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PHOTOSTABILITY OF MECOBALAMIN IN TABLET AND CAPSULE AT THE DISPENSING LEVEL

(photostability/mecobalamin/solid dosage forms)

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Photostability of mecobalamin in solid dosage forms was investigated at dispensing level. Commercial products of one tablet and five capsules were used in packaged and bared conditions. The sample products were exposed to light for 20 days at 1500 lux. Assay was by high-performance liquid chromatography. The amount of mecobalamin in tablet and capsules decreased with lapse of photoirradiation time. Significant difference in the rate of photodegradation was observed between the capsule dosage forms, possibly due to light-transmission properties of capsule shells or plastic blister films. Mecobalamin in one tablet and two capsules was stable in both cases of packaged and bared, and there was no significant difference in mecobalamin remaining between packaged and bared samples.

Many pharmaceutical products are often susceptible to deterioration caused by light. Solid dosage forms such as tablets and capsules are photo-protected with a coating of sunscreening agents or an encapsulation into light-resistant capsule shells (1-3). Furthermore, these tablets and capsules are usually covered with light-resistant films to protect them from photochemical deterioration by a package system such as strip packs (SP) or press-through packs (PTP) (4). It is important that photosensitive drugs should be designed to maintain or enhance the stability of the active ingredient or other component(s) at the dispensing level and at the patient's level. The effects of storage in the dispensing package are usually not well defined since the stability testing of drugs is done at manufacturer's

level. Therefore, stability studies of each drug in the actual package in which it will be stored at hospital and at patients' levels must be performed.

Mecobalamin, widely used for treatment of peripheral nervous system disorders, is known to be affected by light (5,6). In our previous reports (7,8), pharmaceutical studies were performed to compare the quality of mecobalamin tablets with mecobalamin capsules available in Japan. In this study, photostability of mecobalamin in tablet and in capsule under dispensing conditions was assessed.

MATERIALS AND METHODS

Materials

The mecobalamin products used were one sugar-coated tablet containing 500μg of mecobalamin and five hard gelatin capsules containing 250μg of mecobalamin. Table I shows the characteristics of dosage forms and of packages for these products.

Table I. CHARACTERISTICS OF DOSAGE FORMS AND PACKAGES

Product	Dosage form (color)*	Package color**	Labeled amount (μg)
A	sugar coated tablet (white)	red	500
B	hard gelatin capsule (red/red)	red	250
C	hard gelatin capsule (red/red)	colorless	250
D	hard gelatin capsule (Pink/red)	red	250
E	hard gelatin capsule (pink/red)	red	250
F	hard gelatin capsule (pink/red)	red	250

* For capsule, color shows body/cap
** Color shows plastic blister film

Light expopsure test

The tablet and capsule covered with PTP (packaged sample) and removed from PTP (bared sample) were used in this test. The samples were placed in a box equipped with four fluorescent lamps (FLR, 20W, white) and exposed to light for 20 days. The distance between the light source and the samples was 90cm. The illumination on the surface of the samples was 1500±30 lux, as measured with an illuminometer.

Determination of mecobalamin

Remaining mecobalamin was determined by high-performance liquid chromatography (HPLC) after extraction by the following method. The tablet was crushed into powder. The milled tablet or the content of the capsule was transferred to a centrifuge tube and shaken with 5ml of distilled water. After centrifugation, 5μl of supernatant solution was subjected to HPLC. The HPLC conditions were as follows; column, Ncleosil NH_2(4.6mm i.d. × 15cm); mobile phase, 28% (v/v) 0.02M tartrate-phosphate buffer and 72% (v/v) acetonitrile; flow rate, 0.8ml/min; detector, ultraviolet 254nm. All the operations were carried out under red light in a dark room to protect the mecobalamin from photodegradation.

Table II. PERCENTAGE OF MECOBALAMIN REMAINING IN TABLET AND CAPSULES AFTER 20 DAYS EXPOSURE TO LIGHT

Product	Drug remaining (%)	
	Packaged	Bared
A	94.9	91.9
B	86.5	86.5
C	88.3	89.3
D	69.3	55.7
E	84.4	73.3
F	89.2	78.4

RESULTS

The results of stability studies are presented in Table II. After 20 days exposure to light, no significant difference in percent residue of mecobalamin was found between the packaged and the bared samples of Products A, B and C, and mecobalamin in either packaged or bared samples retained more than 85% of its initial drug content. However, a significant difference in mecobalamin remaining was observed between the packaged and the bared samples of Products D, E and F. Loss of mecobalamin was considerably greater in the bared samples.

The time-courses of degradation for mecobalamin in the packaged and in the bared samples are shown in Figs. 1 and 2, respectively. It should be noted that mecobalamin in solid dosage forms showed a biphasic decrease in the cases of both the packaged and the bared. The initial decrease was more rapid than

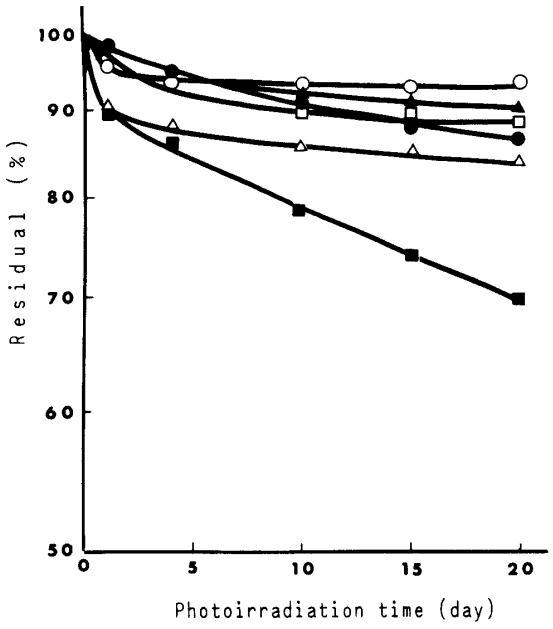

Fig.1. Photodegradation curve of mecobalamin in packaged tablet and capsules after irradiation with fluorescent lamp at 1500 lux.
○:A, ●:B, □:C, ■:D, △:E, ▲:F

