.0	0.0086±0.0007	0.0058±0.0008	68±9
50mW			
0.1	0.0043±0.0004	0.0015±0.0005	30±10
0.3	0.0070±0.0009	0.004±0.001	40±10
0.7	0.014±0.002	0.012±0.002	90±10
1.0	0.06±0.01	0.06±0.01	100±20

Table S3. Release kinetics of per cent per day (%.d⁻¹) for neat PLLA. ^a K Release kinetics (per cent per day) calculated from day 2 to day 15. ^b K_{NIROFF} release kinetics via NIROFF, constant for a specific formulation through all duty cycles. ^c K_{NIROX} contribution of release kinetics via NIROX, is calculated $K_{NIROX}(DC) = K(DC) - K_{NIROFF}$, where $K(DC)$ is release kinetics as function of DC and K_{NIROFF} is a constant of neat PLLA

1% ZnO/PLLA

Duty cycle (DC, NIR)	K (%.d⁻¹)	K_{NIROX} (%.d⁻¹)	K_{NIRZO}^d (%.d⁻¹)	K_{NIROX}/K (%)	K_{NIRZO}/K^h (%)
K_{NIROFF}	0.0071±0.0008	-	-	-	-
10mW					
0.5	0.010±0.003	0.0018±0.0006	0.001±0.001	18±6	10.0±10
1.0	0.008±0.001	0.0009±0.0008	NA ^g	10±10	NA
50mW					
0.1	0.0090±0.0007	0.0015±0.0005	0.000±0.001	17±6	0±10
0.3	0.016±0.001	0.004±0.001	0.004±0.002	25±6	30±10
0.7	0.052±0.005	0.012±0.002	0.033±0.006	23±4	60±10
1.0	0.09±0.01	0.06±0.01	0.02±0.01	90±10	20±10

Table S4 Release kinetics of per cent per day (%.d⁻¹) for 1% ZnO/PLLA matrix. ^d K_{NIRZO} contribution of release kinetics via NIRZO, is calculated by $K_{NIRZO}(DC) = K(DC) - K_{NIROX}(DC) - K_{NIROFF}$, where $K(DC)$ is total release kinetics as a function of DC, $K_{NIROX}(DC)$ is calculated from PLLA matrix illustrated in **Table S3** and K_{NIROFF} is a constant of PLLA/ZnO matrix.

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1% UCNP/PLLA

Duty cycle (DC, NIR)	K (%.d ⁻¹)	K_{NIROX} (%.d ⁻¹)	K_{NIRUV}^e (%.d ⁻¹)	K_{NIROX}/K (%)	K_{NIRUV}/K^i (%)
K_{NIROFF}	0.0030±0.0005	-	-	-	-
10mW					
0.5	0.0068±0.0005	0.0018±0.0006	0.0020±0.0009	27±9	30±10
1.0	0.0050±0.0003	0.0020±0.0008	NA	40±20	NA
50mW					
0.1	0.0029±0.0002	NA	NA	NA	NA
0.3	0.011±0.001	0.004±0.001	0.004±0.002	36±9	40±20
0.7	0.023±0.002	0.012±0.002	0.009±0.003	52±9	40±10
1.0	0.069±0.006	0.06±0.01	0.01±0.01	90 ±10	10±10

Table S5 Release kinetics of per cent per day (%.d⁻¹) for 1% UCNP/PLLA matrix. ^e K_{NIRUV} contribution of release kinetics via NIRUV, is calculated $K_{NIRUV}(DC) = K(DC) - K_{NIROX}(DC) - K_{NIROFF}$, where $K(DC)$ is a function of DC, $K_{NIROX}(DC)$ is calculated from neat PLLA in **Table S3** and K_{NIROFF} is a constant of 1% UCNP/PLLA matrix.

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5% UCNP/PLLA

Duty cycle (DC, NIR)	K (%.d ⁻¹)	K_{NIRIX} (%.d ⁻¹)	K_{NIRUV} (%.d ⁻¹)	K_{NIRIX}/K (%)	K_{NIRUV}/K (%)
K_{NIRIFF}	0.0062±0.0008	-	-	-	-
10mW					
0.5	0.0099±0.0008	0.0018±0.0006	0.002±0.001	18±6	2±1
1.0	0.014±0.001	0.0058±0.0008	0.002±0.001	41±6	41±7
50mW					
0.1	0.0099±0.0009	0.0015±0.0005	0.002±0.001	15±5	20±1
0.3	0.013±0.001	0.004±0.001	0.003±0.002	31±8	20±20
0.7	0.059±0.004	0.012±0.002	0.042±0.004	20±3	71±7
1.0	0.14±0.02	0.06±0.01	0.08±0.02	43±7	50±10

