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Short Communication

Rational Design of a Dual-Mode Optical and Chemical Prodrug

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Purpose. The purpose of this study is to demonstrate the rational design and behaviour of the first dual-mode optical and chemical prodrug, exemplified by an acetyl salicylic acid-based system.
Methods. A cyclic 1,4-benzodioxinone prodrug was synthesised by reaction of 3,5-dimethoxybenzoin and acetyl salicoyl chloride with pyridine. After purification by column chromatography and recrystallization, characterization was achieved using infrared and NMR spectroscopies, mass spectrometry, elemental analysis and single crystal X-ray diffraction. Light-triggered drug liberation was characterised via UV-visible spectroscopy following low-power 365 nm irradiation for controlled times. Chemical drug liberation was characterised via UV-visible spectroscopy in pH 5.5 solution.
Results. The synthetic method yielded pure prodrug, with full supporting characterisation. Light-triggered drug liberation proceeded at a rate of 8.30×10^{-2} s^{-1}, while chemical, hydrolytic liberation proceeded independently at 1.89×10^{-3} s^{-1}. The photochemical and hydrolytic reactions were both quantitative.
Conclusions. This study demonstrates the first rational dual-mode optical and chemical prodrug, using acetyl salicylic acid as a model, acting as a paradigm for future dual-mode systems. Photochemical drug liberation proceeds 44 times faster than chemical liberation, suggesting potential use in drug-eluting medical devices where an additional burst of drug is required at the onset of infection.

KEY WORDS: acetyl salicylic acid; hydrolysis; light; prodrug; triggered release.

INTRODUCTION

The ability to precisely control the release of therapeutics from a suitable platform remains a key goal in the development of advanced drug delivery systems, both for medical device and dosage form design. In particular, systems capable of triggered release offer the potential of delivering an ideal drug release profile where the dose and location of delivery can be controlled by an external trigger, or where the release can be triggered by an event such as onset of infection (1,2).

A technology which allows drugs to be liberated from prodrugs, using independent types of trigger depending on the mode of release needed, is therefore highly desirable. This paper describes a paradigm for such a dual-mode system using two independent triggers—light and chemical environment. The ability to use either of two modes would give the ability to liberate drug either rapidly (using, in this case, a photochemical trigger) or slowly (using, in this case, a chemical trigger).

The photochemistry of esters, carbonates and carbamates of 3,5-dimethoxybenzoin (3) is an area of active current investigation (4–9). Such systems have been developed largely as photochemical protecting groups in synthesis because of their photochemical lability and high deprotection step yield due to the lack of side-reactions (10). As an example, Fig. 1 illustrates the photolysis of esters of 3,5-dimethoxybenzoin which, as the deprotection step, quantitatively liberates free carboxylic acid and 4,6-dimethoxy-2-phenylbenzofuran side product **1**. We seek to exploit the clean photochemistry of these systems to the optically-triggered liberation of useful chemical entities such as drugs (e.g., an acidic drug RCO_2H in Fig. 1) (11). Systems triggered by an external stimulus such as light (12,13), pH (14), ultrasound (15), magnetism (16) or heat (17,18) offer potential in pulsatile drug delivery. Light, however, is a particularly attractive trigger as it can be very precisely controlled in terms of wavelength, intensity and position of application, which is routinely exploited in photodynamic therapy (PDT). In PDT applications cytotoxic singlet oxygen is generated only where light of appropriate wavelength photoexcites an administered sensitizer, typically in a tumor (19). For our system, medical device components such as urinary catheter coatings, which are easily accessible to external light sources and often ideally require a burst of drug release at the onset of infection, are particularly

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ABBREVIATIONS: 2, 2-[1-(3,5-dimethoxyphenyl)-2-oxo-2-phenylethoxy]-2-methyl-1,3-benzodioxin-4-one; NMR, nuclear magnetic resonance; PDT, photodynamic therapy; TMS, tetramethylsilane.

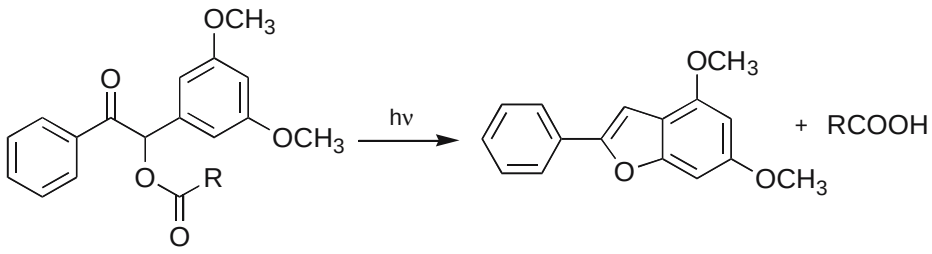

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Fig. 1. Photolysis of esters of 3,5-dimethoxybenzoin.

attractive potential applications for this type of triggered release.

