Tunable Chemical Release from Polyester Thin Film by Photocatalytic Zinc Oxide and Doped LiYF₄ Upconverting Nanoparticles

Cheng, Ting; Ortiz, Raphael Francois; Vedantham, Kumar; Naccache, Rafik; Vetrone, Fiorenzo; Marks, Robert S.; Steele, Terry W. J.

2014

Cheng, T., Ortiz, R. F., Vedantham, K., Naccache, R., Vetrone, F., Marks, R. S., et al. (2015). Tunable Chemical Release from Polyester Thin Film by Photocatalytic Zinc Oxide and Doped LiYF₄ Upconverting Nanoparticles. *Biomacromolecules*, 16(1), 364-373.

<https://hdl.handle.net/10356/80577>

<https://doi.org/10.1021/bm501567m>

© 2014 American Chemical Society. This is the author created version of a work that has been peer reviewed and accepted for publication by *Biomacromolecules*, American Chemical Society. It incorporates referee's comments but changes resulting from the publishing process, such as copyediting, structural formatting, may not be reflected in this document. The published version is available at: [<http://dx.doi.org/10.1021/bm501567m>].

Downloaded on 26 Apr 2023 16:02:13 SGT

1 Tunable chemical release from polyester thin film
2 by photocatalytic zinc oxide and doped LiYF₄
3 upconverting nanoparticles

4 *Ting Cheng^a, Raphael Francois Ortiz^a, Kumar Vedantham^a, Rafik Naccache^c, Fiorenzo*
5 *Vetrone^c, Robert S. Marks^{a,b}, Terry W.J. Steele^{a,*}*

6 ^a School of Materials Science & Engineering, College of Engineering, Nanyang
7 Technological University, 50 Nanyang Avenue, Singapore 639798, Singapore

8 ^b Department of Biotechnology Engineering, Faculty of Engineering Sciences, Ben Gurion
9 University of the Negev, P.O. Box 653, Beer Sheva 84105, Israel

10 ^c Institut National de la Recherche Scientifique – Énergie, Matériaux et Télécommunications,
11 Université du Québec, 1650 Lionel-Boulet, Varennes, QC, Canada, J3X 1S2

12 ^{*} Corresponding Author. Tel.:65-65927594; fax: 65-67909081; Email: wjsteele@ntu.edu.sg
13
14
15
16

ABSTRACT

Once manufactured or implanted polyester release kinetics tend to be fixed with little modulation possible for optimal local chemical concentrations. Here a typical implantable polyester (PLGA) was fabricated into thin films (~50 μm thick) with additives of photocatalytic ZnO nanoparticles, doped LiYF_4 nanoparticle upconverting nanoparticles, or combination thereof and irradiated with either 6 mW ultraviolet (365 nm) light emitting diodes or 50 mW near infrared (980 nm) laser diodes to induce polymer photooxidation. Irradiated polyester films with the aforementioned photoadditives had enhanced release kinetics up to 30 times more than non-irradiated, neat films with extended release times of 28 days. Near infrared, ZnO-mediated photocatalysis had the highest light on/light off ratio release kinetics of 15.4 while doped LiYF_4 upconversion nanoparticles paired with ZnO nanoparticles had the highest linear R^2 correlation of 0.98 with respect to duty cycle and release kinetics. Future applications of the technology will aim toward modulation of previously developed polymeric reagents/drugs for real-time, feedback optimized release.

KEYWORDS: PLGA, photocatalysis, upconversion, chemical release,

TEXT

Maintaining local chemical concentrations from biodegradable chemical delivery systems is a considerable challenge to research scientists and pharmaceutical engineers. Numerous laboratories have demonstrated tailored chemical release kinetics of various small molecules chemicals from resorbable matrices, such as poly (D,L-lactic-co-glycolic acid) (PLGA) by changing the lactide/glycolide ratio, molecular weight, porosity, additives, or polymer end-group chemistry.¹⁻⁸

However, those methods create static formulations with fixed release profiles. Others have continued to develop ‘smart polymers’ than can trigger chemical release upon external stimuli, including pH, temperature, and mechanical activation.⁹⁻¹¹. However, these strategies rarely allow real-time control or tuning of the chemical concentration to be within a known therapeutic/toxicity range, aka therapeutic index as displayed in Figure 1A. One strategy to allow variable dosing within the therapeutic index is to formulate a responsive chemical delivery formulation where the release kinetics can be controlled by an external stimulation. An internal biosensor could then be coupled for continuous feedback and adjustment of release kinetics to match chemical clearance rates. The duty cycle can then be adjusted to determine the release rates required, as seen in Figure 1B. The duty cycle represents the ratio in which the light source is activated in one cycle. The one complete duty cycle is usually in milliseconds (10 ms in the Results below) and hence the a duty cycle of 0.3 represents a repeating light source activation of 3 ms followed by 7 ms of inactivation.

Near infrared (NIR) photo-stimulation is an ideal candidate, as the stimulation can be applied externally and the chemical delivery system ideally designed for environmental resorbability--allowing reduced risk of ecosystem or implant complications. Recent photo-stimulated chemical release systems that take advantage of specific photoactive functional groups, including photocleavable *O*-nitrobenzyl¹²⁻¹⁴ and coumaryl group polymers¹⁵⁻¹⁷ have

61 been described. Alternatively, the gold photothermal effect can be employed for photo-
62 stimulated chemical delivery incorporating thermal sensitive polymers¹⁸. These photo-
63 stimulated strategies suffer from photo-chemical pairings that limit them to photo- or
64 thermal-susceptible crosslinking or functional groups.

65 A more general method could be employed across all resorbable matrices through
66 incorporation of free-radical mediated degradation--through photocatalytic or photooxidative
67 mechanisms. These methods accelerate polymer backbone cleavage resulting in increasing
68 oligomer solubility and ultimately raising small molecule release kinetics as oligomers
69 diffuse into medium¹⁹. Photocatalytic TiO₂ was incorporated into a biodegradable polymer
70 for accelerated release of capsule contents--however TiO₂ itself is not considered readily
71 wastewater treatment friendly or resorbable.²⁰

72 The encapsulated small hydrophobic molecule used in this study was fluorescein diacetate
73 (FDAC), which has been used as a reporter towards microorganism activity/cell viability in
74 water and soil^{21, 22} and also as a hydrophobic drug mimic.²³

75 Herein we design and compare various methods of photo-stimulated chemical delivery
76 systems whose components are known to be resorbable or biocompatible. The designs
77 considered have the advantage of a platform-ubiquity. In theory, they could be applied across
78 various biodegradable matrices e.g polyesters, polyanhydrides, polyamides, etc. We describe
79 three variant methods of photo-stimulation, where release kinetics can be mediated by
80 externally applied UV light, NIR light, or in situ UV light creation through upconversion
81 nanoparticles (UCNPs). It was our hypothesis that local free radical initiation by
82 photocatalytic ZnO nanoparticles, UV-mediated photooxidation, or combination thereof
83 allows tunable release kinetics through photon-dependent stimulation.

Figure 1. Schematic of an ideal photo-stimulated chemical delivery design that A) keeps the chemicals in therapeutic range and B) allows duty cycle controlled release kinetics.

