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Technical note

Light protection of chemotherapy drugs for infusion

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ABSTRACT

Specific chemotherapy drugs which require to be delivered by continuous infusion over time can have their effectiveness impaired by exposure to optical radiation. Mechanisms and processes of drug preparation and patient administration associated with light sensitive drugs were monitored within a Chemotherapy Unit. Levels of ambient light at locations of drug preparation/administration and levels of protection afforded by optical filter elements such as infusion lines were determined using a double grating Bentham Dmc150 spectroradiometer. Models of light exposure were developed for separate components of drug preparation and infusion delivery systems where the latter included the fluid bag with protective light cover, drip chamber and giving set line. In addition, the attenuation coefficient of Dacarbazine at the concentration typically used in patient treatments was determined using specially manufactured measurement cells. The relative contributions to light absorption of the drug bag, drip chamber and patient line were identified for specific types of giving sets, spectral content/intensity of light exposure and specific drug light absorption profiles. This indicated significant differences in the level of light protection afforded by specific giving sets and either single or double layer protection of the drug bag reservoir. It is not clear, however, if these variations could lead to significant differences of levels of drug de-activation and/or creation of undesirable photo-products such as in the case of Dacarbazine. Such techniques, however, provide a means of identifying how light exposure can be maintained at levels as low as reasonably possible as a precautionary measure.

1. Introduction

1.1. Background

It is generally acknowledged that while numerous injectable products are identified with 'protect from light' precautions, there is often a lack of clarity regarding safe levels of light exposure during their preparation and administration. It is generally assumed that sufficient care is undertaken with light exposure during the process of manufacturing, packaging and distribution to the end user and storage in the end user facility to ensure the viability and safety of photosensitive products prior to preparation and use in the clinical environment in accordance with guidance such as ICH Q1B [1]. Baertschi et al. [2] describe how the safe preparation and delivery of light sensitive products requires to be validated within the context of the mode of delivery of the specific pharmaceutical product. This assessment will relate, for example, to the length of time of preparation and delivery procedures and the corresponding levels of light exposure within specific clinical environments. Baertschi et al. [2] also provide a useful review of methods for determination of the stability of photosensitive pharmaceutical products and where, for example, test light spectra referenced within ICH Q1B [1] include D65 (outdoor sunlight simulation) [3] ID65 (sunlight filtered through window glass simulation) and cool white fluorescent lamps. In addition, reference is made to the range of illuminance targets in units of Lux for a range of tasks and applications. Baertschi et al. [2] also describe how the process of validation of safe preparation and administration of photosensitise drugs is significantly affected by the length of the in-use product period, the incident light intensity and any specific light protection measures employed – such as the use of a light protective bag or light protective intravenous tubing.

The process of validation described by Baertschi et al. [2] is essentially an empirical one, where the stability of a drug preparation being investigated is determined by assay after specific periods of exposure consistent with the drug delivery protocols and environmental conditions at the point of use. This method of testing could confirm, for example, that a specific product would be safe to administer within a treatment environment using cool white fluorescent illumination but that is would not be safe to deliver the product under conditions of intense indoor lighting or in an outdoor daylight setting.

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1.2. Scope of investigation

Investigation was undertaken of the routine preparation and administration of Dacarbazine within a Chemotherapy Unit with determination of levels of light exposure and effectiveness of optical filter components in the infusion delivery system. In this example, a measure of the relative effectiveness of light shielding was determination of the light energy absorbed by Dacarbazine. This allowed comparison of the relative effectiveness of specific types of light filters employed within specific giving sets for specific conditions of illumination.

There has been a long history of the awareness of the photodegradation of chemotherapy drugs such as Dacarbazine [4–6] and the requirement to minimise light exposure at all stages of drug preparation and administration. Subsequent investigation by Asahi et al. [7] has identified Diazo-IC as the photodegradation product of Dacarbazine which leads to pain at the infusion site.

While observations of the potential loss of clinical effectiveness of Dacarbazine with light exposure [8] involve detailed anti-tumour analysis, this is typically not matched by determination of the spectral content and intensity of optical exposure of samples of Dacarbazine. Also, while a detailed review of the photostability of a range of chemotherapy drugs by Benvenuto et al. [9] indicated that Dacarbazine demonstrated 10% or less change in concentration over 24 h, this did not reference in detail the intensity or spectral content of the light exposure. Also, El Aatmani et al. [10] observed stability of Dacarbazine in daylight for 2 h and for fluorescent light for up to 72 h, though again without detailed spectral analysis of light exposure.

1.3. Light exposure measurement

Light levels at the location of drug preparation were initially determined in the Pharmacy Unit, and also at locations of patient treatment within the Chemotherapy Unit. Dacarbazine was administered to patients using a specific infusion device (Plum A, Hospira Inc, Lake Forest, USA). An assessment was undertaken of the properties of optical filters provided to protect the bag contents and the drug within giving set lines, including the drip chamber. Determination of light levels at the location of drug delivery and characteristics of the optical filter components were undertaken using a double grating Bentham Dmc150 spectroradiometer (Bentham Instruments, Reading, UK) which incorporated a photomultiplier detector which undertook spectral measurements at 1 nm intervals in the range 250–800 nm. Light was collected using a cosine corrected D6 detection head (Bentham Instruments, Reading, UK) attached to a 2 m fibre optic cable.

