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Cumulative illuminometer and shelf life of drugs in daylight indoors

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Abstract

An instrument used for measuring cumulative illuminance via pulse counting method was introduced. Photodegradation of drugs in daylight and various lamplights was studied. The shelf life of drugs in daylight indoors was predicted with hydroxyprogesterone caproate injection as a model. The cumulative illuminance of unsteady daylight was measured with the patented pulse counting method in the experiment. The equivalent influences of light from different sources on the photostability of the model drug were observed. Results show that the daylight can be replaced by lamplight in photostability studies. The photodegradation of hydroxyprogesterone caproate injection obeys the zero order kinetics: $c = c_O - k(Et)$, and its shelf life in daylight indoors is about 1.1 years. © 1998 Elsevier Science B.V. All rights reserved.

Keywords: Cumulative illuminometer; Photostability; Daylight; Lamplight; Shelf life prediction; Hydroxyprogesterone caproate injection

1. Introduction

In drug stability studies and shelf life predictions, the influences of temperature and humidity are often considered; however, the influence of light is not. The prediction of shelf life of drugs according to their photostability has not been reported. Some drugs, such as hydroxyprogesterone caproate injection, are very unstable in light but quite stable at high temperature. The shelf life of these drugs mainly depends on the illuminance of incident light. Therefore, it is necessary to look for a method to predict the shelf life of these drugs in daylight indoors.

The rate of photodegradation of drugs is closely related to the wavelength of the incident light. In some reported studies of photostability of

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drugs, different lamps were used as light sources; moreover, monochromatic light, obtained from light filter or grating, was also used in some cases (Akimoto et al., 1989; Matsuda et al., 1989; Sugimoto et al., 1981). Since lights from different lamps have different spectral distributions, the rates of photodegradation due to lamplight vary significantly (for hydroxyprogesterone caproate injection, the rate under a UV mercury-arc lamp is about 47 times greater than under an iodine-tungsten lamp); therefore, they cannot be compared with each other meaningfully, and none of them can express quantitatively the photostability and be used to predict the shelf life of drugs in daylight indoors.

In order to predict the shelf life of drugs in daylight indoors, it is important to use daylight as a light source and cumulate its illuminance. However, it is rather difficult to do so because of the unsteady illuminance of daylight. In 1988, Akimoto et al. (1988) studied the photostability of nifedipine and its derivatives in solution by actinometry (evaluating the cumulative illuminance of sunlight via the concentration measurement of the product yield by a known chemical photo-reaction). This method is too complicated to be generalized. In the 1990s, Zhan (1991) measured the cumulative illuminance of unsteady daylight with a patented pulse counting method and studied the photostability of vesnarinone in solid state (Zhan et al., 1995). This method is simple and accurate; however, the shelf life of the drug has not yet been found.

In the present paper, the cumulative illuminance of unsteady daylight was also measured with our pulse counting method (Zhan, 1991), and the photodegradation of hydroxyprogesterone caproate injection in stronger daylight outdoors was studied and the shelf life of the injection in weaker daylight indoors was predicted by kinetic studies. Furthermore, the equivalent influences of light from different sources on the photostability of the injection were studied. So it is indicated that the shelf life of the injection in daylight indoors can be studied via lamplight in the exposure experiment.

2. Experimental

2.1. Drugs and reagents

Hydroxyprogesterone caproate was received from the Pharmaceutical Factory of the West China University of Medical Sciences. It contains 99.1% of $C_{27}H_{40}O_4$. The injection (250 mg/ml) was prepared by our department. Ethyl alcohol, isoniazid, and hydrochloric acid were AR grade.

2.2. Instruments

A UV spectrophotometer (UV-240, Shimadzu Co., Japan), an illuminometer (ST-80C, Jangsu, China), and a self-made cumulative illuminometer (Zhan, 1991) were used.

2.3. Light sources and apparatus

Daylight (outdoors in sunny days in shadow), UV mercury-arc lamp (125 W), fluorescent mercury-arc lamp (125 W), iodine-tungsten lamp (1000 W), AC voltage regulator (1 kVA), and an exposure box (self-made, to hold the lamp and samples, black inside, the distance between the lamp and samples adjustable) were used.

2.4. Measurement of the cumulative illuminance of daylight

Since the illuminance of daylight is unsteady, it is impossible to obtain the cumulative illuminance (Et) simply as the product of illuminance E and exposure time t. Instead, the Et should be obtained by the integral $\int_0^t E\mathrm{d}t$. A patented self-made cumulative illuminometer was used to measure this integral.

The assembly of the cumulative illuminometer is shown in Fig. 1.

There is an ordinary illuminometer in the dashed frame in Fig. 1. A silicon photosensor is used to linearly convert the illuminance of the incident light to the voltage. The illuminance voltage is amplified by an amplifier. An A/D converter is used to convert the amplified illuminance voltage analog to digital, which is displayed as the illuminance by a liquid crystal display.