EXPERIMENTAL SECTION

Materials. Poly (DL-lactide-co-glycolide) (PLGA 50/50) [cat# 18404] with inherent viscosity (i.v.) 1.03dL/g [$\sim$ 100kDa molecular weight (Mw), with methyl ester end group] was purchased from Purac, (The Netherlands). Dichloromethane (DCM) [cat# DS1432] was purchased from Tedia (USA). Fluorescein diacetate (FDAC) [cat# F7378] and ZnO [cat# 544906] was purchased from Sigma-Aldrich. Light-emitting diodes (XSL-365-5E), peak wavelength 365nm, 6mW optical power, were purchased from Roithner Lasertechnik (Austria). NIR laser diodes (L9805E2P5), peak wavelength 980nm, 50mW optical power, were purchased from Thorlabs (China).

Synthesis and Characterization of the $\text{Tm}^{3+}/\text{Yb}^{3+}$ Doped LiYF_4 Upconversion

Nanoparticles (UCNP). $\text{LiYF}_4:\text{Tm}^{3+}$ (0.5% (mol/mol)), Yb^{3+} (25% (mol/mol)) upconverting nanoparticles (UCNPs) were prepared using a slightly modified version of the thermal decomposition synthesis reported previously and described in detail in the supporting information.^{24, 25}

Preparation of ZnO/PLGA and UCNP/ZnO/PLGA Thin Films. Thin films of FDAC/PLGA (10% (w/w)) were manufactured as previously described.^{3, 23, 26} Briefly, PLGA formulations with ZnO nanoparticles ($R_h=254.58$ nm), 8 mg of ZnO nanoparticles were directly added to 800 mg of dissolved PLGA (10% (w/w) in DCM), vortexed, and immediately knife casted to yield a final 1% (w/w) of ZnO/PLGA. Similarly, UCNP/PLGA and UCNP/ZnO/PLGA films had ratios of 1/1 (w/w) and 100/1/100 (w/w/w), respectively.

High-Throughput *In-Vitro* FDAC Release Study. The high-throughput quantification of FDAC was previously published²³.

Microplate Mounted UV LED and NIR Laser Diode Arrays. An 8x12 LEDs array with 9mm pitch was made on a custom printed circuit board (PCB) to match the dimension of 96 well plates. LEDs in each column are connected in series to a constant current sink (see Supplementary Information for LED schematic). The current was 20mA and 40mA for UV LEDs and NIR LED respectively. The average intensity of each column is individually controlled by a pulse width modulation (PWM) signal. The modulation frequency was 100Hz and the duty cycle had a resolution of 1000 steps.

FDAC Release Through UV and NIR Activation. Reference film (no ZnO) and PLGA/ZnO films were irradiated at 365 nm (6 mW optical power, XS-365-5E LED from Roithner Lasertechnik, Austria) from 0.0 to 1.0 duty cycle at 100 Hz in pentuplicate. The UV LED illuminated 100% of the 6 mm film punchout. Liquid samples (20 uL) were taken periodically and quantified for FDAC release over 28 d. Release medium was subsequently replaced.

Reference film (no ZnO and UCNP), PLGA/ZnO, PLGA/UCNP, and PLGA/UCNP/ZnO films were irradiated at 980 nm (16 mW optical power, L9805E2P5 diode laser from Thorlabs, China) from 0.0, 0.3, and 1.0 duty cycles at 100 Hz in pentuplicate. NIR laser diode illuminated 60% of the 6 mm film punchouts. Liquid samples (20 uL) were taken periodically and quantified for FDAC release over 28 d. Release medium was subsequently replaced.

Optical power (actual intensity at sample) was measured with a power meter (Newport Corp. Singapore, Model# 1918R) and a thermopile sensor (1.9cm separation) having a diameter of 9.5mm (model 919P-003-10). Wavelength bands range from 363-370 nm (XS-365-5E LED) and from 970-983 nm (L9805E2P5 diode laser).

Statistics. One-way ANOVA test was conducted to determine the significant difference between samples under various duty cycles, and *post-hoc* Tukey's multiple-comparison test was carried out between pairs. A value of $P < 0.05$ was considered statistically significant.

RESULTS

Three methods of photostimulated chemical release based on zinc oxide (ZnO) photocatalysis, upconversion nanoparticles (UCNP), and combination thereof (ZnO + UCNP) as seen in Figure 2.

Figure 2. Theoretical review for optical stimulated chemical delivery A) ZnO mediated photocatalysis generates free radicals under UV/NIR irradiation; B) upconversion nanoparticles (UCNP) converts NIR light to UV light; C) ZnO mediated photocatalysis by in situ UV generated from UCNP; D) overlap of the emission spectrum of UCNP at 980 nm excitation with the absorbance spectrum of ZnO nanoparticles.

PLGA thin films (<50 μm thick) with additives of photocatalytic zinc oxide nanoparticles (ZnO), upconverting nanoparticles (UCNP), a combination thereof (ZnO+UCNP), or no additive (PLGA), were manufactured and photostimulated with either UV (365 nm) LEDs or NIR (980 nm) laser diodes. The release kinetics of the non-fluorescent fluorescein diacetate (FDAC) acted as our model small molecule and was loaded at 10% w/w FDAC/PLGA in all films. FDAC has similar release kinetics as hydrophobic drugs in PLGA films²³ and it was insensitive to the UV or NIR intensities deployed in this manuscript (data not shown). After release, FDAC was hydrolysed into fluorescein and correlated to the photo-dependent stimulation, aka duty cycle, as exemplified in Figure 1B. Duty cycle was varied by pulsed

width modulation ($f = 100$ Hz) from UV or NIR LEDs mounted into 96-well microplates (wiring layout shown in Figure S3). The computer controlled LED microplates were stacked directly on microplates containing the PLGA/FDAC/photoadditive formulations described above.

Surface concentrations ($\mu\text{g}\cdot\text{cm}^{-2}$) of FDAC varied from batch to batch due to the slight differences in film thickness inherent in knife casting viscous polymer solutions to yield thin films. To normalize chemical surface concentrations and the effects it plays on chemical release kinetics, we report the chemical delivery in per cent per day ($\%\cdot\text{d}^{-1}$) in the tables and figures that follow, as it allows for a more accurate comparison across sample formulations. For formulation design across laboratories, we also report the more practically useful $\mu\text{g}\cdot\text{cm}^{-2}\cdot\text{d}^{-1}$ kinetic rates in Figure 5.

