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Commercial pharmaceutical glass containers as probes for the post-sterilization dosimetry of liquid drugs

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HIGHLIGHTS

- TL and OSL of glass containers of liquid drugs are explored towards the post-sterilization dosimetry.
- OSL and TL dose response can be fitted with linear functions for doses up to 30 kGy.
- Presence of VDT is evident in both glass containers studied with linear responses for doses up to 30 kGy.
- No saturation of the traps involved (even the VDT) is observed for doses up to 25 kGy.
- Estimation of the sterilization dose in liquid drugs seems feasible with TL or OSL of the containers.

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ABSTRACT

Drug sterilization with ionizing radiation is a well-established technology, which is gaining ground the last decades since it allows the adequate sterilization of heat-sensitive pharmaceutical preparations. In a previous study (Kazakis et al., 2015a), the possibility to identify irradiated **liquid-state** drugs by means of TL measurements on their glass containers was explored with very promising findings.

The present work constitutes a continuation and extension of the previous work, employing additional TL measurements, along with new OSL measurements, on the same glass containers of two widely used liquid drugs, (Hexalen® and Voltaren®), for beta-doses up to 30 kGy, while an investigation of the presence of very deep traps (VDT), i.e., traps with their peak maximum temperature beyond the 500 °C, also took place.

Results indicate that dose estimation, after the ionizing sterilization of a liquid drug, using the glass containers is possible in many ways. Both direct OSL and TL dose response can be fitted with a linear function for doses up to 6 kGy and 14 kGy for Hexalen and Voltaren respectively. For higher doses, up to 30 kGy, the intensity continues to increase, though in a lower rate, and the response can be fitted with a linear function as well, indicating that no saturation is reached. Presence of VDT is evident in both glasses with their thermally assisted OSL (TA-OSL) and subsequent photo-transferred residual TL (RTL) dose response exhibiting linear behavior in two distinctive dose areas. In any case, no saturation of the VDT is observed for doses up to 25 kGy. The above is very important, since it would allow the estimation of the sterilization dose even if the glass container has been exposed to light or heated to temperatures up to 500 °C.

Thus, all findings are very promising and support the idea of using the glass containers of commercial liquid drugs as probes for the post-sterilization dosimetry of these drugs and for normal and/or accidental dosimetry.

1. Introduction

Sterilization with ionizing irradiation, mainly gamma radiation, is gaining ground the last decades and is being applied to several fields, such as foods and drugs. This sterilization method is ideal for

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heat-sensitive products (e.g. drugs), while its high penetrating power allows the sterilization of the products while being packed in their final package (Abuhanoglu and Ozer, 2010; Frohnsdorff, 1981; Silindir and Ozer, 2009).

Establishment of a method to identify irradiated drugs would be very interesting and useful for both the consumers and the manufacturers. The former would become aware of the potential degradation of the pharmaceutical preparation as a result of its exposure to ionizing radiation, while the latter would be able to evaluate in-situ the actual radiation dose absorbed by the products and confirm that it conforms to the minimum sterilization dose as dictated by the current legislation. It would also interest a government agency whose role would be to validate the sterilization process of the drug companies and to certify that drugs have indeed been sterilized with the minimum dose, which can actually be referred to as post-sterilization dosimetry.

To this respect, several studies have been conducted employing electron spin resonance (*ESR*) spectroscopy to detect irradiated **solid-state** drugs (e.g. Onori et al., 1996; Basly et al., 1997; Gibella et al., 2000; Raffi et al., 2002; Polat and Korkmaz, 2006; Juárez-Calderón et al., 2009; Aleksieva and Yordanov, 2012), while only a handful have been published using Thermoluminescence (e.g. Stocker et al., 1999; Raffi et al., 2002).

In a recent study, Kazakis et al. (2014) investigated the luminescent properties of five common commercial **solid** drugs by means of Optically Stimulated Luminescence (*OSL*) and Thermoluminescence (*TL*) with very promising findings towards the post-sterilization dosimetry of solid drugs. More recently, Kazakis et al. (2015a) studied the thermoluminescence behavior of two commercial liquid-drug **glass** containers, since they are equally and jointly exposed to the ionizing radiation during the sterilization process, in an effort to extend the use of the above methods (TL and OSL) to the post-sterilization dosimetry of **liquid-state** drugs as well. Both glass containers exhibited a linear TL dose response for beta-doses up to 6 kGy, with a stable behavior through time, while no significant sensitization of the main peaks was observed. In addition, results were also indicating the presence of very deep traps (VDT), i.e., traps which correspond to TL glow peak with their peak maximum temperature beyond the 500 °C, in both containers. Thus, preliminary results were encouraging supporting the adequacy of drugs' glass containers as appropriate probes for the post-sterilization dosimetry of commercial liquid drugs.