A prodrug is a drug which is initially in an inactive (or significantly less active) form which is converted into the active compound by processes such as metabolism, hydrolysis or, in this context, external stimulus (20,21). Acetyl salicylic acid (aspirin) is a prodrug of the pharmacologically-active salicylic acid; other prodrugs of aspirin and salicylic acid have been reported which are non-acidic (22–24) or demonstrate enhanced absorption characteristics (25). These compounds are advantageous as they cause less gastric irritation and hydrolyze to free drug after passing out of the stomach, the hydrolysis being triggered by elevated pH. The liberation of aspirin from prodrugs reported to date are thus chemically-triggered. Given the interest in prodrugs of this type, acetyl salicylic acid is chosen as an appropriate model to demonstrate the operation of the dual-mode chemical and optical system. In this paper we describe the first system which liberates a model drug upon application of either of two types of stimulus. Specifically, acetyl salicylic acid drug is liberated from prodrug 2-[1-(3,5-dimethoxyphenyl)-2-oxo-2-phenylethoxy]-2-methyl-1,3-benzodioxin-4-one **2** by an optical stimulus or an appropriate chemical environment. Both triggers of liberation of drug operate independently or in tandem and at much different rates.

MATERIALS AND METHODS

Materials

Acetylsalicyloyl chloride, acetyl salicylic acid and salicylic acid were obtained from Aldrich Chemical Co., Poole, Dorset, UK. Pyridine, anhydrous magnesium sulfate, sodium carbonate, hydrochloric acid, calcium chloride and sodium hydroxide were obtained from BDH Chemicals Ltd., Poole, Dorset, UK. Dichloromethane, diethyl ether, chloroform, ethanol and acetonitrile were obtained from Lab-Scan Limited, Dublin, Ireland.

Preparation of 2-[1-(3,5-dimethoxyphenyl)-2-oxo-2-phenylethoxy]-2-methyl-1,3-benzodioxin-4-one, 2

3,5-dimethoxybenzoin (0.25 g, 0.918 mmols), synthesized according to the published procedure (1), and acetylsalicyloyl chloride (0.45 g, 2.27 mmols) were dissolved in dry dichloromethane and refluxed for 27 h. After this time 2 drops of dry pyridine were added to the reaction mixture and the solution refluxed for a further 42 h. The reaction mixture was cooled and poured over a saturated aqueous solution of sodium carbonate (50 ml). The aqueous layer was extracted with diethyl ether (3 × 50 ml). Excess pyridine was removed by washing the combined ethereal layers with dilute hydrochloric acid (2 × 25 ml) followed by distilled water (2 × 25 ml). The ethereal layer was dried over anhydrous magnesium sulfate and solvent removed under reduced pressure to give a cream-colored oil which was recrystallized from ethanol to give a white crystalline solid material (49.97 mg, 33%, m.p. = 96–98°C). Nuclear magnetic resonance spectra were recorded on a General Electric GN-Ω500 instrument. Chemical shifts are given in parts per million (ppm, δ), downfield of tetramethylsilane (TMS), used as an internal standard. A Nicolet Protégé 460 spectrometer interfaced with Omnic E.S.P. software was used to record infrared spectra as potassium bromide discs (Sigma, Poole, Dorset, UK)) from 4000 cm^{-1} to 400 cm^{-1}. Mass spectra were recorded on a Finnegan MAT 900 XLT high resolution double focussing mass spectrometer operating at 70 eV. Melting points were recorded on an Electrothermal 9100 melting point apparatus and are uncorrected. Elemental analysis was determined using a Perkin-Elmer PE-240 automatic CHN analyser.

^{1}H NMR data for **2**: δ_H ($CDCl_3$): 7.90 (coinc. doublets, 3H), (d, 2H, *J* = 7.5, Ar (1)-2 and-6H and d, 1H, Ar(3)-1H); 7.50–7.47 (m, 1H, Ar(1)-4H); 7.35 (t, 2H, *J* = 7.9, Ar(1)-3 and-5H); 7.12 (t, 1H, *J* = 7.7, Ar(3)-3H); 6.98 (t, 1H, *J* = 7.7, Ar(3)-2H), 6.87 (d, 1H, *J* = 8.5, Ar(3)-4H); 6.46 (d, 2H, *J* = 1.85, Ar(2)-2 and -6H); 6.31 (s, 1H, Ar(2)-4H); 6.05 (s, 1H, ArCH); 3.70 (s, 6H, 2 × OCH_3); 1.87 (s, 3H, CH_3) where Ar(1) = phenyl, Ar(2) = 3,5-dimethoxyphenyl and Ar(3) = benzodioxin-4-onyl, s = singlet, d = doublet, t = triplet. Infrared data, υ_{max}/cm^{-1} (KBr) for **2**: 2955 (CH); 1756 (C = O, ester); 1686 (C = O, ketone). Mass spectrometry data (electron impact) for **2**: m/z (%): 435 (M^{+1}, 15), 359 (100), 272 (5). Elemental analysis data for **2**: $C_{25}H_{22}O_7$ requires: C 69.12%, H 5.40%; found: C 69.22%, H 5.40%.