UV Stimulation of ZnO Additives Allows A Linear Correlation of Release Kinetics with Duty Cycle. PLGA films were manufactured with a 1% w/w of ZnO nanoparticles/PLGA and subjected to UV LED irradiation from 0.1 to 1.0 duty cycle (10-100% exposure) up to 28 d. Representative cumulative FDAC release profiles of 0.1, 0.3, 0.5, and 1.0 DC (duty cycle) are displayed in Figures 3A, 3B, 3C, and 3D, respectively. For comparison, control films of PLGA without (w/o) ZnO and ZnO films at 0.0 DC were also included. These films are important to account for background diffusional kinetics or kinetic rates via non-photon mediated pathways. In this way, release kinetics can be corrected based on UV-mediated (PLGA, no additive) or ZnO mediated chemical mechanisms when subjected to various UV LED duty cycles. Upon addition of the 1% ZnO nanoparticles, a large cumulative release profile shift was noted in the 3D graphs of FDAC release vs DC vs Time. The large shift can be seen in the overlayed 3D contour graph seen in Figure 3E. In general, the time needed to reach 30, 50, or 70% cumulative release was shifted 4-6 d earlier when compared at identical DC. Figure 3E also illustrates the versatility of the UV-

stimulated ZnO formulation--depending on the DC employed, 30% release could be tuned to day 7 or 25 and 70% release to day 11 or 28. A plot of release kinetics of per cent per day ($\% \cdot d^{-1}$) versus duty cycle had a linear R^2 correlation of 0.966 and 0.997 for UV-mediated (PLGA, no additive) or ZnO mediated films, respectively. No statistical differences were noted at duty cycles of 0.0 (Off) or 0.1. The linear correlation in the duty cycle range of 0.3 to 1.0 suggests that the release kinetics are dose-dependent or photon-dependent--which is ideal for control of light stimulated chemical depots.

Figure 3. Cumulative release profiles (up to day 28) of fluorescein diacetate (FDAC) vs time from FDAC/PLGA thin films and FDAC/ZnO/PLGA thin film in control group (0.0 DC) and under UV light of A) 0.1 DC; B) 0.3 DC; C) 0.5 DC; D) 1.0 DC; E) tuned release profile by DC and addition of ZnO; F) comparison of release kinetics (up to day 15 days) of FDAC released from PLGA sample either with or without ZnO under various DC UV exposure. DC, duty cycle.

Accelerated Chemical Release by NIR Activation and ZnO Photocatalyst. Cumulative release profiles of FDAC from PLGA films w/o and with ZnO under NIR irradiation of DC 1.0 is represented in Figure 4A. Films with both formulations at 0.0 DC (no NIR light, reference) were also plotted. Again, the background release kinetics was calculated from those reference PLGA films without any additives. Comparison of release kinetics for each film under NIR irradiation of 0.0, 0.3 and 1.0 DC is displayed in Table 1. Surprisingly, NIR light showed an acceleration effect on FDAC release from PLGA film w/o ZnO, as release kinetics increased 6- fold compared to PLGA film with no NIR stimulation. The release kinetics was enhanced with the presence of ZnO, regardless of NIR duty cycle. The ZnO additive raised the release kinetics more than 2x higher compared to reference PLGA film at both 0.3 and 1.0 DC. However, unlike UV-mediated release kinetics, the NIR-mediated release kinetics showed non-linear dose-independent or photon-independent behaviour. For example, there was no significant increase in release kinetics when the NIR duty cycle increased from 0.3 to 1.0 ($p > 0.05$). The R^2 correlation of release kinetics of per cent per day ($\% \cdot d^{-1}$) versus duty cycle was 0.69 and 0.78 for NIR-mediated (PLGA, no additive) or ZnO mediated films, respectively, as listed in Table 3.

Table 1

201

Figure 4. Cumulative release profiles (up to day 28) fluorescein diacetate (FDAC) vs time from FDAC/PLGA thin films and those incorporating with A) ZnO; B)UCNP; C) UCNP + ZnO in both control group (0.0 DC) and under NIR light of 1.0 DC; D) all films in control group (0.0 DC) up to day 16; E) all films under NIR light of 1.0 DC up to day 16; F) comparison of release kinetics (up to day 15 days) of FDAC released from PLGA sample either with or without UCNP and/or ZnO at 0.0, 0.3, and 1.0 NIR exposures.

202

203

Table 2

204

205 ***In Situ* NIR to UV Emission Allows a Linear Release Profile through 28 Days.** Figure
206 4B represents cumulative FDAC release from PLGA film w/o and with UCNP under NIR
207 irradiation. For simplicity, only 0.0 and 1.0 DC release profiles are displayed. Films at 0.0
208 DC were regarded as background diffusion kinetics. Release kinetics for both films at 0.3 and
209 1.0 DC are listed in Table 1. Similarly, both films showed dose-independent behaviour under
210 NIR irradiation, as the release kinetics for PLGA film with UCNP increases only 7% when
211 DC was elevated from 0.3 to 1.0. The R^2 correlation of release kinetics versus DC is 0.78 for
212 PLGA film with UCNP. A distinctive behaviour for PLGA film with UCNP is the linear
213 release profile of FDAC through 28 d at 95% (1.0 DC) FDAC release with R^2 correlation of
214 0.981.

215 **ZnO and UCNP Photoadditives Combination Shows DC-dependent Kinetics and**
216 **Linear Release.** The cumulative release profiles for FDAC from PLGA films w/o and with
217 additives irradiated under 0.0 DC and 1.0 DC NIR laser diode are shown in Figure 4C. The
218 release kinetics for both film with 0.0 DC, 0.3 DC, and 1.0 DC are listed in Table 2. The

calculated result showed that the release kinetics for PLGA film with both UCNP and ZnO additives is linearly correlated with NIR duty cycle. The release kinetics increased 71% when NIR irradiation varied from 0.3 DC to 1.0 DC, ~60% more increment compared with PLGA films with either photoadditive. The R^2 correlation of 0.98 of release kinetics to DC suggests irradiation dose-dependent behaviour, indicating the potential application of NIR light controlled chemical delivery with the presence of both additives. Linear release behaviour throughout 28 days was also observed.

For comparison, Figure 4D and 4E display release profiles of FDAC from reference PLGA, ZnO/PLGA, UCNP/PLGA and UCNP+ZnO/PLGA films when the NIR was off (DC 0.0) or completely on (1.0 DC). PLGA film with ZnO showed lowest background release (DC 0.0), not significantly different from reference PLGA film; while PLGA film with UCNP showed highest background release, more than 8 times higher than the reference PLGA film. Films showed same trend when exposed to NIR light. Figure 4F compares release kinetics of those films under NIR irradiation of 0.0, 0.3 and 1.0 DC. For PLGA w/o additives, the release kinetics can be varied in a small range from $0.15\% \cdot d^{-1}$ to $0.98\% \cdot d^{-1}$ with NIR irradiation in an on/off event, hence the on/off ratio, which is defined as the ratio of release kinetics when the NIR irradiation is completely on (DC 1.0) and off (DC 0.0), would be $0.98/0.15=6.5$. PLGA with 1% w/w ZnO additives only enhances release kinetics up to $2.18\% \cdot d^{-1}$ with NIR irradiation, similarly, in a dose-independent way. However it had the highest on/off ratio of 15.6 among all the films. PLGA with UCNP additives can vary the release kinetics dramatically up to $4.7\% \cdot d^{-1}$ under NIR light non-linearly; the on/off ratio of 3.6 was relatively small due to the high background release kinetics. PLGA with both additives showed the NIR dose-dependent release kinetics ranges up to $3.6\% \cdot d^{-1}$ with the on/off ratio of 4.7.

Figure 5 compares both relative ($\% \cdot d^{-1}$) and real ($\mu g \cdot cm^{-2} \cdot d^{-1}$) release kinetics for all the formulations mentioned above under varied stimulation conditions.

