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Light-Triggered Molecule-Scale Drug Dosing Devices

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The ability to control drug dosing in terms of quantity, location, and time is a key goal for drug delivery science,[1] as improved control maximizes therapeutic effect while minimizing side effects.[2] Systems responsive to a stimulus such as temperature,[3] pH,[4] applied magnetic[5] or electrical[6] field, ultrasound,[7] light,[8] or enzymatic action[9] have been proposed as triggered delivery systems. However, these systems are indirectly triggered, as they induce a macroscopic change in the matrix into which the drug is incorporated.[10] To date, no method to externally, directly trigger precise drug doses to a targeted area has been demonstrated. Here we show a molecular method for light-triggered drug delivery of various drug classes using low energy, long wavelength radiation, with the drug dose being precisely controlled by the duration of applied light. Together with an appropriate polymer matrix, the molecular unit acts as a molecule-scale drug dosing device, with control potentially at the level of a single drug molecule.

The high level of control which can be exerted on light delivered to a molecule in terms of wavelength, duration, intensity, and location can be exploited through a light-controlled drug liberation reaction to give control of the quantity of drug released (the dose), the timing of the release event, and its location. Importantly, this control operates potentially at the level of the single molecule, allowing conjugate-incorporated media to act as drug dosing devices, with dosing controlled at the molecular scale.

3,5-Dimethoxybenzoin (3,5-DMB) derivatives have been used previously as protecting groups in organic synthesis which can be subsequently removed by application of light.[11] Molecules with carboxylic acid or secondary amine functional groups can be protected in this way by reaction with 3,5-DMB to give esters and carbamates, respectively. Following subsequent reaction at other parts of the molecule, the protecting group can simply and quantitatively be removed by optical irradiation (Scheme 1). Although this photochemical reaction has found applications in synthesis, the liberation of drugs using this method is unprecedented. This system is thus extended here to triggered drug delivery, where conjugates with 3,5-DMB with a range of model drugs provide for the liberation of drug through deprotection by optical irradiation.

We use either dicylcohexylcarbodiimide-mediated or direct, acid chloride esterification methods to synthesize light-sensitive conjugates **2**−**4** of three model drugs; acetyl salicylic acid, ibuprofen, and ketoprofen, respectively (Chart 1).

The behavior of **2**−**4** is characterized by irradiating a solution using 365 nm UV-A radiation. UV−visible spectra of a solution of **3** are shown in Figure 1. As the photochemical reaction proceeds, the UV−visible spectrum of the reaction mixture changes (Figure 1), reflecting the formation of **1** and drug and the consumption of conjugate. The solution absorption spectrum exhibits a band at 300 nm assigned to 5,7-dimethoxy-2-phenylbenzofuran **1**.[11] The isosbestic points at 231 and 262 nm indicate the reaction proceeds with no side products. The identity of reaction products was verified by chromatographic separation, followed by spectroscopic analysis to be solely the corresponding drug and **1**. The reaction proceeded in an analogous fashion to related nondrug examples,[12] and all three conjugates **2**−**4** behaved similarly.

Scheme 1. Generalized Photochemical Reaction of 3,5-Dimethoxybenzoin Esters

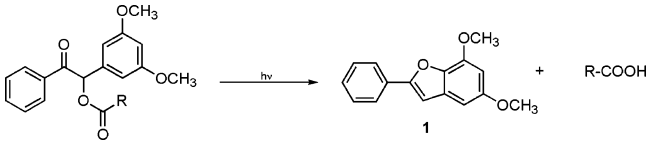
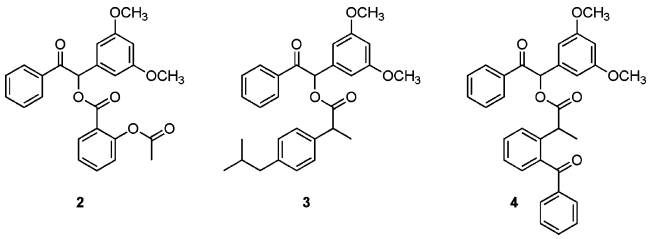


Chart 1. Chemical Structures of Acetyl Salicyl, Ibuprofen, and Ketoprofen Esters of 3,5-Dimethoxybenzoin, **2**, **3**, and **4**, Respectively



A solution of **2** in acetonitrile was then exposed to alternating periods of light and dark using the same conditions for light conditions as previously. Precise control of the drug liberation, and hence dosing, is demonstrated by monitoring the progress of the reaction of **2** after various periods of exposure to light and dark conditions, shown in Figure 2. The distinctive "stepped" profile of the reaction progress shows that the drug liberation reaction proceeds under light conditions, and that in dark conditions liberation of drug is stopped completely. The dose of liberated drug thus correlates with the duration of exposure to light. In this example, six periods of dosing and nondosing are alternated; this can be extended to any discrete dose required, in principle to the level of control provided from the light source, which includes molecule-scale control from low bursts of light deliverable from a laser source.