Single Crystal X-Ray Structure Determination of 2

Crystals of **2** of suitable quality and size for X-ray structural analysis were obtained from recrystallization as described above. X-ray diffraction data were collected on a Bruker-AXS SMART diffractometer using the SAINT-NT software (26) with graphite monochromated Mo-K_α radiation. A crystal was mounted on to the diffractometer at low temperature under nitrogen at *ca.* 120 K. The structure was solved using direct methods and refined with the SHELXTL version 5 (27). The non-hydrogen atoms were refined with

anisotropic thermal parameters. Hydrogen atom positions were located from a difference map and fully refined. The function minimised was $\Sigma[w(|F_o|^2 - |F_c|^2)]$ with reflection weights $w^{-1} = [\sigma^2 |F_o|^2 + (g_1P)^2 + (g_2P)]$ where $P = [\max |F_o|^2 + 2|F_c|^2] / 3$. Crystal data for compound **2**: $C_{25}H_{22}O_7$ (2):- $M = 434.43$, monoclinic, space group $P2_1 / c$, $a = 18.7858$ (18) Å, $b = 10.1880$ (10) Å, $c = 11.0051$ (11) Å, $\beta = 103.123$ (2)°, $U = 2051.3$ (3) Å^3, Z = 4, $\mu = 0.103$ mm^{-1}, $R_{int} = 0.0941$, transmission range (max,min) = 0.9887, 0.9707. A total of 16407 reflections were measured for the angle range $3 < 2\theta < 50$ and 4815 independent reflections were used in the refinement. The final parameters were $wR2 = 0.1093$ and $R1 = 0.0504$ [$I > 2\sigma I$]. For crystallographic data in CIF format see supplementary material.

Characterization of Photolysis of 2

A solution of compound **2** (1.54×10^{-4} M) in acetonitrile was irradiated using a 15 W Hg discharge lamp at 365 nm in a 1 cm path length quartz cuvette. The reaction vessel was maintained at a distance of 10 mm from the light source and UV-visible absorption spectra were recorded between 200–350 nm using a Pye Unicam UV1 UV-visible spectrophotometer at various time intervals. The total irradiation time for the reaction was 11 min 25 s. Subsequently, to characterise the products of photolysis the solvent was removed under reduced pressure yielding a yellow oil. Thin layer chromatography indicated the presence of two components, which were separated by means of preparative-scale thin layer chromatography using chloroform as the eluant. The identity of the products was verified by means of ^{1}H NMR, infrared spectroscopy and mass spectrometry.

Characterization of Hydrolysis of 2

Hydrolysis was characterised at both pH 5.5 and pH 7.7. For the former, a solution of compound **2** (1.50×10^{-4} M) was prepared in 3:2 (v/v) acetonitrile:water and adjusted to pH 5.5 using dilute hydrochloric acid (0.10 M). For the latter, a solution of compound **2** (1.50×10^{-4} M) in 3:2 (v/v) acetonitrile:water was adjusted to pH 7.7 using dilute sodium hydroxide (0.10 M). UV-visible absorption spectra were recorded between 220–350 nm using a Pye Unicam UV1 UV-visible spectrophotometer at various time intervals for each solution in a 1 cm path length quartz cuvette.

Subsequently, to characterise the products of hydrolysis the solvent was removed under reduced pressure yielding a colorless oil. Separation of the products by preparative-scale thin layer chromatography using chloroform as the eluant allowed the identification of the products by means of ^{1}H NMR, infrared spectroscopy and mass spectrometry.

RESULTS AND DISCUSSION

The synthesis of 2-substituted 2-methyl-4H-1,3-benzodioxin-4-one derivative **2** was achieved by reaction of 3,5-dimethoxybenzoin (3) with acetyl salicoyl chloride in dichloromethane in the presence of pyridine over 3 days according to Fig. 2. Following work-up, purification by column chromatography over silica gel with chloroform as eluant and recrystallization from ethanol, **2** was obtained in 33% yield. The reaction of acetyl salicoyl chloride with alcohols to give cyclic 1,4-benzodioxinones has been reported previously (24,28–32) and is assumed to proceed by a two-step nucleophilic addition mechanism, involving primary attack at the carbonyl carbon of the acetyl side-chain of acetyl salicylic acid by the alcoholic oxygen of 3,5-dimethoxybenzoin, followed by intramolecular cyclisation to **2** by nucleophilic attack of the alkoxide formed in the primary step at the carbon of the acyl chloride side-chain. **2** was characterised by ^{1}H NMR and infrared spectroscopy, mass spectrometry and elemental analysis. Data from these techniques is complementary and is consistent with spectroscopically and analytically pure compound with the structure assigned to **2**.