Table S6 Release kinetics of per cent per day (%.d⁻¹) for 5% UCNP/PLLA matrix. ^e K_{NIRUV} contribution of release kinetics via NIRUV, is calculated $K_{NIRUV}(DC) = K(DC) - K_{NIRIX}(DC) - K_{NIRIFF}$, where $K(DC)$ is a function of DC, $K_{NIRIX}(DC)$ is calculated from neat PLLA in Table S3 and K_{NIRIFF} is a constant of 5% UCNP/PLLA matrix.

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PLLA/UCNP/ZnO (100/1/1)

Duty cycle	K (%.d⁻¹)	K_{NIROX} (%.d⁻¹)	K_{NIRZO} (%.d⁻¹)	K_{NIRUV} (%.d⁻¹)	K_{NIRPH}^f (%.d⁻¹)	K_{NIRPH}/K^j (%)
0.0 (off)	0.0046±0.0006 ^b	-	-	-	-	-
10mW						
0.5	0.0084±0.0007	0.0018±0.0006	0.001±0.001	0.0020±0.0009	0.002±0.001	20±10
1.0	0.0097±0.0004	0.0058±0.0008	NA	NA	NA	NA
50mW						
0.1	0.0081±0.0007	0.0015±0.0005	0.000±0.001	0.0000±0.0005	0.0020±0.0009	20±10
0.3	0.016±0.002	0.004±0.001	0.004±0.002	0.004±0.002	0.007±0.002	40±10
0.7	0.48±0.04	0.012±0.002	0.033±0.006	0.009±0.003	0.46±0.04	96±8
1.0	1.4±0.2	0.06±0.01	0.02±0.01	0.01±0.01	1.4±0.2	100±10

Table S7 Release kinetics of per cent per day (%.d⁻¹) for PLLA/UCNP/ZnO (100/1/1) matrix. ^f K_{NIRPH} contribution of release kinetics via NIRPH, is calculated $K_{NIRPH}(DC) = K(DC) - K_{NIROX}(DC) - K_{NIRZO}(DC) - K_{NIRUV}(DC) - K_{NIFOFF}$, where $K(DC)$ is total release kinetics as a function of DC, $K_{NIROX}(DC)$ is calculated from **Table S3**, $K_{NIRZO}(DC)$ is calculated from **Table S4**, $K_{NIRUV}(DC)$ is calculated from **Table S5** and K_{NIFOFF} is a constant of PLLA/UCNP/ZnO (100/1/1) matrix. ^g Percent contribution of FDAC release via NIROX ^h Percent contribution of FDAC release via NIRZO ⁱ Percent contribution of FDAC release via NIRUV ^j Percent contribution of FDAC release via NIRPH ^k NA. Not applicable

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PLLA/UCNP/ZnO (100/5/1) matrix

Duty cycle (DC, NIR)	K (%.d ⁻¹)	K_{NIRPX} (%.d ⁻¹)	K_{NIRZO} (%.d ⁻¹)	K_{NIRUV} (%.d ⁻¹)	K_{NIRPH} (%.d ⁻¹)	K_{NIRPH}/K (%)
0.0 (off)	0.024±0.0008 ^b	-	-	-	-	-
10mW						
0.5	0.038±0.002	0.0018±0.0006	0.001±0.001	0.002±0.001	0.011±0.002	29±5
1.0	0.029±0.001	0.0058±0.0008	NA	NA	NA	NA
50mW						
0.1	0.51±0.02	0.0015±0.0005	0.000±0.001	0.002±0.001	0.48±0.02	94±4
0.3	0.56±0.03	0.004±0.001	0.004±0.002	0.003±0.002	0.53±0.03	95±5
0.7	0.75±0.02	0.012±0.002	0.033±0.006	0.042±0.004	0.75±0.02	100±3
1.0	1.09±0.03	0.06±0.01	0.02±0.01	0.08±0.02	1.00±0.03	92±3