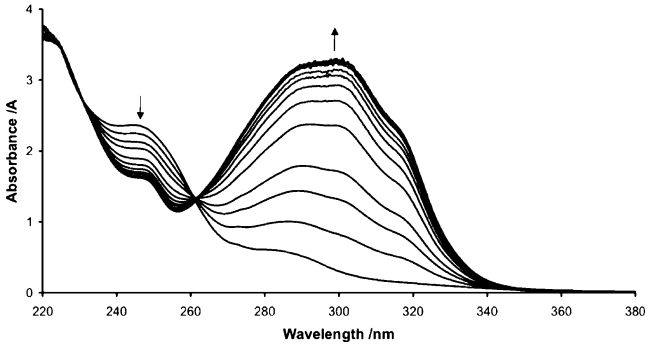


Figure 1. Overlaid UV−visible absorption spectra of **2** in acetonitrile after various periods of irradiation using 365 nm light. Arrows indicate trends in absorbance with time. Irradiation times used were 0, 15, 30, 60, 120, 180, 240, 300, 360, 480, 600, 1200, and 1800 s.

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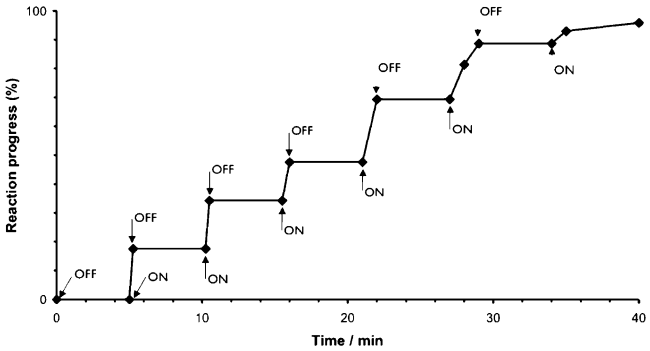

Figure 2. Progress of formation of ibuprofen and **1** from **2** in acetonitrile in light and dark conditions. "On" indicates the beginning of a period of light irradiation; "off" indicates the beginning of a period in dark conditions.

To translate triggered molecular behavior to macroscale drug dosing, judicious choice of a polymer scaffold into which the active molecule is incorporated is necessary. Such scaffolds are well-established in drug delivery. In the current context, an appropriate scaffold must meet several requirements. First, the conjugate should not readily diffuse intact from the scaffold. The scaffold must be optically transparent at the wavelength used for drug liberation, and that reaction must proceed efficiently in this medium, in a comparable manner to solution. Finally, following photolysis, the drug must be able to diffuse readily from the scaffold, and the benzofuran side-product must be retained in the scaffold and not released into the body. We meet these requirements and translate the solution behavior to molecule-scale drug dosing devices using a limited-porsity hydrogel comprising a hydrated copolymer of 2-(hydroxyethyl) methacrylate and methyl methacrylate, crosslinked with ethylene glycol dimethacrylate. Conjugates **2**−**4** were loaded separately into this medium at 5% w/w.

Irradiation of sections of conjugate-loaded polymers immersed in phosphate-buffered saline, followed by spectroscopic characterization of both the polymer and species subsequently released into solution allowed the photolysis and drug release to be characterized. The photochemical reaction proceeds as in solution, and the subsequent behavior of the reaction products meets the requirements of a drug dosing device. As an illustrative example, polymers loaded with **2** liberate ibuprofen and **1** as reaction products. Importantly, ibuprofen is soluble in the aqueous buffer but **1** is practically insoluble. Ibuprofen thus diffuses readily from the polymeric scaffold, where it could thereafter exert its therapeutic effect.

Following photolysis, the drug was shown by UV−visible spectroscopy to be released rapidly from the scaffold into buffer. Fluorescence and UV−visible spectroscopies indicate <0.5% of **1** is released into buffer over the course of the experiment. Fluorescence spectroscopic analysis of the scaffold after release confirmed >99.5% of **1** is retained. A control sample of scaffold kept in dark conditions showed no detectable release of drug or generation of **1**, indicating that neither photochemical nor hydrolytic liberation of the drug occurs under the conditions employed and that photolysis is spatially restricted to regions to which light is applied. The polymeric scaffold thus allows light-triggered drug liberation to proceed and facilitates release (dosing) of only ibuprofen after liberation. Scaffolds loaded with **3** and **4** behave in an analogous manner, showing the general applicability of our approach.

This study represents a platform for development of a range of polymer-supported devices, which allow controlled delivery of drugs to locations where administration is difficult, such as nonblood contact devices. Use of a photochemical system in tissue contact applications will be limited if tissue-damaging wavelengths are required; however, in this study, minimally damaging 365 nm UV-A radiation of low power was used.[13] The wavelength used is less important for nontissue contact applications. As an example, drug delivery from the interior lumen of a urinary catheter is a key objective for anti-infective behavior which could be addressed with this technology. Electromagnetic radiation can be delivered through a fiber optic coupled to a remote light source, and there would be no direct tissue contact and therefore no potentially damaging effect from the applied light.

In conclusion, a new paradigm for precise control of drug dosing using light is demonstrated. The results give proof of concept for several drugs, and the general synthetic method will be adaptable to drugs of other classes. The ability to control light is translated here to the delivery of precise doses in well-defined locations. Triggered drug delivery can thus be achieved and controlled with extreme precision in terms of kinetic rate and total dose, through combinations of wavelength, intensity, and duration of exposure.

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Supporting Information Available: Details of chemical syntheses, methods for preparation of light-triggered polymers containing the compounds, and protocols for photolysis experiments in solution and on materials. This material is available free of charge via the Internet at http://pubs.acs.org.

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