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Improvement of the photostability of ubidecarenone microcapsules by incorporating fat-soluble vitamins

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Summary

Ubidecarenone was microencapsulated together with one of the three fat-soluble vitamins, i.e. tocopherol, tocopherol acetate and phytonadione, by the spray-drying method to improve the photostability of ubidecarenone at ordinary and elevated temperatures under intensified ultraviolet irradiation. The irradiation apparatus consisted of a mercury vapor lamp and a grating monochromator with a xenon lamp. All microencapsulated ingredients underwent photolysis following apparent first-order degradation kinetics. The photolytic degradation of ubidecarenone was inhibited most markedly by the incorporation of phytonadione, but no satisfactory inhibition was obtained by tocopherol acetate. The degradation rate constant of ubidecarenone decreased rapidly with the increase in amount of phytonadione, whereas it did not decrease very much with increasing amounts of tocopherol. The competitive degradation effect where the more the percent degradation of vitamin was, the less was that of ubidecarenone was clearly confirmed in phytonadione system irrespective of irradiation wavelength. The inhibitory effects related closely to the photostability and light absorption properties of vitamins added. The protection of ubidecarenone from photolytic degradation could also be achieved at higher temperatures, but the activation energy was not affected significantly by the incorporation of any vitamin.

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Introduction

Ubidecarenone (2,3-dimethoxy-5-methyl-6-decaprenyl benzoquinone) is widely used in Japan in the treatment of angina pectoris in oral solid dosage form. The drug is, however, very photolabile in the solid state according to our quantitative study at ordinary and elevated temperatures with high intensity ultraviolet light (Matsuda and Masahara, 1983). The stability of its commercial preparations has also been evaluated under the irradiation of a fluorescent lamp from the view point of quality assurance (Ogawa et al., 1982; Hirayama et al., 1983). In those studies ubidecarenone was shown to undergo photolytic degradation with the production of several unknown degradation products.

Pharmaceutical preparations of such a photolabile drug have been adequately protected from photolytic degradation by the use of light-resistant package systems. Though these techniques are certainly among the satisfactory methods for photostabilization during the storage period in the storehouse of hospital pharmacies, there is still considerable possibility of exposure to harmful light once these preparations have been refilled in unit dose dispensing systems. Indeed, hospital pharmacists have called patients' attention to a decrease in the drug potency resulting from their careless handling. Therefore, extensive dispensing information is required to maintain the labeled potency of this drug. If possible, more rational design for photostabilization should be directed toward the dosage matrix itself. However, as far as we know, no quantitative study on the solid-state photodecomposition of a drug has been published except for our paper (Matsuda and Masahara, 1983). We have as yet little information on the improvement of physicochemical stability against light (Kaminski et al., 1979; Nyqvist and Nicklasson, 1982). Previously, we have shown that the coating of tablets with a polymer film containing ultraviolet absorber is an excellent method for protection from light (Matsuda et al., 1978).

The microencapsulation of ubidecarenone together with fat-soluble and photolabile vitamins by spray-drying may be another possible technique for photostabilization, because these vitamins, incorporated in microcapsules, are likely to play a useful role as a competitor or photostabilizer in photolytic degradation, similar to an antioxidant against autoxidation. In the present investigation the effect of addition of these vitamins on the photostability of microencapsulated ubidecarenone was examined under the same irradiation condition as that reported previously (Matsuda and Masahara, 1983).

Materials and Methods

Materials

Ubidecarenone used in this study was the same as that described in the previous report (Matsuda and Masahara, 1983). Tocopherol, tocopherol acetate and phytonadione used as photostabilizers were all Japanese Pharmacopeia (JP) grades. Hydroxypropylmethylcellulose (HPMC); (TC-5R, Shin-Etsu Chemicals, Japan) was used as a coating material.