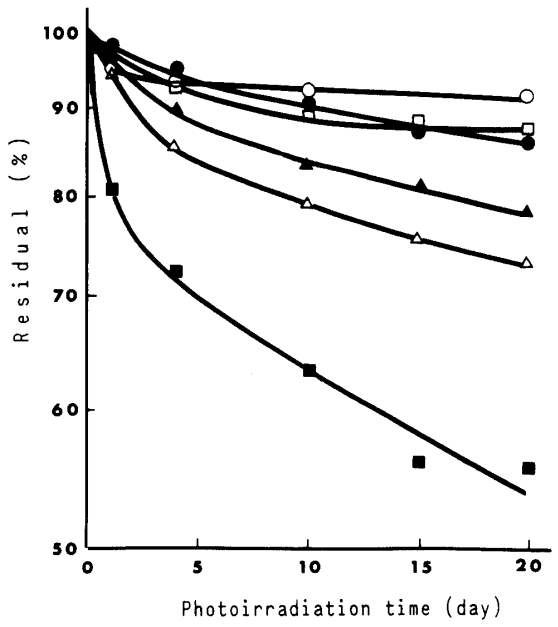

Fig.2. Photodegradation curve of mecobalamin in bared tablet and capsules after irradiation with fluorescent lamp at 1500 lux.
○:A, ●:B, □:C, ■:D, △:E, ▲:F

Table III. HALF-LIVES OF MECOBALAMIN IN TABLET AND CAPSULES AFTER PHOTOIRRADIATION AT 1500 LUX

Product	Half-life (days)	
	Packaged	Bared
A	675	521
B	154	127
C	273	267
D	44	24
E	177	67
F	283	95

the terminal decrease for both the packaged and the bared samples. The percentage of mecobalamin remaining (R) can be represented by the following equation

$$R=A\cdot e^{-k_1 t} + B\cdot e^{-k_2 t}$$

where k_1 and k_2 are degradation rate constants of the initial phase and the terminal phase, and t is duration of exposure to light. The theoretical half-lives of mecobalamin calculated for the packaged and the bared samples are shown in Table III. In the cases of both the packaged and the bared samples, large differences in half-life were observed among the products. Some products (Products A, B and C) showed a small difference in half-life between the packaged and the bared samples. On the other hand, there was a considerable difference in half-life between the packaged and the bared samples of Products D, E and F. The half-lives of these products in the bared samples were about 34-55% of those in the packaged samples.

The area under the photodegradation curve (AUPC) of mecobalamin after 20 days photoirradiation was calculated in order to make a more exact evaluation of mecobalamin stability in solid dosage forms. The result was expressed as percentages of the area that showed a complete stability for 20 days, and is shown in Table IV. The packaged samples of Products A, B and C were very stable and showed 90% or higher stability. The differences in stability between the packaged and the bared samples of these products were smaller than 1%. The packaged sample of Product F showed a 90% or higher stability when exposed to light, but the stability of Products D and E was less than 90%. The bared samples of Products D, E and F had a remarkably low degree of stability when exposed to light compared with the packaged samples, and their stability was 5-14% lower than the

Table IV. AREA UNDER PHOTODEGRADATION CURVE(AUPC) OF MECOBALAMIN IN TABLET AND CAPSULES AFTER 20 DAYS EXPOSURE TO LIGHT

Product	AUPC (%)	
	Packaged	Bared
A	93.7	93.0
B	91.8	91.3
C	91.2	90.8
D	79.7	65.4
E	86.8	81.6
F	92.8	85.5

packaged samples. In the bared samples, Products D, E and F were less stable than Products A, B and C.

DISCUSSION

Coating a tablet with light-resistant materials or encapsulation into light-resistant capsule shells were found to be useful for the stabilization of photosensitive pharmaceuticals (4,9). The coating of Product A and the capsule shells of Products B and C showed excellent light-resistant properties. It is considered that the dosage forms of Products A, B and C are designed to maintain or enhance the stability of the active ingredient. An apparent decline in mecobalamin stability was found in the bared samples of Products D, E and F. This result indicated that the capsule shells and the package films of these products are insufficient to protect mecobalamin from light. It is considered that the stability of mecobalamin in capsule dosage forms is associated not so much with the light-resistant properties of the package films as with those of the capsule shells.

In general, the solid oral dosage forms such as tablets and capsules were not only dispensed with SP or PTP, but also repackaged in other packaging materials which had no light-resistant properties after the original packages were removed for unit dose dispensing (10). Products repackaged at the dispensing level are stored for relatively short periods, but during that interval, the product can be exposed to harsh storage conditions in the hands of the patient. Therefore, it is necessary that a product should be stable after being removed from SP or PTP and after being repackaged in other films at the

dispensing level. On the basis of our observations, the stability of mecobalamin in one tablet and two capsule forms can be considered satisfactory.

For the stability evaluation of a drug, the half-life and the degradation rate constant are useful in cases where the drug shows a first-order degradation, but these do not provide sufficient criteria for a biphasic degradation profile. Special regard should be paid to the stability evaluation of drugs which showed a biphasic time-course change rather than a linear time-course change. In other words, it is necessary to take into account both the magnitude of change and the lapse of time for the purpose of predicting the stability of the active ingredient (10). In this respect, the area under the degradation curve can be regarded as one of the parameters for the evaluation of drug stability.

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