The salicylate ester produced from reaction of the alcohol group of 3,5-dimethoxybenzoin with the acyl chloride of acetyl salicoyl chloride was also isolated from the reaction mixture as part of the chromatographic separation as a side-product (40%). This is a competing side reaction observed in related syntheses of 1,4-benzodioxinones and our reaction conditions have been optimized to minimize the yield of this with respect to compound **2**. As a simple ester of 3,5-dimethoxybenzoin, this compound is also a candidate for the dual-mode release paradigm. While it photochemically liberates acetyl salicylic acid, it would found to be unreactive under the mild hydrolysis conditions employed in the study of **2** at both pH 5.5 and pH 7.7. This is in agreement with the study of related simple esters of 3,5-dimethoxybenzoin in our laboratory, and is attritubuted to the steric hindrance to nucleophilic attack which such systems show. Optimization of yield of **2** was achieved by using dichloromethane as solvent

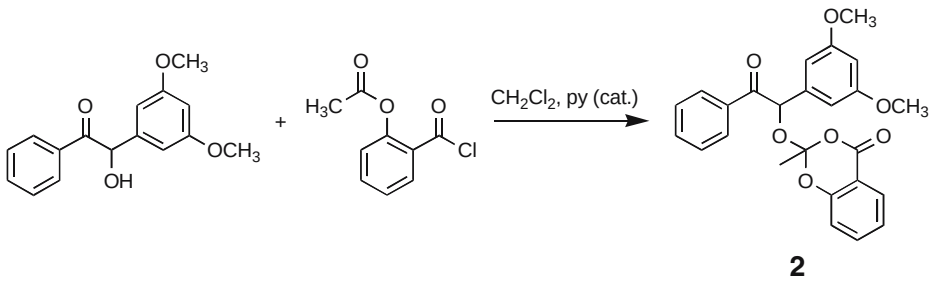

Fig. 2. Synthesis of dual-mode prodrug 2.

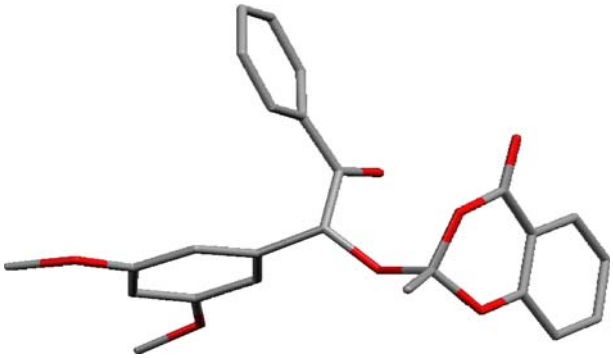

Fig. 3. Solid-state molecular structure of 2.

and employing a relatively long reaction time, and further optimization may be possible through use of low temperatures, longer reaction times or dilute conditions (30).

Crystals of **2** suitable for X-ray diffraction were grown from ethanol at ambient temperature and the solid-state molecular structure is shown in Fig. 3, with hydrogen atoms omitted for clarity. Single crystal X-ray analysis allows an unambiguous assignment of the molecular structure of **2** to be made, and the structure corroborates the analytical data from by ^{1}H NMR and infrared spectroscopy, mass spectrometry and elemental analysis. The compound crystallizes in the $P2_1/c$ spacegroup without solvent of crystallization.

The photolysis behaviour of **2** was characterised in 3:2 (v/v) acetonitrile:water at pH 7.7 using UV-visible spectroscopy. The solution was irradiated with 365 nm UV light from a 15 W Hg discharge lamp at a distance of 10 mm from the lamp coverplate and UV-visible spectra of the product mixture were recorded at various irradiation times. The spectral changes observed are shown in Fig. 4. The changes are ascribed to formation of acetyl salicylic acid and 4,6-dimethoxy-2-phenylbenzofuran, **1**. These products are likely to form from an initial photochemical reaction of **2** to give the acetyl salicoyl ester of 3,5-dimethoxybenzoin, which subsequently photochemically reacts c.f. Fig. 1 to give the observed products. Analogous behaviour of this first step has been observed previously (33), and photochemical rearrangement of **2** to the simple acetyl salicoyl ester of 3,5-dimethoxybenzoin proceeds via cleavage into a radical pair, followed by a radical rearrangement and recombination to give the product. On the timescale of the photochemistry experiment, hydrolysis of acetyl salicylic acid to salicylic acid is negligibly slow. The reaction conditions were chosen to be non-hydrolytic to demonstrate clean photochemistry; under the hydrolytic conditions described below, the acetyl salicylic acid produced would, naturally, be labile. The photochemical reaction products were confirmed as solely **1** and acetylsalicylic acid from the reaction mixture by preparative thin layer chromatography using chloroform as eluant and subsequent ^{1}H NMR analysis. The photochemical reaction was found to be quantitative with no detectable side-products. The rate of the reaction can be estimated from the rate of appearance of the band at 292 nm, which is assigned to **1**. This assignment is in agreement with a spectrum obtained from a sample of pure **1** prepared separately by photolysis of the benzyl ester of 3,5-dimethoxybenzoin followed by chromatographic separation according to the literature (3). The rate of acetyl salicylic acid production, which is the same as the rate of production of **1**, was found from the absorbance data to be first order with a rate constant of 8.30×10^{-2} s^{-1}. The photochemical reaction therefore gives identical products to that of the simple acetylsalicoyl ester of 3,5-dimethoxybenzoin, due to its photoinduced radial rearrangement (9). The photolysis experiment therefore shows that rapid, controlled liberation of a drug can be achieved using light of appropriate wavelength as an external trigger.