Microencapsulation

Ubidecarenone, 86 mg (0.1 mM), and various amounts of tocopherol, tocopherol acetate or phytonadione in molar ratios ranging from 1 : 2 to 1 : 40 were dissolved in a mixture (1000 ml) of methylene chloride and methanol (9 : 1) then, given amounts of HPMC were added. To keep the content of ubidecarenone in the microcapsule constant (2.3% w/w), the amount of added HPMC was altered according to the difference between the fixed total weight (3.784 g) of the solutes and the weight of ubidecarenone plus vitamins.

The solution was fed into a mini-spray drier (Yamato Kagaku, Japan) through a peristaltic pump at a flow rate of 20 ml/min. The inlet temperature of the drying chamber was maintained at 35–50°C which was almost equal to or below the melting point (48°C) of ubidecarenone. The experiment was carried out in the dark. The yield of microcapsules was 35–45%. Each sample was stored at 0–4°C in an air-tight container in the dark.

Differential thermal analysis of microcapsules

The thermograms of intact ubidecarenone crystals, spray-dried HPMC, both ingredients mixed physically according to the formulation of microencapsulation, microcapsules containing ubidecarenone alone, and those containing both ubidecarenone and each vitamin in various molar ratios were recorded by a thermal analyzer (Model DTA-30, Shimadzu, Japan) in an open-pan system. Dried nitrogen gas was used as a carrier gas. The heating rate was 10°C/min and the DTA range was ± 5 μV.

Ultraviolet irradiation

The same irradiation apparatus, a 400 W mercury vapor lamp and a grating monochromator with a 5 kW xenon lamp, as those described in the previous paper (Matsuda and Masahara, 1983) were employed. In accelerated stability studies, microcapsules (exactly weighed to 5 mg) were spread on a quartz-glass plate as uniformly as possible, covered with another quartz-glass plate, and exposed to ultraviolet light. To examine the effect of irradiation wavelength on the photolytic degradation of each ingredient, 1 mg of the same sample was subjected to exposure to the light in the grating monochromator in the same manner as the stability studies. The photostability of microcapsules at elevated temperatures was also examined in the same thermostated jacket as used previously (Matsuda and Masahara, 1983)

HPLC analysis

A liquid chromatograph (Model LC-3A, Shimadzu, Japan) was used to detect microencapsulated phytonadione, tocopherol acetate and tocopherol at wavelengths of 275, 284 and 290 nm, respectively. A prepacked column (Chemcosorb 5-ODS-H, Chemco, Japan) was operated at 30°C and a flow rate of 0.6 ml/min. A 0.5% v/v solution of methylene chloride in methanol was used as a mobile phase. Ethanolic solutions of tocopherol acetate (2 mg/ml) and pyrene (10 μg/ml) were used as internal standard solutions for both phytonadione and tocopherol, and tocopherol

acetate, respectively. After irradiation, samples on the quartz-glass plate were washed several times with 10-ml portions of a mixed solvent of methylene chloride and methanol (1 : 1), 100 μl of the internal standard solution was added, and the mixed solution was evaporated to dryness under vacuum. The residue was dissolved in 2 ml of the above mixed solvent and 5 μl of this solution was injected by the on-flow technique to determine simultaneously ubidecarenone and each vitamin. The chromatograms for the samples after irradiation showed that no mutual chemical reaction between the two ingredients occurred in the microcapsules. The amount of each ingredient was expressed by the mean of three determinations.

Light absorption and transmission measurements

To determine the light absorption properties of vitamins in the ultraviolet region (290–400 nm) closely relating to the photostability of ubidecarenone, a drop of phytonadione or tocopherol was placed on a quartz-glass plate. The absorption spectra in terms of the semi-integral attenuance spectra (Shibata, 1974a) of these samples were recorded by a multipurpose spectrophotometer (Model MPS-50L, Shimadzu, Japan) using air as the absorption control.

The transmission properties of the microcapsule wall in the same wavelength region were estimated using free films of HPMC with various thicknesses (40–106 μm) which were prepared by the casting method (Matsuda et al., 1980); the transmission curves of these films were recorded by the same spectrophotometer as that described above.