Figure 5. Comparison of release kinetics (up to day 15 days) of fluorescein diacetate (FDAC) released from neat PLGA sample either with or without UCNP and/or ZnO under UV or NIR irradiation. Release kinetics in terms of $\% \cdot d^{-1}$ A) without any additives (neat PLGA, reference); C) ZnO additive; E) ZnO + UCNP additives combined; Release kinetics in terms $\mu g \cdot cm^{-2} \cdot d^{-1}$ for films B) without any additives (neat PLGA, reference); D) ZnO additive; F) ZnO + UCNP additives combined.

DISCUSSION

UV and NIR Irradiation Accelerates Polyester Degradation and Subsequently

Increases FDAC Release Kinetics Even Without Photoadditives.

Hydrophobic small molecules, such as FDAC and paclitaxel (both have logP of 4), strongly absorb into the biodegradable polyester matrices, making diffusion based release strategies difficult to control by formulation (with the exception of nanoparticles), and nearly impossible to modulate once implanted. It is generally accepted that these hydrophobic chemicals are shuttled from the bulk polymer matrix by degraded soluble oligomer fragments (~1 kDa), or if added as an additive, by amphiphilic molecules such as PEG^{19, 26, 27}. Thus, by controlling rates of polyester erosion, one should be able to control the release kinetics of encapsulated hydrophobic chemicals.

In this manuscript, we demonstrated how ultraviolet (UV) and near infrared (NIR) light proved to be an effective way of modulating the release kinetics of FDAC in a variety of formulations, with and without additives that induce photooxidation (herein photoadditives) of PLGA. Changes in light intensity directly affect the reaction mechanisms and reaction rates of photocatalysis and photooxidation; therefore we chose to normalize the light intensity and modulate the release kinetics on duty cycle alone.^{28, 29} This is foreseen as a simpler method of controlling release kinetics and easier to implement in future medical devices.

Both UV light and NIR light alone was found to induce photooxidation of the PLGA/FDAC films and enhance the FDAC release kinetics. UV light emitting diodes (LED, 365 nm peak) used in this experiment was able to generate ionizing UV-A radiation (350-400 nm), leading to polymer degradation by photooxidation. The NIR laser diode (980nm) was also capable of accelerating degradation, either by photo- or thermal-oxidation³⁰⁻³². It is also possible that the water uptake by PLGA matrix was heated by NIR light via vibrational absorption of the molecules thus further accelerating the degradation of carrier.³³ When compared side-by-side, the 6 mW UV LED had ~4 times the release kinetics than the 50 mW NIR laser diode at 1.0 DC. A strong linear correlation (>0.9) with respect to duty cycle and release kinetics (%.d⁻¹) was present for UV LED stimulated release, but not for the NIR laser diode.

However, the poor penetrability of UV wavelengths through biopolymers (e.g. proteins, polyesters) compared to NIR light makes the latter a more preferable triggering source. The NIR laser diode source had a measured optical power of 42 mW/cm² (at sample), which is below the limit set for human skin exposure (726 mW/cm² at 980-nm).³⁴ Higher intensity NIR laser diodes are available and our future work aims to investigate which intensities are optimal.

UV Irradiation of ZnO Nanoparticle Additives Demonstrate ZnO-mediated Photocatalysis While The Mechanism of Polymer Degradation Displays a Duty Cycle Dependence. Zinc oxide nanoparticles (ZnO), will generate free radicals (mainly hydroxyl radicals, •OH) upon exposure to UV light (aka photocatalysis).³⁵⁻³⁸ The reactive hydroxyl radicals initiate oxidative degradation of the polymeric matrix *via* production of free radicals on the polymer backbone through hydrogen abstraction³⁹. Hence, the inclusion of ZnO photoadditives into polyester matrices should modulate the release kinetics based on changes in UV or NIR duty cycle (discussed below). A parallel slope between two curves in Figure

3F would have been expected if the photonic catalyst nature of ZnO nanoparticles was ineffectual under these conditions. However, the statistical increase in slope with 1% w/w ZnO/PLGA (6.5 ± 0.2 vs. 4.0 ± 0.4) compared with PLGA alone suggests *in situ* photocatalysis was activated within the polyester matrix. It should be noted that ZnO may act as a lewis acid through dissolved Zn^{2+} cations and acid catalyze the hydrolysis of PLGA.⁴⁰ An increase in kinetics was noted in some PLGA thin film batches, but not all, giving no clear indication of cation mediated hydrolysis.

To simplify the duty cycle contribution to the main mechanisms likely responsible for polymer degradation, we assume that the release kinetics (after subtraction of background, see Table 3) were the result of 1) UV-mediated photooxidation and 2) ZnO-mediated photocatalysis. Other light dependent mechanisms may be present, such as glass transition temperature effects, as discussed below. At low duty cycles, 63% of the release kinetics was dominated by photocatalysis and 37% by UV-mediated photooxidation. This can also be qualitatively seen in Figure 3E at the 10% cumulative release lines; at low duty cycles from 0.1-0.5, a large time shift resulted from the addition of ZnO due to the presence of photocatalysis, however as the duty cycle increased past 0.5, little difference existed between the formulations with or without ZnO because the UV-mediated photooxidation was the dominant degradation mechanism. This underscores the necessity of employing duty cycle as a method of mediating release kinetics--it may allow control of both chemical release kinetics, and a degree of control by which degradation pathway the polymer is undergoing autooxidation.

Table 3

PLGA Release Kinetics Was Increased up to 30 times through The Inclusion of NIR Activated Photoadditives ZnO, UCNP, or Both. We assumed there would be minimal

difference in release kinetics when PLGA was exposed to NIR light. PLGA has little absorbance in the NIR range and NIR isn't likely to appreciably drive photocatalysis due to the large differences in the conduction and valance band energies of ZnO at 3.3 eV, similar to titanium oxide at 3.2 eV^{41, 42}. To our surprise ZnO additives displayed significantly faster release kinetics, which was non-linearly dependent on the diode duty cycle, as seen in Table 1. This effect likely results from the increase in optical density of the PLGA/ZnO films, as the ZnO scattering coefficient is known to increase the light scattering efficiency of polymer/ZnO composites.^{43, 44} Materials with sufficient optical density have been seen to increase in temperature up to 1°C under NIR stimulation.⁴⁵ Drug release kinetics can change dramatically if temperature transitions are near the polymer glass transition temperature (T_g),⁴⁶ as is the case for PLGA T_g (36-40°C). Supporting this mechanism was the increase in per cent (NIR Scattering, Table 2) as the duty cycle was raised from 0.3 to 1.0--an increase in light scattering would shift temperature even more.

ZnO is known as a biocompatible and bioresorbable additive⁴⁷, a key advantage for for environmental applications or implantable medical devices, especially when compared to other efficient photocatalysts such as titanium dioxide. Even with small loading amount of 1% w/w ZnO/PLGA, it had the highest on/off ratio of 15.4 and increased chemical delivery ~23 times more at 1.0 duty cycle than neat PLGA under no activation conditions. Another advantage was the ZnO's low background release kinetics under no light conditions, but this was subject to batch-to-batch differences. However, one downside was that these formulations did not exhibit a strong linear correlation with the NIR duty cycle. Although improbable, the photocatalytic mechanism creates the possibility that long-lived free radicals could diffuse out of the PLGA matrix and disturb the surrounding environment (i.e. inflammation of soft tissues).