The wavelength of light used in photolysis is of considerable importance as UV wavelengths are potentially dam-

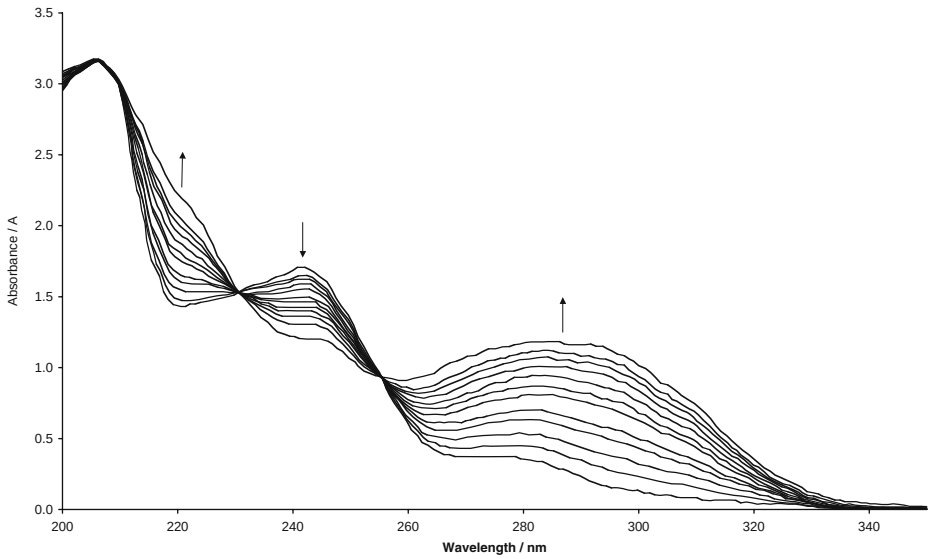

Fig. 4. Overlaid UV-visible spectra following photolysis of 2 at various times. Irradiation times are 0, 20, 40, 70, 90, 155, 185, 230, 290, 350, 440 and 685 s.

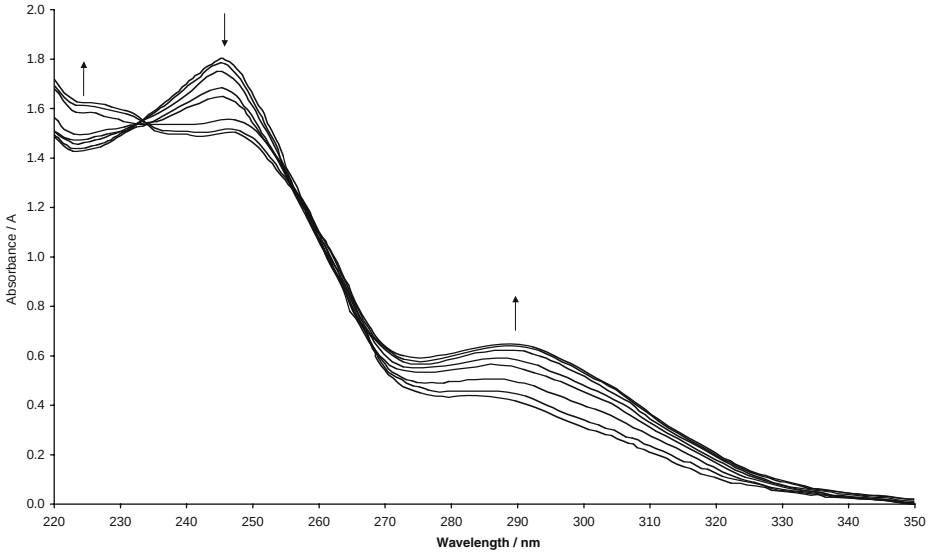

Fig. 5. Overlaid UV-visible spectra following hydrolysis of 2 at various times. Reaction times are 0, 21, 45, 70, 117, 189, 309 and 501 hr.

aging to biological systems. In this study, minimally-damaging 365 nm UV-C radiation of low power was used, compared with 254 nm high power irradiation used in synthetic deprotection procedures used in the literature (2–9). We therefore demonstrate that a wavelength other than that close to the wavelength of maximum absorbance is still capable of rapid liberation of drug. Indeed, excitation at 365 nm represents excitation of 158 nm bathochromic to the wavelength of maximum absorbance (207 nm) and 73 nm from the longest wavelength absorbance band (292 nm) (see $t = 0$ spectrum in Fig. 4) in the 3,5-dimethoxybenzoin system. This is attributable to the fact that excitation of even a very small fraction of molecules from the ground state, S_0, into the first electronic excited state, S_1, allows the photochemical reaction to proceed for these molecules. Even though the quantum yield is low at this wavelength, the photon flux is sufficient to drive the reaction rapidly. In the context of application of the system, its use in tissue contact applications will be limited if tissue-damaging wavelengths are required for use. For medical device coating applications, however, the wavelength used is less important. For example, for such a system incorporated into a urinary catheter coating, which can be easily exposed to light through a fibre optic coupled to a remote light source there would be no direct tissue contact and therefore no potentially damaging effect from the applied light. Nonetheless, if longer wavelengths are