Scanning electron microscopy

The photomicrographs of microcapsules were taken by a scanning electron microscope (Model JSM-T20, Jeol, Japan) at a magnification of ×5000.

Results and Discussion

State and photolytic degradation of the ingredients in microcapsules

In a previous paper (Matsuda and Masahara, 1983) it was shown that due to its low melting point, ubidecarenone cannot easily be crystallized by the solvent evaporation method; it took more than 24 h to crystallize under cooling conditions. Since all vitamins used in the present study were actually in the liquid state, the binary system in microcapsules also might be in the homogeneous state. Fig. 1 illustrates an example of the DTA curves for the intact ubidecarenone crystals, spray-dried HPMC, a physical mixture of these powders and microcapsules prepared in the two extreme molar ratios of phytonadione to ubidecarenone. The thermogram of ubidecarenone: (a) showed a sharp endothermic peak at 48°C, while that of spray-dried HPMC; and (b) revealed no appreciable endothermic phenomenon. The thermogram of the physical mixture of both ingredients changed to a compositive pattern of (a) and (b), still keeping the same endothermic peak as that for the intact ubidecarenone crystals. On the other hand, the thermograms of microcapsules did not show any endothermic peak irrespective of the presence of phytonadione,

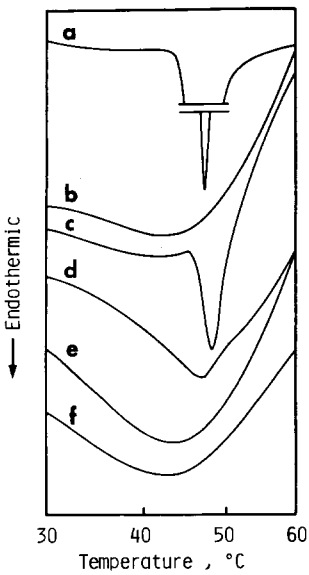

Fig. 1. DTA thermograms of intact ingredients and microcapsules: a, ubidecarenone; b, hydroxypropylmethylcellulose; c, a physical mixture of a and b; d, microcapsules without phytonadione; e, microcapsules with phytonadione (2:1); f, microcapsules with phytonadione (40:1). The numbers in parentheses represent the molar ratio of phytonadione to ubidecarenone.

suggesting the absence of crystalline material in the microcapsules. The same results were obtained from microcapsules containing other vitamins. The microcapsules observed directly by a microscope were quite transparent. These results lead to the conclusion that ubidecarenone is microencapsulated in the liquid state without crystallization and that the systems in microcapsules are homogeneous.

In the scanning electron photomicrographs of ubidecarenone microcapsules prepared with and without tocopherol (Fig. 2), the spherical microcapsules were < 5 μm in diameter for all formulations. The light transmission properties of HPMC films in the wavelength region above 290 nm became better with the decrease in film thickness. The transmittances of a film of 40 μm-thickness were 80% and over 90% at 290 and above 370 nm, respectively. Calculating from the weight fraction of HPMC in formulations and the mean particle diameter of microcapsules in Fig. 2, the wall thickness of microcapsules was negligibly small compared with that of the free film. Therefore, the microcapsule wall could actually be regarded as being transparent over the whole wavelength region investigated.

Before examining the photostabilizing effects of vitamins, the photostabilities of microcapsules containing each vitamin and those containing ubidecarenone alone were evaluated. The results are given in Fig. 3 showing the semilogarithmic plot of percent remaining of each ingredient against irradiation time. A good linear relationship existed between both variables for any ingredient, except for the initial stage of irradiation. These results suggest that all ingredients degrade following apparent first-order kinetics. The validity of the results in Fig. 3 can be well confirmed by the