Lanthanide nanoparticles have been reported to have fluorescent emissions at wavelengths shorter than their excitation wavelengths--a phenomenon known as upconversion⁴⁸. Doped LiYF₄ based upconversion nanoparticles (UCNP) are unique in that 1) they emit UV wavelengths and 2) their UV intensity is as bright as the NIR emissions, as seen in Figure 2D. The in situ generated UV light was employed herein for PLGA photooxidation and subsequent modulation of release kinetics with (see below) and without ZnO.

The highest release kinetics (%.d⁻¹) of any of the NIR activated films were observed with the UCNP photoadditives, with release kinetics 30 times faster than non-irradiated PLGA. The emission of UV light from UCNP directly initiated NIR→UV photooxidation and subsequent polymer cleavage reactions--a key advantage of this setup is that the in situ UV light generated is absorbed within the PLGA matrix and has little probability of affecting the surrounding environments. We base our speculation on this since the UV intensity decreases exponentially from the UCNP sources and due to the relatively high UV absorbance of polyesters and encapsulated chemical. The UCNPs also brings a variety of engineering and sensing advantages other than high release kinetics. Stimulation of UCNPs at 980 nm allows various spectral emissions that can be used to drive photocatalysis of metal oxides (ZnO), while the higher wavelengths maybe of equal importance for use as a biosensor i.e. feedback of NIR laser positioning. UCNP additive linear R² correlation with respect to release kinetics and duty cycle was higher than the ZnO additives, but still not considered strong, as seen in Table 3. Large amounts (> 1 %.d⁻¹) of background release were present as well, likely due to the high loading of 1/1 w/w UCNP/PLGA--this was deemed necessary for the activation of ZnO, discussed next and due to their small diameter ~ 77 nm. Other limitations of this new technology include questions on their bioresorbility and biocompatibility, which have not been fully characterized, especially in primates⁴⁹. Where bioresorbility and biocompatibility

are of prime importance, we suggest employing formulations based on the ZnO, PLGA, and the drug of interest.

Alternatively, the UCNP UV emission can be coupled to ZnO to generate free radicals, as the ZnO UV absorbance overlaps with the UCNP UV emissions, as seen in Figure 2D. The combination of UCNP and ZnO photoadditives lead to an exceptional improvement in modulating release kinetics by duty cycle as the linear R^2 correlation was higher at 0.98 than either photoadditive alone, as seen in Table 3. However, both additives together failed to show any synergistic behaviour--they had slower release kinetics combined compared with each additive separately, making it difficult to conclude the presiding oxidation pathway. This system was also the most complex formulation--both additives and the additive ratios will need to be optimized for best performance in our future work.

Cross Platform Application with Existing Polymeric Matrices towards Novel Therapeutics and On-line Water Monitoring System. Other groups have also developed photo-triggered chemical delivery systems, linking chemicals with nanoparticles via photoactive functional groups, using either UV, NIR, or NIR $\rightarrow$ UV activation strategies^{13, 14, 16, 17, 50, 51}. Upconverting nanoparticles of various designs have also been applied towards NIR triggered chemical or prodrug delivery^{50, 52, 53}. While these investigations display great strides in targeting specific tissues, their designs limit them to controlled release on the hour timescale and often require continuous illumination (DC 1.0) with extremely high NIR laser intensities ($> 1\text{W.cm}^{-2}$). The latter maybe needed for *in vivo* activation. The strengths and novelty of the thin film additive formulations described herein allow minimal changes in design to already known chemical delivery systems, such as polymeric drug matrices based on antimicrobial and anti-inflammatory drugs^{54, 55}. We foresee applications of this technology where local, near-surface tissues would benefit from long term delivery. Such applications might include therapeutic medical devices or environmental monitoring systems,

for example, vasoconstriction disorders (e.g. Raynaud's phenomenon), inoperative local malignancies, or on-line micro-organism monitoring with variable/controllable detection limits with FDAC as the probe.

CONCLUSION

Herein we have demonstrated how UV, NIR, and *in situ* NIR→UV irradiation can be employed to modulate drug release kinetics from PLGA films. PLGA (with no photoadditives) responds to both UV LED and NIR diode laser stimulation, although only UV-mediated photooxidation displayed a high linear R^2 correlation with respect to release kinetics and duty cycle. Inclusion of photoadditives allowed accelerated polymer degradation and subsequent chemical release through ZnO-mediated photocatalysis and UCNP-mediated photooxidation. The NIR irradiated photoadditives increased release kinetics by up to 30 times versus that of non-irradiated PLGA films. In terms of biocompatibility and bioresorbability, ZnO additives maybe the safest for in vivo medical devices but the combination of ZnO + UCNP displayed the highest linear correlation of light dose and release rates. Future applications of the technology will aim toward modulation of previously developed polymeric drugs and similar chemical delivery devices.

Supplementary Information Available

Supporting information includes the synthesis and characterization of the UCNP and related Results and Discussion. This material is available free of charge *via* the Internet at <http://pubs.acs.org>.

ACKNOWLEDGEMENT

Funding was greatly appreciated from the Ministry of Education Tier 1 Grant: Rapid 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 work was also supported by National Research Foundation of Singapore, CREATE programme of Nanomaterials for Energy and Water Management (13-04-00364 A). The authors are also grateful for financial support from the Natural Sciences and Engineering Research Council (NSERC) of Canada and the Fonds de recherche du Québec – Nature et technologies (FRQNT).