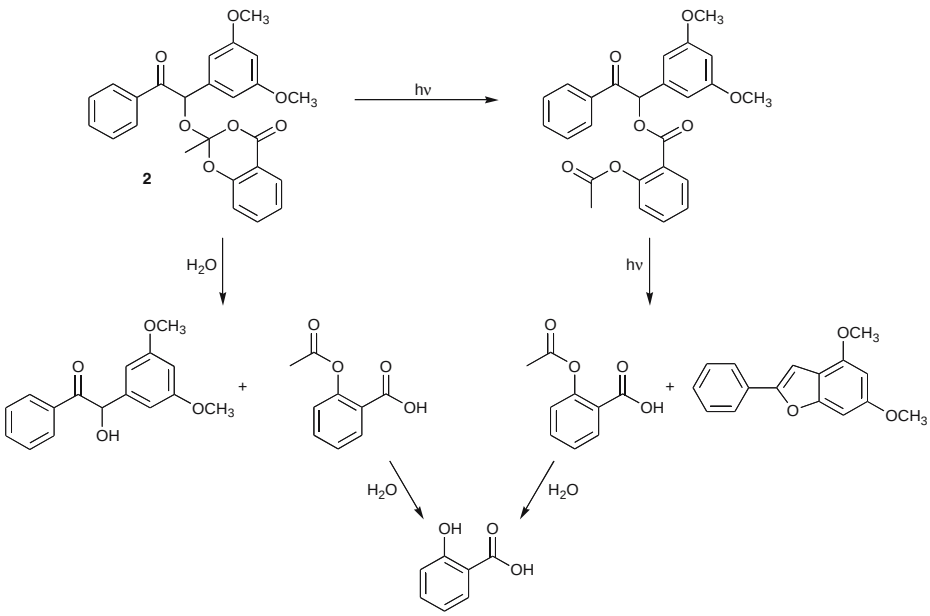

Fig. 6. Scheme showing steps in independent production of acetyl salicylic acid from 2 by photochemical and hydrolytic routes.

required using this paradigm, for example for light-triggered drug release from a sub-cutaneous implant, non-damaging wavelengths of light (>400 nm) which can give millimetre-scale penetration through skin, could be used for the 3,5-dimethoxybenzoin chromophore, with only a small reduction in quantum yield (and hence kinetic rate of drug liberation) compared to the currently-described system. This is based on the fact that absorbance of this chromophore is similar at 365 and 400 nm.

The hydrolytic behaviour of related 1,4-benzodioxinones of acetyl salicylic acid has been reported previously (29,30,32) and it was therefore expected that the hydrolysis of **2** would yield acetyl salicylic acid, as in the photochemical route of liberation (which can subsequently hydrolyze to salicylic acid), and 3,5-dimethoxybenzoin. Hydrolysis was monitored via UV-visible spectroscopy using a 1.5×10^{-4} moldm^{-3} solution of **2** in 3:2 (v/v) acetonitrile:water. At pH 7.7 no spectral changes were observed over 1 month, indicating that **2** is stable in neutral conditions. At pH 5.5 hydrolysis of a solution of the same concentration was shown to proceed and was quantitated via UV-visible spectroscopy. Overlaid absorption spectra at various times after dissolution are shown in Fig. 5. The progress of the hydrolysis is accompanied by a hyperchromic shift in absorbance at 295 nm, associated with the generation of salicylic acid (λ_{max} = 301 nm in this solvent mixture) and 3,5-dimethoxybenzoin (λ_{max} = 291 nm in this solvent mixture). At this pH the production of acetyl salicylic acid, not salicylic acid, is the rate determining step (29,30,32); the rate of breakdown of acetyl salicylic acid to salicylic acid is rapid relative to the hydrolysis of **2**; from the absorbance data the rate of acetyl salicylic acid production was first order in **2** with a rate of 1.89×10^{-3} s^{-1}, which, importantly, is approximately 44 times slower than the photolysis reaction. The final products of the reaction were confirmed to be 3,5-dimethoxybenzoin and salicylic acid by preparative thin layer chromatography using chloroform as eluant and subsequent ^{1}H NMR analysis. Hydrolysis of this type is catalysed by both acid and base (30), therefore small deviations from neutral pH can act as a trigger for drug liberation through hydrolysis in this system.