In this respect, the present work is an extension of the previous study of Kazakis et al. (2015a), in order to shed light on its findings and to explore further attributes of the glass containers. For this purpose, both OSL and TL are used, while higher beta-doses, up to 30 kGy, are also applied, towards the suitability of commercial pharmaceutical glass containers for normal and/or accidental dosimetry and for the post-sterilization dosimetry of liquid drugs, i.e., in order to be further employed as a direct indicator of the dose absorbed by the liquid preparation.

2. Experimental procedure

2.1. Drug selection and sample preparation

The glass containers studied were the same with those of the previous work (Kazakis et al., 2015a), namely Hexalen® bottle and Voltaren® ampoules. All drugs were supplied from a pharmacy in sealed boxes and before their expiration date as suggested by the manufacturer. Please note, from here on, unless otherwise stated, the terms Hexalen and Voltaren refer to the respective glass containers rather than the pharmaceutical substance.

More details about the selection of the drugs, the cleaning of the glass containers and the preparation of the samples can be found in Kazakis et al. (2015a). Glass grains of size 75–150 μm were selected for the TL and OSL measurements.

2.2. Instruments and methods

For the TL and OSL measurements a Riso TL/OSL reader (model TL/OSL-DA-15) was used, equipped with a $^{90}Sr/^{90}Y$ beta particle source capable of delivering a nominal dose rate of about 3.56 Gy/min at the time of the measurements. The system is also equipped with blue LEDs emitting at 470 nm arranged in six clusters each containing seven individual LEDs (maximum total power ~40 mW/cm^2 at the sample) (Botter-Jensen et al., 2000). A 9235QA photomultiplier tube, combined with a Hoya U-340 and a heat absorbing Pilkington HA-3 filters, was used for light detection.

All TL measurements were performed in a nitrogen atmosphere with a low constant heating rate of 2 °C/s up to a maximum temperature of 500 °C/s, except for the case of the VDT study (heating up to 620 °C). In addition, in all Continuous Wave Blue OSL measurements (CW-BSL hereafter) the stimulation time was 1500 s, while the power of the blue LEDs was kept constant at 85% of its maximum. It must also be noted that in all cases a background signal was also acquired, which was subsequently subtracted from the original signal of the main measurement for the various dose response calculations.

In all cases, **multiple** aliquots were used with the mass of the measured sample at about 10.0 mg. It should be noted that all sample carriers (cups) were first cleaned with the method suggested by Kazakis et al. (2015b) in order to ensure that the acquired sample signal is free of any spurious and/or contamination signals originating from the empty sample carriers, since high doses are applied in the present study.

In order to ensure the repeatability of the results, several measurements were conducted in two different samples for each glass container. In the present study, **beta**-doses from 50 up to 30,000 Gy were applied, which is considered more than adequate in the frame of the post-sterilization dosimetry of pharmaceuticals with ionizing radiation, since in most cases the required dose for pharmaceutical products varies between 1 and 25 kGy of **received gamma**-dose depending on the nature of the product (e.g. Abuhanoglu and Ozer, 2010; Frohnsdorff, 1981).

3. Results and discussion

3.1. CW-BSL dose response

In order to investigate the CW-BSL dose response of the glass containers the following protocol was adopted for various beta-doses and different aliquots:

It should be noted that, in Step 3, the 140 °C was selected for the pre-heat of the samples, based on the TL glow curves acquired in the previous study (Kazakis et al., 2015a) in order to empty all traps that correspond to the first peak (center temperature ~90 °C) in both glass containers. In the same respect, the CW-BSL at Step 5 was acquired at 100 °C, in order to avoid any recuperation and to keep the shallow traps empty, dealing only with the medium-deep and deep traps.

It should be noted that Steps 7 and 8 are required in order to thoroughly investigate and actually prove the presence of VDT, while the role of Step 6 is twofold, since it records the residual TL signal after the CW-BSL, while at the same time it empties all traps up to 500 °C, which is a prerequisite in order to study the VDT in Steps 7 and 8. In the previous study of the glass containers (Kazakis et al., 2015a) the presence of the VDT was only deduced by the **residual** TL response above ~350 °C, which exhibited a dose-dependent behavior. For this purpose, since OSL measurements