REFERENCE

1. T. W. Steele;C. L. Huang;E. Widjaja;F. Y. Boey;J. S. Loo;S. S. Venkatraman. *Acta Biomater.* **2011**, 7, 1973-1983.
2. T. W. J. Steele;C. L. Huang;S. Kumar;A. Iskandar;A. Baoxin;F. Y. Chiang Boey;J. S. C. Loo;S. S. Venkatraman. *NPG Asia Mater.* **2013**, 5, e46.
3. C. L. Huang;S. Kumar;J. J. Z. Tan;F. Y. C. Boey;S. S. Venkatraman;T. W. J. Steele;J. S. C. Loo. *Polym. Degrad. Stab.* **2013**, 98, 619-626.
4. X. S. Wu;N. Wang. *J. Biomater. Sci., Polym. Ed.* **2001**, 12, 21-34.
5. K. A. Athanasiou;G. G. Niederauer;C. M. Agrawal. *Biomaterials* **1996**, 17, 93-102.
6. M. Vert;S. M. Li;G. Spenlehauer;P. Guerin. *J. Mater. Sci. Mater. Med.* **1992**, 3, 432-446.
7. G. M. Zentner;R. Rathi;C. Shih;J. C. McRea;M. H. Seo;H. Oh;B. G. Rhee;J. Mestecky;Z. Moldoveanu;M. Morgan;S. Weitman. *J. Controlled Release* **2001**, 72, 203-215.
8. L. Zhang;J. M. Chan;F. X. Gu;J.-W. Rhee;A. Z. Wang;A. F. Radovic-Moreno;F. Alexis;R. Langer;O. C. Farokhzad. *ACS Nano* **2008**, 2, 1696-1702.
9. P. Gupta;K. Vermani;S. Garg. *Drug Discovery Today* **2002**, 7, 569-579.
10. D. Schmaljohann. *Adv. Drug Del. Rev.* **2006**, 58, 1655-1670.
11. K. Y. Lee;M. C. Peters;K. W. Anderson;D. J. Mooney. *Nature* **2000**, 408, 998-1000.
12. C. de Gracia Lux;C. L. McFearn;S. Joshi-Barr;J. Sankaranarayanan;N. Fomina;A. Almutairi. *ACS Macro Lett.* **2012**, 1, 922-926.
13. G. Liu;C.-M. Dong. *Biomacromolecules* **2012**, 13, 1573-1583.
14. S. S. Agasti;A. Chompoosor;C.-C. You;P. Ghosh;C. K. Kim;V. M. Rotello. *J. Am. Chem. Soc.* **2009**, 131, 5728-5729.
15. H. C. Kim;S. Kreiling;A. Greiner;N. Hampp. *Chem. Phys. Lett.* **2003**, 372, 899-903.
16. Q. Jin;F. Mitschang;S. Agarwal. *Biomacromolecules* **2011**, 12, 3684-3691.
17. H.-C. Kim;S. Härtner;M. Behe;T. M. Behr;N. A. Hampp. *J. Biomed. Opt.* **2006**, 11, 034024-034024-034029.
18. M. S. Yavuz;Y. Y. Cheng;J. Y. Chen;C. M. Cobley;Q. Zhang;M. Rycenga;J. W. Xie;C. Kim;K. H. Song;A. G. Schwartz;L. H. V. Wang;Y. N. Xia. *Nat. Mater.* **2009**, 8, 935-939.
19. M. Korber. *Pharm. Res.* **2010**, 27, 2414-2420.
20. K. Katagiri;K. Koumoto;S. Iseya;M. Sakai;A. Matsuda;F. Caruso. *Chem. Mater.* **2009**, 21, 195-197.
21. R. J. Chrost;A. Gajewski;W. Siuda. *Advanc. Limnol* **1999**, 54, 167-183.
22. O. Nybroe;P. E. Jørgensen;M. Henze. *Water Res.* **1992**, 26, 579-584.
23. T. W. Steele;C. L. Huang;S. Kumar;E. Widjaja;C. Boey;F. Yin;J. S. Loo;S. S. Venkatraman. *J. Pharm. Sci.* **2011**, 100, 4317-4329.
24. J.-C. Boyer;F. Vetrone;L. A. Cuccia;J. A. Capobianco. *J. Am. Chem. Soc.* **2006**, 128, 7444-7445.

25. R. Naccache;F. Vetrone;V. Mahalingam;L. A. Cuccia;J. A. Capobianco. *Chem. Mater.* **2009**, *21*, 717-723.
26. T. W. J. Steele;C. L. Huang;S. Kumar;S. Irvine;F. Y. C. Boey;J. S. C. Loo;S. S. Venkatraman. *Acta Biomater.* **2012**, *8*, 2263-2270.
27. T. G. Park. *J. Controlled Release* **1994**, *30*, 161-173.
28. L. P. Yang;Z. Y. Liu. *Energy Convers. Manage.* **2007**, *48*, 882-889.
29. E. Hrabarova;K. Valachova;I. Juraneck;L. Soltes. *Chem. Biodivers.* **2012**, *9*, 309-317.
30. A. A. Shah;F. Hasan;A. Hameed;S. Ahmed. *Biotechnol. Adv.* **2008**, *26*, 246-265.
31. B. Singh;N. Sharma. *Polym. Degrad. Stab.* **2008**, *93*, 561-584.
32. D. L. Williams;J. C. Timmons;J. D. Woodyard;K. A. Rainwater;J. M. Lightfoot;B. R. Richardson;C. E. Burgess;J. L. Heh. *J. Phys. Chem. A* **2003**, *107*, 9491-9494.
33. M. L. Viger;W. Sheng;K. Doré;A. H. Alhasan;C.-J. Carling;J. Lux;C. de Gracia Lux;M. Grossman;R. Malinow;A. Almutairi. *ACS Nano* **2014**, *8*, 4815-4826.
34. N. M. Idris;M. K. Gnanasammandhan;J. Zhang;P. C. Ho;R. Mahendran;Y. Zhang. *Nat. Med.* **2012**, *18*, 1580-U1190.
35. M. A. Behnajady;N. Modirshahla;R. Hamzavi. *J. Hazard. Mater.* **2006**, *133*, 226-232.
36. A. L. Linsebigler;G. Lu;J. T. Yates Jr. *Chem. Rev.* **1995**, *95*, 735-758.
37. C. S. Turchi;D. F. Ollis. *J. Catal.* **1990**, *122*, 178-192.
38. J. Domenech;A. Prieto. *J. Phys. Chem.* **1986**, *90*, 1123-1126.
39. K. H. Cheeseman;T. F. Slater. *Br. Med. Bull.* **1993**, *49*, 481-493.
40. Y. Zhang;S. Zale;L. Sawyer;H. Bernstein. *J. Biomed. Mater. Res.* **1997**, *34*, 531-538.
41. V. Srikant;D. R. Clarke. *J. Appl. Phys.* **1998**, *83*, 5447-5451.
42. S. Boujday;F. Wunsch;P. Portes;J. F. Bocquet;C. Colbeau-Justin. *Sol. Energy Mater. Sol. Cells* **2004**, *83*, 421-433.
43. P. P. Jeeju;A. M. Sajimol;V. G. Sreevalsa;S. J. Varma;S. Jayalekshmi. *Polym. Int.* **2011**, *60*, 1263-1268.
44. G. Nenna;A. D. Del Mauro;E. Massera;A. Bruno;T. Fasolino;C. Minarini. *J. Nanomater.* **2012**, Doi 10.1155/2012/319398.
45. A. Abdo;A. Ersen;M. Sahin. *IEEE/EMBC Annu. Int. Conf.*, 33rd **2011**, 3987-3989.
46. M. A. Ouimet;S. S. Snyder;K. E. Uhrich. *J. Bioact. Compat. Polym.* **2012**, *27*, 540-549.
47. Z. Li;R. Yang;M. Yu;F. Bai;C. Li;Z. L. Wang. *J. Phys. Chem. C* **2008**, *112*, 20114-20117.
48. V. Mahalingam;F. Vetrone;R. Naccache;A. Speghini;J. A. Capobianco. *Adv. Mater.* **2009**, *21*, 4025-4028.
49. G. Chen;H. Qiu;P. N. Prasad;X. Chen. *Chem. Rev.* **2014**, *114*, 5161-5214.
50. Y. Yang;B. Velmurugan;X. Liu;B. Xing. *Small* **2013**, *9*, 2937-2944.
51. G. Liu;L. Zhou;Y. Su;C.-M. Dong. *Chem. Commun.* **2014**, *50*, 12538-12541.
52. Y. L. Dai;H. H. Xiao;J. H. Liu;Q. H. Yuan;P. A. Ma;D. M. Yang;C. X. Li;Z. Y. Cheng;Z. Y. Hou;P. P. Yang;J. Lin. *J. Am. Chem. Soc.* **2013**, *135*, 18920-18929.
53. J. A. Liu;W. B. Bu;L. M. Pan;J. L. Shi. *Angew. Chem. Int. Ed.* **2013**, *52*, 4375-4379.
54. R. Delgado-Rivera;R. Rosario-Melendez;W. Yu;K. E. Uhrich. *J. Biomed. Mater. Res. A* **2014**, *102*, 2736-2742.
55. N. D. Stebbins;M. A. Ouimet;K. E. Uhrich. *Adv. Drug Del. Rev.* **2014**, 10.1016/j.addr.2014.04.006.