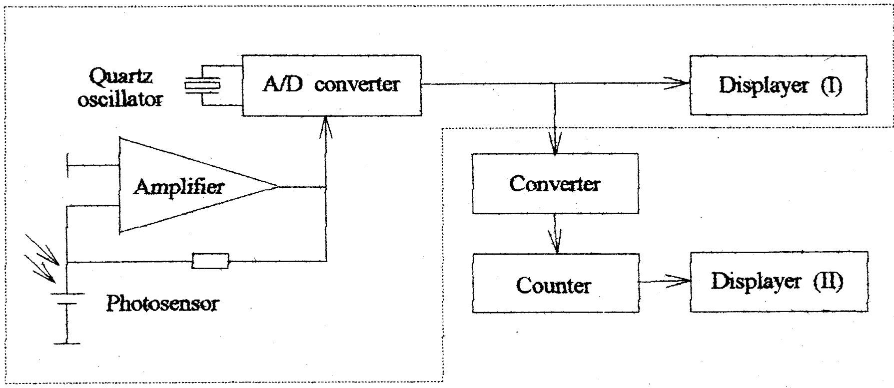

Fig. 1. The assembly of the cumulative illuminometer.

Outside the dashed frame in Fig. 1 is a specialty of the cumulative illuminometer. The digital number (illuminance) is taken out of the ordinary illuminometer by a converter and cumulated by a counter. The cumulated digital number is then displayed as the cumulative illuminance by another liquid crystal display.

For the cumulative illuminometer, the illuminance range is $0–200 \times 10^3$ lx with resolution rate 1/2000 and the accuracy 3%. The cumulative illuminance range is $0–10^{13}$ lx/s with resolution rate 10^{-8} and the accuracy 3%.

2.5. Exposure experiments

2.5.1. Exposure to daylight

The hydroxyprogesterone caproate injection (250 mg/ml) was sealed into 1 ml colorless ampoules. About 50 such ampoules and the photosensor were placed together outdoors in sunny days in shadow at the beginning of the experiment and the illuminance of incident light was cumulated by the cumulative illuminometer. Five ampoules were taken at each suitable interval and the concentration of the samples was measured by spectrophotometry (Chinese Pharmacopoeia, 1990).

2.5.2. Exposure to lamplight

About 50 ampoules were placed in the exposure box at a suitable distance from the lamp. The temperature of the sample was kept at $\leq 35°C$ (with an electric fan if necessary). The illuminance E was measured with the illuminometer in a place where the samples were placed and the cumulative illuminance (Et) was obtained as the product of illuminance E and exposure time t. Five ampoules were taken out of the exposure box at each suitable interval and the concentration of samples was measured with spectrophotometry.

3. Results

3.1. The photodegradation of hydroxyprogesterone caproate injection in light from various sources

The relationships between the cumulative illuminance and the relative concentration of hydroxyprogesterone caproate injection in daylight and lamplight are shown in Table 1 and Fig. 2, from which the photodegradation of hydroxyprogesterone caproate injection is known to obey zero-order kinetics:

$$c = c_0 - k(Et) \quad (1)$$

A straight line can be obtained from the plot of the relative concentration versus the cumulative illuminance. The intercept is c_0; and the slope equals to k. The regression parameters are shown in Table 2.

3.2. Prediction of the shelf life of drugs in daylight indoors

From Eq. (1) or the c–(Et) line in Fig. 2, the

Table 1
Relationship between the relative concentration of hydroxyprogesterone caproate injection and the cumulative illuminance

Daylight (6 klx ≤ E ≤ 18 klx)		UV mercury-arc lamp (E = 15.4 klx)		Fluorescent mercury-arc lamp (E = 10.7 klx)		Iodine-tungsten lamp (E = 23.3 klx)	
Et (klx·h)	c (%)	Et (klx·h)	c (%)	Et (klx·h)	c (%)	Et (klx·h)	c (%)
0	100 ± 0.1*	0	100 ± 0.1	0	100 ± 0.1	0	100 ± 0.1
150	96.6 ± 0.3	62	93.6 ± 0.2	257	91.9 ± 0.2	487	98.6 ± 0.2
300	92.6 ± 0.2	123	87.9 ± 0.2	514	82.5 ± 0.2	974	98.0 ± 0.2
463	88.5 ± 0.3	185	81.7 ± 0.3	770	73.7 ± 0.1	1462	96.4 ± 0.2
609	84.0 ± 0.3	246	72.5 ± 0.2	1027	66.0 ± 0.1	2436	94.3 ± 0.2
756	78.7 ± 0.3	308	70.5 ± 0.2	1351	53.3 ± 0.1	3410	91.5 ± 0.2
910	74.9 ± 0.2	370	639 ± 0.3	1541	49.5 ± 0.3	4385	90.4 ± 0.2
1053	71.4 ± 0.2					5359	88.1 ± 0.3
1210	69.1 ± 0.2					6334	85.7 ± 0.2
1354	65.6 ± 0.2					7308	85.5 ± 0.2
1507	60.8 ± 0.2						