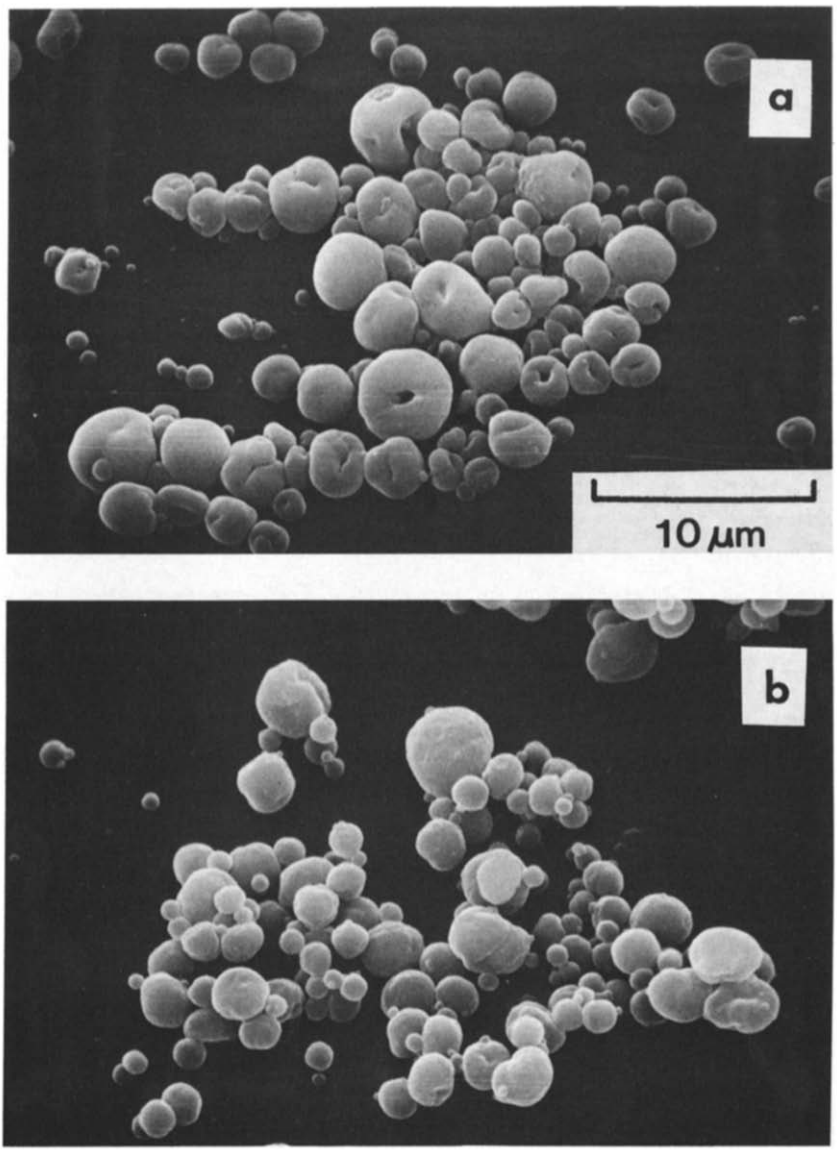

Fig. 2. Scanning electron microphotographs of microcapsules of ubidecarenone without tocopherol (a) and with tocopherol (20 : 1) (b).

logic of Shibata (1974b) that if all light energy is absorbed by an ingredient under any experimental condition, zero-order kinetics is expected theoretically, and that if not, the degradation rate must be proportional to the concentration of the ingredient and first-order kinetics should be established. Since the irradiation energy (1.21×10^8 erg/cm^2; 300–400 nm) after the 1-h irradiation was so high, it seemed likely in this respect that most of the incident light energy could pass through the microcapsules

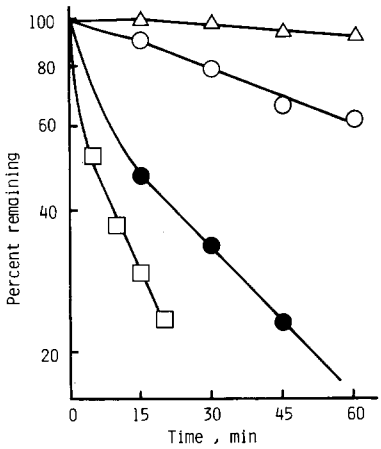

Fig. 3. Photolytic degradation of microencapsulated ubidecarenone, phytonadione, tocopherol and tocopherol acetate: △, tocopherol acetate; ○, tocopherol; ●, ubidecarenone; □, phytonadione.