Table S8 Release kinetics of per cent per day (%.d⁻¹) for PLLA/UCNP/ZnO (100/5/1) matrix. ^f K_{NIRPH} contribution of release kinetics via NIRPH, is calculated $K_{NIRPH}(DC) = K(DC) - K_{NIRPX}(DC) - K_{NIRZO}(DC) - K_{NIRUV}(DC) - K_{NIROFF}$, where $K(DC)$ is total release kinetics as a function of DC, $K_{NIRPX}(DC)$ is calculated from **Table S3**, $K_{NIRZO}(DC)$ is calculated from **Table S4**, $K_{NIRUV}(DC)$ is calculated from **Table S6** and K_{NIROFF} is a constant of PLLA/UCNP/ZnO (100/5/1) matrix. ^g Percent contribution of FDAC release via NIROX ^h Percent contribution of FDAC release via NIRZO ⁱ Percent contribution of FDAC release via NIRUV ^j Percent contribution of FDAC release via NIRPH ^k NA. Not applicable

19
20

Formulations	R ² correlation @ NIR (980 nm) %.d ⁻¹ vs DC	R ² correlation @ NIR (980 nm) μg.cm ⁻² .d ⁻¹ vs DC	R ² correlation @ NIR (980 nm) %.d ⁻¹ vs DC	R ² correlation @ NIR (980 nm) μg.cm ⁻² .d ⁻¹ vs DC
PLLA	0.686	0.731		
PLLA/ZnO	0.948	0.882		
	1% UCNP		5% UCNP	
PLLA/UCNP	0.807	0.760	0.848	0.985
PLLA/UCNP/ZnO	0.797	0.827	0.803 or 0.903 [†]	0.769 or 0.986 [†]

Table S9. Linear R² correlation of release kinetics (%.d⁻¹) and (μg.cm⁻².d⁻¹) versus duty cycle at 50mW 980 nm from 0.0 to 1.0 duty cycle. DC, Duty Cycle. [†]As calculated from 0.1 to 1.0 duty cycle.

21
22

Figure S1 A) FDAC release kinetics from day 1- 7 of PLGA, PLGA with 10 w/w % TiO₂ , and PLGA with 10 w/w % ZnO (100/10) thin films under UV light of $0.5 \pm 0.1 \text{ mW/cm}^2$. B) FDAC release kinetics from day 1- 14 of PLGA, PLGA with 1 w/w % Fe₂O₃, PLGA with 1 w/w % ZnFe₂O₄, and PLGA with 1 w/w % ZnO thin films under UV light of $2.6 \pm 0.3 \text{ mW/cm}^2$. * indicates significant differences as p value is less than 0.05.

Figure S2 Glass transition zones of PLGA and PLLA by differential scanning calorimetry. Temperature were raised from 0 °C to 100 °C at heating rate 10 °C.min⁻¹. PLGA shows glass transition between 36°C to 41°C and PLLA shows glass transition between 60°C to 64°C

Figure S3 TEM micrographs show distribution of photoadditives in cross-sectioned PLLA matrix. A) PLLA/solZnO (colloid) (100/1), B) PLLA/UCNP/solZnO (colloid) (100/1/1) at 16,000X magnification. Red circles highlighting UCNPs.

Figure S4 TEM micrographs EDXMA analysis of 100 nm PLLA cross-sections. A) PLLA/UCNP/ZnO (colloid) (100/1/1) at 20,000X magnification, B) shows the distribution for element fluorine and zinc obtained from EDXMA. Fluorine (red pixels) was from UCNPs (LiYF_4) and zinc (cyan pixels) was from solZnO (colloid).

Figure S5 Crystallinity of PLLA by differential scanning calorimetry. Temperature were raised from 40 °C to 200 °C at heating rate 10 °C.min⁻¹. Melting temperature (T_m) is 180°C, crystallinity (χ_c) is calculated to be 30.3% using equation $\chi_c = (\Delta H_m - \Delta H_{cc}) / \Delta H_m^0$, where ΔH_m (melting enthalpy) and ΔH_{cc} (cold crystallization) are obtained from DSC (45.5 J.g⁻¹ and 17.3 J.g⁻¹ respectively), ΔH_m^0 (melting enthalpy for total crystallized PLLA) is obtained from literature (93.0 J.g⁻¹). [1]

Figure S6 FDAC release profile under 50mW NIR light from PLLA thin films containing A) 1% w/w ZnO (colloid) B) 1% w/w UCNP and 1% w/w solZnO (colloid). C) FDAC release kinetics from day 2 - 15 in two ZnO photoadditives.

[1] Běhálek L, Maršáľková M, Lenfeld P, Habr J, Bobek J, Seidl M. Study of crystallization of polylactic acid composites and nanocomposites with natural fibres by DSC method. Physics in Technology 2013;6:209-16.