497
498
499
500
501
502
503
504
505
506
507
508
509
510
511
512
513
514
515
516
517
518
519
520
521
522
523
524
525

Duty cycle (DC, UV)	PLGA ^a (%.d ⁻¹)	PLGA: photox. ^b	ZnO ^a (%.d ⁻¹)	ZnO: photox. + Photocat ^b	ZnO Photo- catalysis ^c	UV photox. (%)	Photo- catalysis (%)
0.0 (off)	0.54±0.03	0.00±0.04	0.76±0.02	0±0.04	0.00±0.06	NA	NA
0.1	0.92±0.05	0.38±0.06	1.01±0.04	0.25±0.05	-0.13±0.08	NA	NA
0.3	0.85±0.04	0.31±0.05	1.59±0.06	0.83±0.07	0.52±0.08	37	63
0.5	1.30±0.06	0.76±0.07	2.8±0.1	2.0±0.1	1.3±0.1	37	63
0.7	2.4±0.1	1.9±0.1	4.1±0.1	3.3±0.1	1.5±0.2	56	44
0.9	3.2±0.1	2.7±0.2	5.5±0.2	4.7±0.2	2.1±0.3	56	44
1.0 (on)	3.7±0.1	3.2±0.2	6.3±0.2	5.5±0.2	2.4±0.3	57	43

Table 1. FDAC release kinetics for PLGA and ZnO/PLGA films subjected to various UV LED duty cycles. ^aper cent per day (%.d⁻¹). Linear correlation (R²) was > 0.98 for all samples through day 15. ^bRelease kinetics after subtraction of background (0.0 DC) determined under light off conditions. ^cRelease kinetics determined by subtracting **PLGA: photox.+** from **ZnO: photox.+ Photocat.** NA, not applicable. Photox = photooxidation.

547

Duty cycle (DC, NIR)	PLGA ^a (%.d ⁻¹)	PLGA: NIR photox. ^b	ZnO ^a (%.d ⁻¹)	ZnO: NIR photox. +Scattering ^b	ZnO Scattering ^c	NIR photox. (%)	NIR Scattering (%)
0.0 (off)	0.15±0.01	0.00±0.01	0.14±0.01	0±0.01	0.00±0.01	NA	NA
0.3	0.98±0.06	0.83±0.06	2.0±0.1	1.9±0.1	1.0±0.1	45	55
1.0 (on)	0.92±0.06	0.77±0.06	2.18±0.09	2.04±0.09	1.3±0.1	38	62
	PLGA ^a (%.d ⁻¹)	PLGA: NIR photox. ^b	UCNP ^a (%.d ⁻¹)	UCNP: NIR + NIR→UV photox. ^b	UCNP NIR→UV photox. ^d	NIR photox. (%)	UCNP NIR→UV photox. (%)
0.0 (off)	0.15±0.01	0.00±0.01	1.30±0.04	0.00±0.04	0.0±0.04	NA	NA
0.3	0.98±0.06	0.83±0.06	4.4±0.3	3.1±0.3	2.3±0.3	27	73
1.0 (on)	0.92±0.06	0.77±0.06	4.7±0.3	3.4±0.3	2.6±0.3	23	77
	PLGA ^a (%.d ⁻¹)	PLGA: NIR photox. ^b	UCNP+ ZnO ^a (%.d ⁻¹)	UCNP+ ZnO ^b	UCNP&ZnO photox. + photocat. ^e	Synergistic Increase ^f	
0.0 (off)	0.15±0.01	0.00±0.01	0.76±0.05	0.00±0.05	0.00±0.05		
0.3	0.98±0.06	0.83±0.06	2.1±0.1	1.3±0.1	0.5±0.1		
1.0 (on)	0.92±0.06	0.77±0.06	3.6±0.2	2.8±0.2	2.1±0.2	60%	

Table 2. FDAC release kinetics for PLGA and photo-additives of ZnO, UCNP, and combination thereof subjected to various NIR laser diode duty cycles. Linear correlation (R^2) was > 0.97 for all samples through day 15. ^aper cent per day (%.d⁻¹). ^bRelease kinetics after subtraction of background (0.0 DC) determined under light off conditions. ^cRelease kinetics determined by subtracting **PLGA: NIR photox.** from **ZnO:NIR photox.+Scattering**. ^dRelease kinetics determined by subtracting **PLGA: NIR photox.** from **UCNP: NIR + NIR→UV photox.** ^eRelease kinetics determined by subtracting **PLGA: NIR photox.** from **UCNP&ZnO photox. + photocat.** ^fSynergistic increase calculated from % increase from 0.3 DC to 1.0 DC, minus the ~10% NIR radiation kinetic increase as seen with either photo-additive from 0.3 DC to 1.0 DC. NA, not applicable. Photox., photooxidation.

548

549

PLGA/photo-additive 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 @ UV (365 nm) %·d ⁻¹ vs DC	R ² correlation @ UV (365 nm) µg·cm ⁻² ·d ⁻¹ vs DC
PLGA <i>neat</i>	0.689	0.762	0.906 or 0.966 [†]	0.966
ZnO	0.775	0.775	0.974 or 0.997 [†]	0.981
UCNP	0.781	0.829	ND	ND
ZnO + UCNP	0.983	0.950	ND	ND

Table 3. R² correlation of release kinetics (%·d⁻¹) and (µg·cm⁻²·d⁻¹) versus duty cycle at 365 and 980 nm from 0.0 to 1.0 duty cycle, where applicable. ND, not determined. DC, Duty Cycle. [†]As calculated from 0.3 to 1.0 duty cycle.

FIGURES

FIGURE 1

594 FIGURE 2

595

596

597 **FIGURE 3**

598

599

600 FIGURE 4

601

602

604

605

Tunable chemical release from polyester thin film by photocatalytic zinc oxide and doped LiYF₄ upconverting nanoparticles

Supplementary Information

Materials and Methods

Synthesis of LiYF₄ UCNP_s - LiYF₄:Tm³⁺ (0.5 mol%), Yb³⁺ (25 mol%) upconverting nanoparticles (UCNPs) were prepared using a slightly modified version of the thermal decomposition synthesis reported previously [1, 2]. In the first step, stoichiometric quantities of ultra-pure Ln₂O₃ (Ln = Y, Tm, Yb) reagents were mixed in a 50/50 water/trifluoroacetic acid (CF₃COOH) solution and refluxed overnight in order to obtain the corresponding metal trifluoroacetate (CF₃COOLn) precursors. To synthesize the UCNPs, 2.5 mmol of lithium trifluoroacetate was added to the obtained metal trifluoroacetates along with 7.5 mL of oleic acid and 7.5 mL of 1-octadecene and heated to 120 °C for 30 min using a vacuum pump to remove any excess water and/or gases. In a separate 100 mL three neck round bottom flask, 20 mL each of oleic acid and 1-octadecene were also degassed at 120 °C for 30 min. This flask was placed in a heating mantle attached to thermocouple and a temperature controller and its temperature was raised to 325 °C. When the solution reached the desired temperature, the precursor solution previously prepared was injected using an infusion syringe pump (Harvard Apparatus) at a rate of 1.5 mL/min. Following the injection, the solution was allowed to react for 60 min (at 325 °C) with vigorous stirring under an inert atmosphere (Ar gas). After 60 min, the solution was slowly cooled to room temperature. The nanoparticles were washed at least twice by precipitating with ethanol, centrifuging, and redispersing in hexane. The subsequently nanoparticles were stored in a 10 wt% solution in toluene.