without being sufficiently absorbed. The fact that ubidecarenone underwent a rapid degradation immediately after the beginning of irradiation, differing from the solid-state degradation (Matsuda and Masahara, 1983), may be due to the difference in light absorption efficiency among the ingredients. Phytonadione was by far the most labile among them. Tocopherol was more stable than ubidecarenone. Unlike these three ingredients, tocopherol acetate scarcely degradated even under a severe condition of 1-h exposure and was essentially photostable. The results of control stability tests for these vitamins performed in nitrogen gas flow or in the dark indicated no significant difference of the photolytic degradation rate from that of Fig. 3, suggesting that photo-oxidation should not occur in these systems. The relative values of degradation rate constants obtained from the slopes of the lines for phytonadione, tocopherol and tocopherol acetate to that for ubidecarenone were 2.2, 0.37 and 0.081, respectively.

Inhibitory effects of vitamins on the photolytic degradation of ubidecarenone

Fig. 4 shows the time courses of percent of ubidecarenone remaining and vitamin in microcapsules, where each vitamin is incorporated in a molar ratio of 20 : 1. The plot also gave good straight lines on the semilogarithmic scale for a two-component system. As expected from Fig. 3, tocopherol acetate did not degrade at all even after the 1-h irradiation. This result inevitably reflected the photostability of ubidecarenone; the result resembled very much the time-course change in the photostability of ubidecarenone alone, without the evidence of inhibition of the photolytic degradation. On the contrary, the degradation of ubidecarenone could be effectively inhibited by the incorporation of phytonadione or tocopherol. The percent of ubidecarenone remaining after the 1-h irradiation increased to 53.1% and 40.9% by the incorporation of phytonadione and tocopherol, respectively, whereas only 17.1% remained in the tocopherol acetate system. This finding proves that if the photosta-

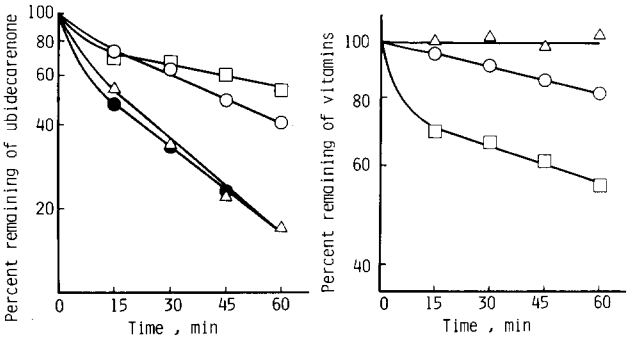

Fig. 4. Photostability of ubidecarenone and vitamins incorporated in a molar ratio of 20:1 in microcapsules: □, phytonadione; ○, tocopherol; △, tocopherol acetate; ●, without vitamins.

bility of a vitamin is poorer, its inhibitory activity is more potent. For this reason, tocopherol acetate was excluded from the subsequent discussion.

The effects of incorporated amounts of tocopherol and phytonadione on the photostability of ubidecarenone are shown in Tables 1 and 2, respectively. Even in the lowest molar ratio of 2:1, the percent of ubidecarenone remaining was greatly increased in the tocopherol system, and the photostability was markedly improved with increasing molar ratio. The improvement of photostability accompanying the increase in molar ratio was more evident in the phytonadione system than in the tocopherol system during the first-order degradation process. In both systems the degradation rate of tocopherol or phytonadione apparently decreased with increasing molar ratio (i.e. the increase in the amounts of vitamins in the microcapsules). This evidence is certainly attributable to the scale effect of the solid-state matrix. The degradation rate constants calculated from the slopes of lines during the first-order degradation process are plotted against molar ratio in Fig. 5. The rate constant for the phytonadione system decreased to about 1/4 of that for ubide-