1.4. Model for light exposure

A model for light exposure of chemotherapy drugs during preparation and patient delivery was developed for the involvement of the giving set bag with light protective cover, the drip chamber and the giving set line. A key determined parameter was identified as the energy absorbed by the drug solution from the incident light. Fig. 1 indicates specific elements of the model namely the drug bag, the drip chamber and the giving set line. The drug bag is considered as a rectangular solid with two flat surfaces defined by its length and width and the area of the perimeter of the bag proportional to the fluid thickness.

The rate of absorption of light energy within the bag in mW at time t, can be estimated as:

$$\mathrm{Bag}_{\mathrm{drug}}(t) = (2(\mathrm{blth}\,\mathrm{bwdth}) + 2(\mathrm{blth} + \mathrm{bwdth})d(t)) \times \sum s_{\mathrm{drug}}(\lambda, d(t))i(\lambda)\mathrm{tr\_bag\&cover}(\lambda) \quad (1)$$

where the bag length is blth and its width bwdth, $d(t)$ is the bag thickness at time t, $i(\lambda)$ is the incident irradiance of light (units mW m^{-2} nm^{-1}), $s_{\mathrm{drug}}(\lambda, d(t))$ is the fractional absorption of the drug

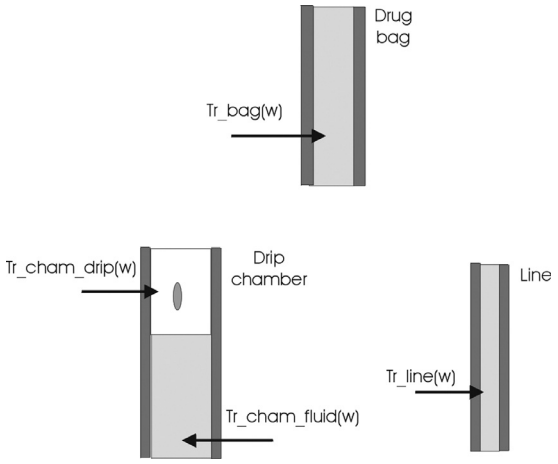

Fig. 1. Elements in model of optical filters used in the process of delivery of chemotherapy drugs: protective drug reservoir bag, drip chamber (upper section), drip chamber (lower section) and connecting line where in e.g. tr_bag(w). w is the wavelength of light.

at wavelength λ and for light path value $d(t)$ and tr_bag&cover(λ) is the transmission value of the bag and plastic filter at wavelength λ. The term $\sum s_{\mathrm{drug}}(\lambda, d(t))i(\lambda)$tr_bag&cover($\lambda$) is summed over the wavelength range 250–800 nm. For a specific drug delivery of 250 ml over a delivery time of 1 h and with the bag dimensions notionally 10 cm × 20 cm Eq. (1) becomes:

$$\mathrm{Bag}_{\mathrm{drug}}(t) = (0.04 + 0.6d(t)) \sum s_{\mathrm{drug}}(\lambda, d(t)) \times i(\lambda)\mathrm{tr\_bag\&cover}(\lambda) \quad (2)$$

where initially the bag is considered to have a uniform thickness of fluid of 12.5 mm.

For the drug line, the rate of absorption of light energy in mW at time t becomes:

$$\mathrm{Line}_{\mathrm{drug}}(t) = 2\pi\ \mathrm{rad\_line}\ \mathrm{length\_line} \sum s_{\mathrm{drug}}(\lambda, t1_{\mathrm{eff}}) \times i(\lambda)\mathrm{tr\_line}(\lambda) \quad (3)$$

where rad_line is the radius of the giving set line, length_line its length, tr_line(λ) is the fractional transmission value of the giving set line at wavelength λ and $s_{\mathrm{drug}}(\lambda, t1_{\mathrm{eff}})$ is the fractional absorption of the light in the giving set line for effective fluid path $t1_{\mathrm{eff}}$. As an approximation, the value of $t1_{\mathrm{eff}}$ is identified as the diameter of the bore of the giving set line.

Some form of optical filter may be present in the drip chamber to protect the standing fluid column and also falling drops of fluid within the chamber. For the component of drip chamber of free standing fluid at the base of the drip chamber, the rate of absorption of light energy in mW at time t can be estimated as:

$$\mathrm{Cham\_fluid}_{\mathrm{drug}}(t) = 2\pi\ \mathrm{rad\_cham}\ \mathrm{length\_cham} \sum s_{\mathrm{drug}}(\lambda, t2_{\mathrm{eff}}) \times i(\lambda)\mathrm{tr\_cham\_fluid}(\lambda) \quad (4)$$

where rad_cham is the radius of the chamber, length_cham is the fluid height in the chamber, tr_cham_fluid(λ) is the fractional transmission value of the drip chamber fluid section at wavelength λ and $s_{\mathrm{drug}}(\lambda, t2_{\mathrm{eff}})$ is the fractional absorption of light at wavelength λ and for effective path length $t2_{\mathrm{eff}}$ of fluid in the drip chamber. As an approximation, the value of $t2_{\mathrm{eff}}$ is identified as the diameter of the drip chamber. One of the giving sets evaluated (reference 'Lifecare 7000', Hospira Inc, Lake Forest, USA) has no specific optical filter in the drip chamber unit while the Braun Infusomat (UV-protect) (B. Braun, Melsungen, Germany) has a component filter in the upper drip chamber element where drips 'free fall' and also a separate filter material to protect the volume of fluid in the lower section of the