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Formation and reactivity of free radicals in 5-hydroxymethyl-2-furaldehyde – the effect on isoprenaline photostability

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Abstract

Solutions of glucose are used as diluents for drugs in various drug infusions. When sterilized by heat small amounts of the substance 5-hydroxymethyl-2-furaldehyde (5-HMF) is produced from glucose. At a hospital ward such infusions may be exposed to irradiation; including UV-light. The photoreactivity of the furaldehyde is investigated. It is shown to photodestabilize the catecholamine isoprenaline. It is shown to be a producer, but also a consumer, of singlet oxygen. The excited triplet, cation and anion radical have been produced by pulse radiolysis and flash photolysis and their absorbance characteristics have been determined. The triplet absorption spectrum showed absorption bands at 320 and 430 nm with molar absorption coefficients of 4700 and 2600 $M^{-1} cm^{-1}$, respectively. The anion radical showed absorption bands at 330 and 420 nm with molar absorption coefficients of 2000 and 300 $M^{-1} cm^{-1}$, respectively. The cation radical had an absorption band at 320 nm with a molar absorption coefficient of 5000 $M^{-1} cm^{-1}$. The quantum yield for the production of singlet oxygen, sensitized by the 5-HMF triplet, was determined to be 0.6, whilst the quantum yield for the triplet formation was 1.0. Aqueous solutions of 5-HMF were found to photoionize to yield the hydrated electron and the cation radical of 5-HMF in a biphotonic process. The influences of pH, buffer and glucose on the formation of transients were evaluated. The reactions between 5-HMF and the solvated electron, the hydroxyl radical and the superoxide were also studied.
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1. Introduction

In a previous study the photostability of several different catecholamines was tested in different infusion media by exposure to radiation above 310 nm [1]. The study indicated that the catecholamines were destabilized by irradiation when the medium was the glucose infusion solution. However, glucose itself does not absorb light above 310 nm. This leads one to suspect that a degradation product is responsible for the destabilizing effect.

Glucose infusion solutions are commonly used vehicles for administering a variety of drugs [2]. During the production of the glucose infusion solution it is sterilized by heat and steam. In this process it has previously been shown that a degradation product is formed. This product has been identified as the furan derivative 5-hydroxymethyl-2-furaldehyde (5-HMF) [3,4]. While the absorption maximum of 5-HMF occurs at 285 nm, the absorption extends to above 340 nm, well within the range of UVR that can penetrate window glass. As the

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infusion solution is used in the hospital setting, light can interact with 5-HMF and possibly cause unwanted reactions to occur.

The aim of this study is to establish the photoreactivity of the furaldehyde and to establish whether 5-HMF is responsible for the photosensitized degradation of catecholamines in glucose infusion solutions.

2. Materials and methods

2.1. Chemicals

5-Hydroxymethyl-2-furaldehyde (purity >99%), isoprenaline, superoxide dismutase (SOD) from bovine erythrocytes, perinaphthenone, sodium azide, sodium bromide, sodium persulfate, benzophenone and 1-octanesulfonic acid were supplied by Sigma–Aldrich Chemie GmbH, Steinheim, Germany. Xanthone was supplied by Sigma, Steinheim, Germany, and recrystallized from ethanol. L-Histidine was supplied by Sigma Chemical company, St. Louis, MO, USA. *t*-Butyl alcohol (puriss p.a.) was supplied by Fluka AG, Switzerland. Potassium dihydrogen phosphate (p.a.) was purchased from Merck, Darmstadt, Germany. Methanol and acetonitrile were supplied by Prolabo, France. Glucose was supplied by Norsk Medisinal Depot, Oslo, Norway. Glucose infusion solutions (50 mg/ml) were obtained from Fresenius Kabi Uppsala, Sweden (Excel™) and Braun, Melsungen, Germany. Deuterium oxide (D_2O) was supplied by Euriso-top, Gif-sur-Yvette, France.