TABLE 1

EFFECTS OF VARIOUS MOLAR RATIOS OF INCORPORATED TOCOPHEROL ON THE PHOTOSTABILITY OF UBIDECARENONE

Time (min)	Percent remaining of									
	U	T	U	T	U	T	U	T	U	T
Molar ratio of T[a] to U[b]	0		2		10		20		40	
15	47.1	–	69.0	96.5	67.4	93.5	67.8	90.8	78.0	96.8
30	33.7	–	53.2	84.9	50.2	86.7	51.5	84.3	57.8	87.5
45	23.2	–	39.8	78.5	39.1	83.8	43.4	80.6	52.2	86.3
60	13.8	–	32.0	72.1	35.3	78.5	34.7	75.8	41.8	81.0

[a] Tocopherol.

[b] Ubidecarenone.

The experiments were carried out at 35°C.

TABLE 2

EFFECTS OF VARIOUS RATIOS OF INCORPORATED PHYTONADIONE ON THE PHOTOSTABILITY OF UBIDECARENONE

Time (min)	Percent remaining of:									
	U	P	U	P	U	P	U	P	U	P
Molar ratio of P[a] to U[b]	0		2		10		20		40	
15	47.1	–	47.9	41.4	60.9	67.5	69.1	69.0	77.2	83.4
30	33.7	–	33.6	28.5	49.7	58.6	66.8	66.3	71.0	76.0
45	23.2	–	28.5	24.6	45.1	54.1	60.3	61.1	63.5	73.4
60	13.8	–	22.4	20.1	37.4	47.9	53.1	55.2	62.9	69.4

[a] Phytonadione.

[b] Ubidecarenone

The experiments were carried out at 35°C.

carenone alone in a molar ratio of 20 : 1, and still continued to decrease in higher ratios. On the other hand, it no longer decreased in molar ratios higher than 10 : 1 in the tocopherol system. It is clear that phytonadione is superior to tocopherol in the inhibitory effect in any molar ratio.

Tables 1 and 2, and Fig. 5 may be interpreted as follows: the irradiation energy of incident light would be separately absorbed by both ubidecarenone and a vitamin, and the amount of energy absorbed by the vitamin would increase with the increase in the amount of its incorporation, because the total amount of light energy which is incident upon a microcapsule remained unchanged. Therefore, the consequent

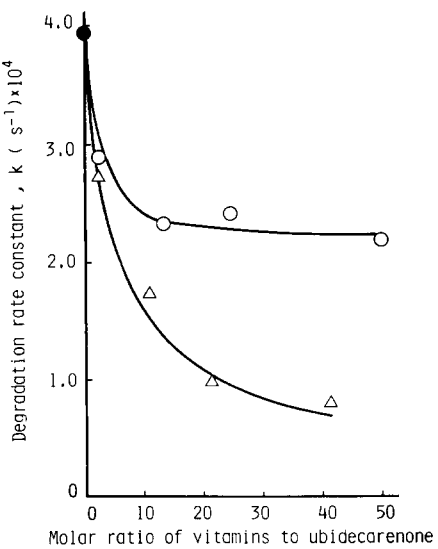

Fig. 5. Effect of incorporated tocopherol or phytonadione on the photolytic degradation rate constant of ubidecarenone: ●, without vitamins; ○, tocopherol; △, phytonadione.

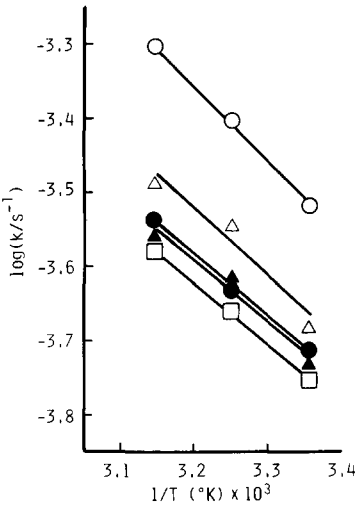

Fig. 6. Arrhenius plot for photolytic degradation of ubidecarenone microencapsulated together with tocopherol in various molar ratios: ○, without tocopherol; △, 2:1; ●, 10:1; ▲, 20:1; □, 40:1.

decrease in the amount of energy absorbed by ubidecarenone may lead to the inhibition of photolytic degradation.