The results from photochemical and hydrolytic studies show that both routes lead independently to the production of acetyl salicylic acid from **2**. The respective pathways are summarized in Fig. 6. It is noteworthy that mild hydrolytic conditions can be employed for the 1,4-benzodioxinone derivative **2**, as simple esters of 3,5-dimethoxybenzoin, including the simple acetyl salicoyl ester, are resistant to hydrolysis as described above, due to the steric hindrance to nucleophilic attack which such systems show. This is relevant, for example, in catheter-associated urinary tract infection, where urease-producing bacteria raise urinary pH above neutral during infection (34). Infection could therefore act as a sensitive trigger to drug liberation for urinary catheter coatings using a system based on this concept. This could potentially operate in tandem with the second, optical trigger to drug liberation, which, as discussed above, could be easily applied via an external fibre optic light source.

From these results, the liberation of drug via the photochemical route is extremely rapid compared to the hydrolysis route and **2** therefore represents a prodrug of acetyl salicylic acid which can be converted with a high degree of control in response to either a chemical or photochemical stimulus. In particular, the photochemical stimulus can be delivered with a high degree of spatial and temporal control. The rapid rate of the subsequent photochemical reaction makes this route useful as a remote method of pulsatile delivery (35). The model system **2** therefore represents an important new class of compound which can be potentially used in triggered drug delivery.

In summary, the study demonstrates a paradigm for dual mode chemical and optical drug release from a suitable prodrug, where the trigger to drug liberation can be either rapid or slow. The sustained release via relatively slow hydrolysis and triggered, rapid release via photolysis of drugs which we demonstrate is highly relevant to the infection of medical devices. Slow, sustained release of an antimicrobial can be used for prophylaxis of infection (36), or at its onset, but the ability to deliver a large dose rapidly (via photolysis through application of an external light source in this instance) is highly advantageous if bacterial colonisation of the device surface (and hence infection) begins.

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REFERENCES

1. K. Park (ed.). *Controlled Drug Delivery. Challenges and Strategies*, ACS, Washington, D.C., 1997.
2. D. D. Breimer. Future challenges for drug delivery. *J. Control. Release* **62**:3–6 (1999).
3. J. C. Sheehan and R. M. Wilson. Photolysis of desyl compounds. A new photolytic cyclisation. *J. Am. Chem. Soc.* **86**:5277–5281 (1964).
4. J. C. Sheehan, R. M. Wilson, and A. W. Oxford. The photolysis of methoxy-substituted benzoin esters. A photosensitive protecting group for carboxylic acids. *J. Am. Chem. Soc.* **93**:7222–7228 (1971).
5. M. C. Pirrung and C. Huang. Photochemical deprotection of 3,5-dimethoxybenzoin (DMB) carbamates derived from secondary amines. *Tetrahedron Lett.* **36**:5883–5884 (1994).
6. J. F. Cameron, C. G. Willson, and J. M. J. Fréchet. Photogeneration of amines from α-keto carbamates: photochemical studies. *J. Am. Chem. Soc.* **118**:12925–12937 (1996).
7. M. Cano, M. Ladlow, and S. Balasubramanian. Studies on the chemical stability and functional group compatibility of the benzoin photolabile safety-catch linker using an analytical construct. *J. Com. Chem.* **4**:44–48 (2002).
8. H. B. Lee and S. Balasubramanian. Studies on dithiane-protected benzoin photolabile safety catch linker for solid-phase synthesis. *J. Org. Chem.* **64**:3454 (1999).
9. Y. Shi, J. E. T. Corrie, and P. Wan. Mechanism of 3′,5′-dimethoxybenzoin ester photochemistry: heterolytic cleavage intramolecularly assisted by the dimethoxybenzene ring is the primary photochemical step. *J. Org. Chem.* **62**:8278–8279 (1997).
10. V. N. R. Pillai. Photoremovable protecting groups in organic synthesis. *Synthesis* 1–27 (1980).
11. C. Rooney, G. Hayes, and C. P. McCoy. Photolytic release of ibuprofen from a 3,5-dimethoxybenzoin ester within a p(HEMA-co-MMA) polymer matrix. *J. Pharm. Pharmacol.* **55**:S43 (2003).