2.2. Quantification by HPLC

The method for quantification of isoprenaline has been described in a previous work [1]. The method for quantification of 5-hydroxymethyl-2-furaldehyde used at Nova-Pak® C-18, 3.9 × 15 cm column from Waters, USA. The mobile phase was composed of 2% methanol and 1% acetonitrile in 5 mM KH_2PO_4. The flow rate was set to 1.3 ml/min using a Shimadzu LC-9A pump. The furaldehyde was detected at 285 nm (Shimadzu UV–Vis Detector SPD-10A). The samples (20 μl) were injected using a Shimadzu autoinjector SIL-9A. Data acquisition was completed using a Shimadzu C-R3A integrator. The approximate retention time for the substance was 4.5 min.

For validation of the linearity of the analytical method 12 samples of 5-hydroxymethyl-2-furaldehyde (21.5 ng/ml–43 μg/ml) were quantified ($n = 2$). The *linearity* r^2 was found to be $r^2 > 0.99$. The limit of quantification was estimated to be 5 ng/ml. The detection limit was estimated to be 1 ng/ml. The samples of 5-HMF were found to be stable for 24 h under ambient conditions in the dark.

2.3. Irradiation conditions

Photodegradation studies were performed in a Suntest CPS, Heraeus GmbH, Hanau, Germany. The Suntest was equipped with a 1.8 kW xenon lamp with an effect of 765 W/m^2 (310–800 nm). The samples in the Suntest were irradiated in polypropylene test tubes (KEBO Lab, Oslo, Norway) unless specified otherwise.

2.4. Formation of singlet oxygen under monochromatic conditions

Exposure to monochromatic radiation was obtained by use of a Monochromator *f* 3.4, 900 W xenon arc lamp (Applied Photophysics Ltd., Surrey, England), operated with a bandwidth of ±10 nm at the irradiation wavelength (340 nm). The intensity of the radiation was adjusted to 70 mW/cm^2 at the surface of the samples using a Thermophile voltmeter (Applied Photophysics Ltd.). Irradiation was performed in a quartz container under continuous stirring. Solutions of 5-HMF, 70 μg/ml, were irradiated for one hour. This was carried out in the presence or absence of the radical scavenger histidine 2.58 mg/ml. The consumption of oxygen was followed using a Dissolved Oxygen Hand-Held Meter, Oxi 340, and a Dissolved Oxygen Probe CellOx325, both provided by WTW GmbH, Weilheim, Germany.

2.5. Effect of 5-hydroxymethyl-2-furaldehyde on the photostability of isoprenaline

Solutions of isoprenaline, 2 μg/ml, were prepared in 5 mM phosphate buffer (pH 4.4) containing 4.5 μM EDTA. To these solutions either 1.8, 3.5, 8.0, 16.0 or 22.6 μg/ml of 5-HMF was added. The samples were irradiated in the Suntest CPS. Samples were withdrawn at 30, 60, 90, 120 and 180 min ($n = 3$). The amount of isoprenaline remaining was quantified by HPLC.

Solutions containing isoprenaline 2 μg/ml, 4.5 μM EDTA and 3.5 μg/ml 5-HMF in 5 mM phosphate buffer (pH 4.4) were also made. To such solutions two different radical scavengers (*t*-butanol (0.1 and 1 μl/ml) and SOD (30 and 300 U/ml)) were added. Solutions without radical scavengers and dark control samples were included in the study. The solutions (10 ml, $n = 3$) were irradiated in the Suntest CPS. Samples were withdrawn at 30, 60, 120 and 180 min. The amount of isoprenaline remaining was quantified by use of HPLC.

The content of 5-HMF in two commercially available glucose (50 mg/ml) infusion solutions was also determined by HPLC.

The effect of glucose on the photostability of isoprenaline was investigated. Solutions of isoprenaline (2 μg/ml) in 5 mM phosphate buffer (pH 4.4) containing 4.5 μM EDTA and 7 μg/ml 5-HMF with (50 mg/ml)

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