Temperature effect

The incorporating effect of tocopherol on the photostability of ubidecarenone is shown as Arrhenius plots in Fig. 6. The plots gave good straight lines for all molar ratios at 25–45°C. A similar result was obtained in the phytonadione system. Tocopherol and phytonadione also exhibited an inhibitory effect at higher temperatures. However, no significant difference among the values of activation energy was observed as expected from the slopes of the lines; the activation energy for ubidecarenone alone was 4.69 kcal/mol corresponding to an intermediate value between those observed in the solid (6.67 kcal/mol) and liquid (3.14 kcal/mol) state (Matsuda and Masahara, 1983). The values for the tocopherol system ranged from 3.75 (40 : 1) to 4.23 kcal/mol (2 : 1). Thus the Q_{10}-value (Connors et al., 1979) for the temperatures of 25–35°C was only 1.23 even in the highest molar ratio (40 : 1). The results of Arrhenius treatment support the statement of Hanna (1982) that in photolytic degradation, no advantage is gained by higher temperature studies because the activation energy is small and consequently the effect of temperature is small.

Photostability at various wavelengths

Since the binary mixture in microcapsules can be regarded as homogeneous, the degree of photolysis of ubidecarenone must depend on the light absorption properties of vitamins. Figs. 7 and 8 illustrate the action spectra for photolytic degradation of these ingredients, in which the percent of ubidecarenone and vitamins remaining are plotted against irradiation wavelength under the same irradiation intensity of 1.0×10^8 erg/cm^2. A good corresponding relation was obtained between the percent

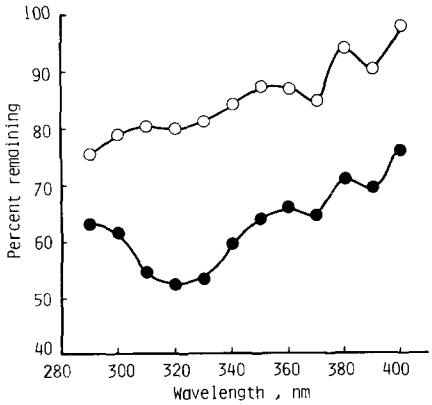

Fig. 7. Effect of irradiation wavelength on the percent remaining of (●) ubidecarenone and (○) tocopherol in microcapsules (irradiation intensity = 1.0×10^8 erg/cm^2).

remaining patterns of ubidecarenone and tocopherol at wavelengths above 320 nm. On the contrary, in the phytonadione system the percent remaining curves of ubidecarenone and phytonadione showed an inverse pattern to each other. A tendency similar to this was also observed in the tocopherol system at wavelengths below 320 nm. The order of photostability among these ingredients observed in the two graphs of Fig. 3 remained unchanged throughout the whole region of irradiation wavelength. Neither the action spectrum of ubidecarenone in Fig. 7 nor that in Fig. 8 resembled that of the intact ubidecarenone crystals observed in the previous investigation (Matsuda and Masahara, 1983). This finding suggests that the degradation of ubidecarenone is strongly controlled by the ingredient added.