12. J. L. West. Drug delivery—pulsed polymers. *Nature Mater.* **2**:709–710 (2003).
13. S. R. Sershen, G. A. Mensing, M. Ng, N. J. Halas, D. J. Beebe, and J. L. West. Independent optical control of microfluidic valves formed from optomechanically responsive nanocomposite hydrogels. *Adv. Mater.* **17**:1366 (2005).
14. E. R. Gillies and J. M. J. Fréchet. Development of acid-sensitive copolymer micelles for drug delivery. *Pure Appl. Chem.* **76**:1295–1307 (2004).
15. G. A. Husseini, G. D. Myrup, W. G. Pitt, D. A. Christensen, and N. A. Y. Rapoport. Factors affecting acoustically triggered release of drugs from polymeric micelles. *J. Control. Release* **69**:43–52 (2000).
16. M. Babincova, P. Sourivong, D. Chorvat, and P. Babinec. Laser triggered drug release from magnetoliposomes. *J. Magn. Magn. Mater.* **194**:163–166 (1999).
17. S. K. Li and A. D'Emanuele. On-off transport through a thermoresponsive hydrogel composite membrane. *J. Control. Release* **75**:55–67 (2001).
18. G. Kong, G. Anyarambhatla, W. P. Petros, R. D. Braun, O. M. Colvin, D. Needham, and M. W. Dewhirst. Efficacy of liposomes and hyperthermia in a human tumor xenograft model: importance of triggered drug release. *Cancer Res.* **60**:6950–6957 (2000).
19. T. J. Dougherty, C. J. Gomer, B. W. Henderson, G. Jori, D. Kessel, M. Korbelik, J. Moan, and Q. Peng. Photodynamic therapy. *J. Nat. Cancer Inst.* **90**:889–905 (1998).
20. W. A. Denny. Prodrug strategies in cancer therapy. *Eur. J. Med. Chem.* **36**:577–595 (2001).
21. I. Kalčić, B. Zorc, and I. Butula. Macromolecular prodrugs.7. Polymer–dopamine conjugates. *Int. J. Pharm.* **136**:31–36 (1996).
22. J. F. Gilmer, L. M. Moriarty, M. N. Lally, and J. M. Clancy. Isosorbide-based aspirin prodrugs II. Hydrolysis kinetics of isosorbide diaspirinate. *Eur. J. Pharm. Sci.* **16**:297–304 (2002).
23. G. Jones. Decreased toxicity and adverse reactions via prodrugs. In H. Bundgaard (ed.), *Design of Prodrugs*, Elsevier, Amsterdam, 1985, pp. 199–233.
24. G. Paris, D. L. Garmaise, D. G. Cimon, L. Swett, G. W. Carter, and P. Young. Glycerides as prodrugs .2. 1,3-Dialkanoyl-2-(2-methyl-4-oxo-1,3-benzodioxan-2-yl)glycerides (cyclic aspirin triglycerides) as anti-inflammatory agents. *J. Med. Chem.* **23**:79–82 (1980).
25. T. Loftsson and N. Bodor. Improved delivery through biological-membranes .10. Percutaneous absorption and metabolism of methylsulfinylmethyl 2-acetoxybenzoate and related aspirin prodrugs. *J. Pharm. Sci.* **70**:756–758 (1981).
26. SAINT-NT. *Program for Data Collection and Data Reduction*, Bruker-AXS, Madison, WI, 1998.
27. G. M. Sheldrick. *SHELXTL Version 5.0, A System for Structure Solution and Refinement*, Bruker-AXS, Madison, WI, 1998.
28. C. Rüchardt and S. Rochlitz. Ambivalent reactivity of *o*-acetylsalicyloyl chloride. *Justus Liebigs Ann. Chem.* **1**:15–23 (1974).
29. M. Ankersen, K. Nielsen, and A. Senning. Synthesis, properties and prodrug potential of 2-methyl-2-oxy-4H-1,3-benzodioxin-4-ones and 2-methyl-2-thio-4H-1,3-benzodioxin-4-ones. *Acta Chem. Scand.* **43**:213–221 (1989).
30. M. Ankersen and A. Senning. Aspirin prodrugs—synthesis and hydrolysis of 2-benzyloxy-2-methyl-4H-1,3-benzodioxin-4-ones. *Acta Chem. Scand.* **43**:793–798 (1989).
31. J. E. Jørgensen and A. B. Hansen. Structure and conformation of 2-methyl-2-(2-naphthyloxy)-4H-1,3 benzodioxin-4-one. *Acta Crystallogr., B Struct. Sci.* **38**:991–993 (1982).
32. K. K. Nielsen and A. Senning. Aspirin prodrugs—synthesis of 2-substituted 2-methyl-4H-1,3-benzodioxin-4-ones and their screening for prodrug potential. *Acta Chem. Scand.* **44**:952–956 (1990).
33. M. R. Diaz-Mondéjar and M. A. Miranda. Photolysis of 2-aryloxy-1,3-benzodioxan-4-ones or 2-arylthio-1,3-benzodioxan-4-ones. *Heterocycles* **22**:1125–1131 (1984).
34. H. L. T. Mobley and J. W. Warren. Urease-positive bacteriuria and obstruction of long-term urinary catheters. *J. Clin. Microbiol.* **25**:2216–2217 (1987).
35. J. Kost and R. Langer. Responsive polymer systems for controlled delivery of therapeutics. *Trends Biotechnol.* **10**:127–131 (1992).
36. R. O. Darouiche, I. M. Raad, S. O. Heard, J. I. Thornby, O. C. Wenker, A. Gabrielli, J. Berg, N. Khardori, H. Hanna, R. Hachem, R. L. Harris and G. Mayhall. A comparison of two antimicrobial-impregnated central venous catheters. *New Eng. J. Med.* **340**:1–8 (1999).