Transmission Electron Microscopy - TEM analysis of the colloidal nanoparticle dispersion were carried out using a Philips CM200 microscope operating at 200 kV equipped with a charge-coupled device (CCD) camera (Gatan). Prior to analysis, 10 μ l of a 1 mg/mL dispersion of LiYF₄ was evaporated on a formvar/carbon film supported on a 300 mesh copper grid (3 mm in diameter). Particle size distributions were obtained using the ImageJ software.

Luminescence measurements - Upconversion luminescence emission measurements were recorded under 980 nm excitation using a Thorlabs fibre-coupled laser diode. The laser was focused on the sample using a lens to obtain a spot with a Gaussian intensity distribution with a 0.4 mm diameter. The emitted light was collected using a lens in a 90° configuration, and then transferred to a spectrophotometer (Avaspec 2048L-USB2) through the use of an optical fiber. A 1 wt% colloidal solution of the UCNPs was prepared in toluene and sonicated for a period of 10 minutes to ensure proper dispersion. The dispersed nanoparticles remained in suspension for periods of excess of 48 hours following dispersion in toluene. The emission spectra were recorded allowing a total of a 10-second collection time.

Microplate LED Array - A 8x12 LEDs array with 9mm pitch was made on a custom printed circuit board (PCB) to match the dimension of 96 well plates. LEDs in each column are connected in series to a constant current sink. The reference current is manually adjustable through a trimmer. The average intensity of each column is individually controlled by a pulse width modulation (PWM) signal. PWM commands are generated with a Raspberry Pi using the pi-blaster software (<https://github.com/sarfata/pi-blaster>). The modulation frequency was 100Hz and the duty cycle had a resolution of 1000 steps.

Results and Discussion

The thermal decomposition synthesis of the LiYF₄ nanoparticles occurs following the addition of the trifluoroacetate precursors, dissolved in a mixture of oleic acid and 1-octadecene, into a secondary reaction flask containing the same solvent system at elevated temperatures. The decomposition process resulted in the formation of oleate-capped nanoparticles with a diamond-like morphology as evidenced by TEM analysis (Supplementary Figure 1a). The oleate anion caps the nanoparticle surface through an electrostatic interaction between its negatively charged carboxylate oxygens and the positively charged nanoparticle surface [3-5]. The particles were observed to self-assemble on the copper grid and did not show any signs of agglomeration following deposition and drying on the TEM grid. Particle size distribution studies showed that the synthesized UCNPs followed a Gaussian size distribution with a mean particle size of 77.2 +/- 9.4 nm along the longitudinal axis (Supplementary Figure 1b) and an aspect ratio of 1.7 (longitudinal:transverse).

Following 980 nm excitation, the upconversion emission spectrum was collected as shown in Supplementary Figure 2a. Four emission bands were observed in the UV to NIR region of the spectrum. Ultraviolet emission centered at 360 nm was assigned to the $^3P_0 \rightarrow ^3F_4$, $^1D_2 \rightarrow ^3H_6$ transitions. Blue upconversion emission was observed at 450 and 479 nm and assigned to the $^1D_2 \rightarrow ^3F_4$ and $^1G_4 \rightarrow ^3H_6$ transitions, respectively, while red emission ascribed to the $^1G_4 \rightarrow ^3F_4$ transition was centered at 650 nm. Finally, intense NIR emission emanating from the $^3H_4 \rightarrow ^3H_6$ transition was centered around 800 nm. The mechanism of upconversion in Tm³⁺/Yb³⁺ co-doped NaGdF₄ nanoparticles is shown below in Supplementary Figure 2b. A 980 nm photon will raise the Yb³⁺ ion to its $^2F_{5/2}$ excited state after which an energy transfer to the Tm³⁺ ion will occur. The excited Yb³⁺ ion will non-resonantly transfer its energy to a Tm³⁺ ion thereby exciting it to the 3H_5 intermediate excited state after which non-radiative decay to the 3F_4 excited state will

occur. A second energy transfer from Yb^{3+} will occur raising the Tm^{3+} ion to the $^3\text{F}_2$ excited state. The Tm^{3+} ion may either decay nonradiatively to the $^3\text{H}_4$ state where 800 nm radiative emission will occur or alternatively, a third energy transfer can excite the Tm^{3+} ion to the $^1\text{G}_4$ state. At this point, there are several possibilities namely $^1\text{G}_4 \rightarrow ^3\text{H}_6$ (blue), or $^1\text{G}_4 \rightarrow ^3\text{F}_4$ (red) emissions may occur. A fourth energy transfer from Yb^{3+} populates the $^1\text{D}_2$ excited state of Tm^{3+} after which blue emission is observed through the $^1\text{D}_2 \rightarrow ^3\text{F}_4$ transition, or alternatively UV emission from the $^1\text{D}_2 \rightarrow ^3\text{H}_6$. Alternatively, a fifth energy transfer will induce excitation to the $^3\text{P}_0$ energy level where UV emission will be observed upon relaxation to the $^3\text{F}_4$ intermediate state (not shown on Supplementary Figure 2b).

Supplementary Figure 1. (a) TEM image of $\text{LiYF}_4: \text{Tm}^{3+}, \text{Yb}^{3+}$ co-doped nanoparticles, (b) particle size distribution of the particles showing a predominant size ranging from 75-90 nm.

Supplementary Figure 2. (a) Upconversion emission spectrum of LiYF₄: Tm³⁺, Yb³⁺ co-doped nanoparticles following 980 nm excitation. Shaded regions correspond to the color of the emission emitted and ascribed to the labelled transitions on the figure, (b) upconversion luminescence mechanism responsible for populating the various emitting states of thulium in the co-doped system.

Supplementary Figure 3. Wiring schematic of LED microplate array.

- [1] J.-C. Boyer, F. Vetrone, L. A. Cuccia, and J. A. Capobianco, *J. Am. Chem. Soc.*, 128, 7444–7445 (2006).
- [2] R. Naccache, F. Vetrone, V. Mahalingam, L. A. Cuccia and J. A. Capobianco, *Chem. Mater.*, 21, 717–723 (2009).
- [3] N. Bogdan, F. Vetrone, G. A. Ozin, and J. A. Capobianco, *Nano Lett.* 11, 835-840 (2011).
- [4] V. D. Köchli, G. C. McKinnon, E. Hofmann, and G. K. von Schulthess, *Magn. Reson. Med.* 31, 309-314 (1994).
- [5] K. Yang, H. Peng, Y. Wen, and N. Li, *Appl. Surf. Sci.* 256, 3093-3097 (2010).