The inhibitory effects of vitamins were evaluated more quantitatively by plotting the percent of ubidecarenone remaining against that of one vitamin (Fig. 9). Irrespective of the irradiation wavelengths, close relationships were established between the two variables. It was of interest to know that the plots gave a single descending straight line in the phytonadione system, whereas the result was a

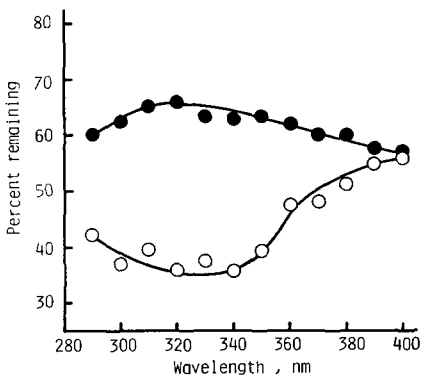

Fig. 8. Effect of irradiation wavelength on the percent remaining of (●) ubidecarenone and (○) phytonadione in microcapsules (irradiation intensity = 1.0×10^8 erg/cm^2).

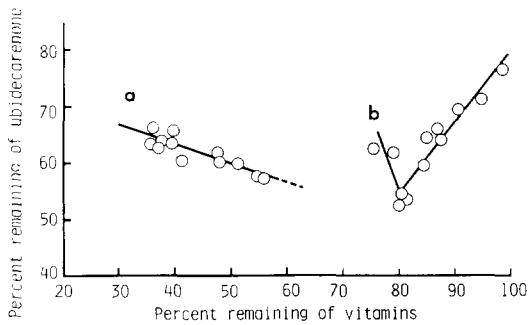

Fig. 9. Relationships between percent remaining of ubidecarenone and that of vitamins in microcapsules irradiated under the same intensity at different wavelengths: a, phytonadione system; b, tocopherol system.

V-shaped graph consisting of two straight lines in the tocopherol system. The critical wavelength giving a point of intersection of the two lines just correspond with 320 nm at which ubidecarenone degraded most remarkably (Fig. 7). The competitive degradation effect of vitamins, which is defined as the increase in percent remaining of ubidecarenone accompanying the lowering in percent remaining of vitamins, appeared clearly in the phytonadione system. The reason for the excellent effect of phytonadione can be attributed to its higher absorbancy over the whole range of irradiation wavelength (Fig. 10). This may lead to the decrease in light energy absorbed by ubidecarenone, resulting in the inhibition of degradation. The same interpretation is applicable to to be tocopherol system at the shorter wavelengths below 320 nm.

However, tocopherol had no satisfactory absorption properties at longer wavelengths, suggesting a poor inhibitory effect. It is also believed to be reasonable that tocopherol is substantially photostable in this wavelength region, because the percent remaining is higher than 80% even under the extreme intensive irradiation (Fig. 7). Therefore, the photolytic degradation of ubidecarenone may take place without any protection by tocopherol in such a situation. The fact that the degradation of

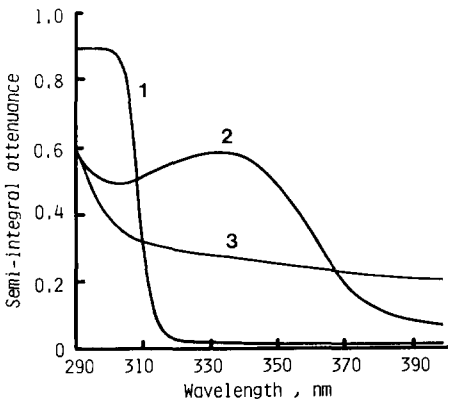

Fig. 10. Semi-integral attenuance spectra of (1) tocopherol, (2) phytonadione and (3) ubidecarenone.

ubidecarenone is nevertheless inhibited to some extent by tocopherol is ascribed to its effective absorption of light energy at about 310 nm radiated from the mercury vapor lamp (Matsuda and Minamida, 1976).

In conclusion, the photostability of ubidecarenone can be improved satisfactorily by microencapsulating together with phytonadione. The major contributing factor to the effectiveness of stabilization is the light absorption properties of the concomitantly incorporated ingredients. In the present work some photolabile vitamins were employed as model ingredients. The problem of therapeutic incompatibility is, therefore, beyond the scope of this investigation. If a non-toxic ultraviolet absorber is available, the photostabilization of ubidecarenone may possibly be more complete.

Acknowledgments

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