*Mean ± S.D. of four experiments.

cumulative illuminance of daylight which is required to reduce the concentration of hydroxyprogesterone caproate injection to the prescription limit (relative concentration 90%) (Chinese Pharmacopoeia, 1990) can be obtained:

$$(Et)_{0.9} = (c_0 - c)/k = (1 - 0.9)/2.6 \times 10^{-7}$$
$$= 3.8 \times 105 \text{ lx} \cdot \text{h}$$

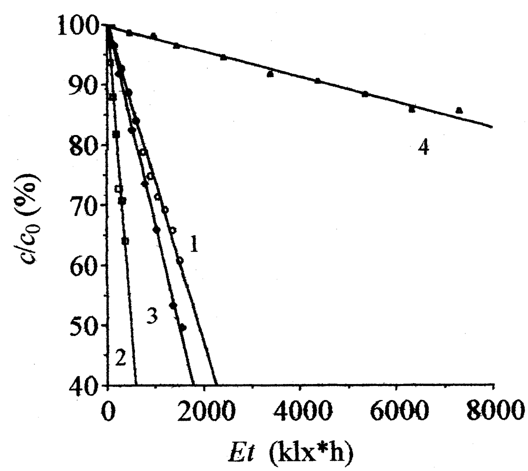

Fig. 2. Relationship between the relative concentration (c) of hydroxyprogesterone caproate injection and cumulative illuminance (Et) of daylight (1), UV mercury-arc lamplight (2), fluorescent mercury-arc lamplight (3), or iodine-tungsten lamplight (4).

From our experiment, the yearly cumulative illuminance of daylight, $(Et)_{\text{year}}$, is found to be about 3.5×10^5 lx·h in a room facing south in Chengdu. Thus, the shelf life of hydroxyprogesterone caproate injection in daylight indoors can be calculated. It is found to be about 1.1 years in our experiment.

$$t_{0.9} = (Et)_{0.9}/(Et)_{\text{year}} = 3.8 \times 10^5/3.5 \times 10^5$$
$$\approx 1.1 \text{ year}$$

3.3. The equivalent relationship between daylight and lamplights

When daylight is used as a light source, the exposure experiment will be affected by the changeable climate. However, lamplight has the advantages of stability and standardization. So it is best to use lamplight for the prediction of the shelf life of drugs in daylight. From the relationship between the photodegradation of hydroxyprogesterone caproate injection and cumulative illuminance of lights from different sources, the equivalent relationship of cumulative illuminance between lights from different sources, in which hydroxyprogesterone caproate injection is made to degrade to definite levels, is shown in Fig. 3 and can be expressed as:

Table 2
The linear regression parameters of the c–Et relationship of hydroxyprogesterone caproate injection

Light source	$k\times10^7$ (lx^{-1} h^{-1})	$c_{0,reg}/c_0$ (%)	r
Daylight	2.6	100.0	−0.9979
UV mercury-arc lamplight	9.8	99.6	−0.9950
Fluorescent mercury arc lamplight	3.4	100.0	−0.9991
Iodine-tungsten lamplight	0.21	99.6	−0.9939

$$(Et)_{Day} = (Et)_{Lamp} \cdot k_{Lamp}/k_{Day} \quad (2)$$

With this equivalent relationship and data from Table 2, we have:

$$(Et)_{Day} = 0.080 \cdot (Et)_{Iodine-tungsten}$$
$$= 1.3 \cdot (Et)_{Fluorescent} = 3.8 \cdot (Et)_{UV}$$

So, lamps can be used as light sources to predict the shelf life of hydroxyprogesterone caproate injection in daylight indoors.

Since radiance reaching the earth is very location-dependent, not only in terms of total illuminance but also in spectral distribution, a protocol should be carried out in each locality to establish the correlation constant relating the relative rates of reaction in each different locality with that in Chengdu.

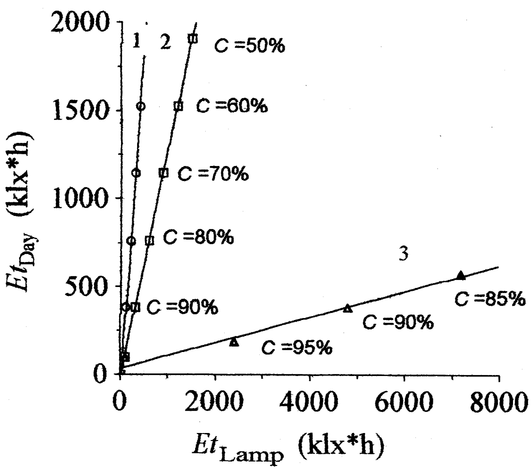

Fig. 3. The equivalent cumulative illuminance relationship between daylight and UV mercury-arc lamplight (1), fluorescent mercury-arc lamplight (2), or iodine-tungsten lamplight (3) on the photodegradation of hydroxyprogesterone caproate injection.

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