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Improvement of photostability of ubidecarenone in the formulation of a novel powdered dosage form termed redispersible dry emulsion

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Summary

Ubidecarenone, which has low photostability and is poorly absorbed in the intestine, was formulated into a novel powdered dosage form designated as a redispersible dry emulsion. In preparing the system, an oily solution containing the drug and a colorant emulsified in an aqueous solution of a surfactant (Pluronic F-68) were spray-dried with a suitable excipient. The resultant dry emulsion particles have good flow properties and readily release the oily droplets to form stable emulsions on rehydration. The redispersibility, i.e., the conversion to the original emulsion from the dry emulsion form, was found to be closely related to the viscosity of the oily carrier. The photostability of the drug dissolved in the oily carriers was much improved in the presence of colorants. The kinetics data for photolytic degradation of the drug in the dry emulsion particle were analyzed to clarify the effect of the amount of excipient and colorant on the photostability of the drug in the particle.

Introduction

Ubidecarenone (2,3-dimethoxy-5-methyl-6-decaprenyl benzoquinone) is a widely used cardiovascular agent formulated into oral dosage form. One of the unfavorable characteristics of the drugs is photolability, which has been confirmed at ordinary and elevated temperatures under high intensity ultraviolet light by Matsuda and Masahara (1983). They attempted to improve the photostability of the drug by means of the competitive degradation of fat-soluble vitamins incorporated with the drug in microcapsule form (Matsuda and Masahara, 1985). Ubidecarenone is also poorly water-soluble and thus hardly absorbed from the gastrointestinal tract. It has been

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reported that the plasma level of the drug is very low after oral administration (Kishi et al., 1981). One method for improving the bioavailability of poorly absorbable drugs is the use of an oily carrier. It has been reported that co-administration of an oil-in-water emulsion (Carrigan and Bates, 1973; Bates and Sequeira, 1975) or of lipophilic carriers (Palin et al., 1982; Kadir et al., 1986) increases drug absorption from the gastrointestinal tract. There is also a patent (Eisai Co., 1981) claiming the use of an oily formulation to improve the bioavailability of ubidecarenone.

Although various dosage forms of oily ingredients such as soft gelatin capsules, powders and tablets are available, the manufacturing generally involves several great difficulties. A solid dosage form, which is preferable for handling and dosing, should exhibit the property of releasing the drug at a sufficiently rapid rate on rehydration in order to ensure satisfactory bioavailability. We have developed a powdered form of oily and waxy drugs, referred to as a redispersible dry emulsion with the characteristics of good redispersibility or drug release (Kawashima et al., 1988; Takeuchi et al., 1991a–c). The system was prepared by spray-drying an emulsified oily material in water with suitable excipients. The resultant particles were found to readily release oily droplets to form stable emulsions when rehydrated. The property of rapid drug release was confirmed in vivo as well as in vitro by measuring the intestinal absorption of an oily drug after oral administration of the dry emulsion to beagle dogs (Takeuchi et al., 1991b).

In the present study, this redispersible dry emulsion system was applied to the photolabile and poorly absorbable drug, ubidecarenone. As the main route for the absorption of ubidecarenone has been suggested to be the lymphatics (Katayama et al., 1972), a well dispersed oily solution of the drug should enhance the extent of drug absorption. Our attention was focused on the photostability of the drug in the particle as well as the redispersibility of the emulsion. To improve the photostability of the drug, various colorants and excipients were incorporated into the system and kinetic analysis of the photolytic degradation of the drug was carried out.

Materials and Methods

Materials

Ubidecarenone was obtained from Eisai Co. and used without further purification. Colloidal silica (Aerosil 200), monodispersed spherical silica and silica-titanium dioxide-zirconium composite particles (ZS-5000IT) were supplied by Nippon Aerosil Co., Sinto Kogyo Co. and Toray Co., respectively. Polyoxyethylene-polyoxypropylene block copolymer (Pluronic F-68) was obtained from Asahi Denka Co. The synthetic pigments, i.e., α-(*o*-tolylazo)-β-naphthylamine (oil yellow OB, Y-3) and Sudan II (oil red XO, R-5) were purchased from Tokyo Kasei Kogyo Co., and riboflavin butylate (RB), β-carotene and capsanthin were available as coloring additives for foods. Medium-chain triglycerides (Panasate 810 and Triester F-810), which have almost the same components, were obtained from Nippon Oil and Fat Co. and Nikko Chemicals Co., respectively. Medium-chain fatty acid-polyalcohol esters (Sefsols 220, 228 and 668) were also purchased from Nikko Chemicals Co. Natural oils (castor oil and olive oil) were of JP grade. The viscosity of oils was measured at 20°C by means of a corn and plate type viscometer (NRM 120-0, Nippon Rheology Instrument Co.).

Preparation of dry emulsion

Ubidecarenone powder (0.25–1.0 g) and a lipophilic colorant (0–0.1 g) were dissolved in an oily carrier (20 g) on a water bath at 30–50°C. After cooling to room temperature, the oily solution was emulsified in a solution of Pluronic F-68 (1000 ml, 0.2% w/v) in the presence of an excipient (5–100 g) by agitation at 20000 rpm for 5 min with a high-speed homogenizer (Physcotron, Nichion Irikakikai Seisakusho Co.). The resultant emulsion was spray-dried in a spray-dryer (L-12 type, Okawara Kakoki Co.) under the following conditions: inlet air temperature, 220°C; outlet air temperature, 120 ± 4°C; rotation speed of atomizer, 16500 rpm; feeding rate of the emulsion, 50 ml/min.

Drug content and redispersibility of dry emulsion

Ubidecarenone in the dry emulsion particles (2.5–10 mg on drug basis) was extracted by treat-

ment with a methanol-chloroform mixture (2:1, 9.5 ml), shaking mixture (V-S type shaker, Iwaki Co.) at 240 spm for 1.5 h. After removing the insoluble ingredients by centrifugation at 3000 rpm for 5 min, the drug concentration of the solution was determined on high-performance liquid chromatography (HPLC). The stationary and mobile phases in HPLC analysis were Nucleosil 100-5C_{18} packed in a column (150 mm × 4.6 mm i.d.) and a methanol-ethanol mixture (1:1), respectively, and the drug separated by the column was spectrophotometrically detected at 275 nm.

To examine the redispersibility of the dry emulsion in an aqueous medium, the dry emulsion (2.5–10 mg on drug basis) was dispersed in water (9.5 ml) by manual shaking (10 times). After allowing the system to stand for 1 h at room temperature, the sedimented particles were collected. The amount of drug remaining in the particles was measured in the same manner as that for the determination of drug content. The redispersibility was calculated from the drug content and percentage remaining.

Micromeritic property tests

The angle of repose of dry emulsion particles was directly measured using piled particles on a circular stainless plate of 2 cm diameter.

The bulk density was determined before and after tapping with a 10 ml measuring cylinder. Tapping was performed mechanically with a tapping instrument (Konishi Seisakusyo Co.), until the apparent volume reached a constant value.

For measuring the contact angle of oils to the Aerosil coated with the surfactant, the colloidal silica dispersed in the Pluronic F-68 solution was spray-dried under the same conditions as for the dry emulsion. The resultant particles were compressed to make a silica disk having a flat surface. The contact angle of 1–2 μl of oil dropped onto the silica surface was measured with a contact-angle meter (CA-A, Kyowakagaku Co.).

Photostability tests

Photostability testing was performed basically according to the preliminary procedures for the standard photostability test of drugs for the Japanese pharmacopoeia (Yatani et al., 1988).

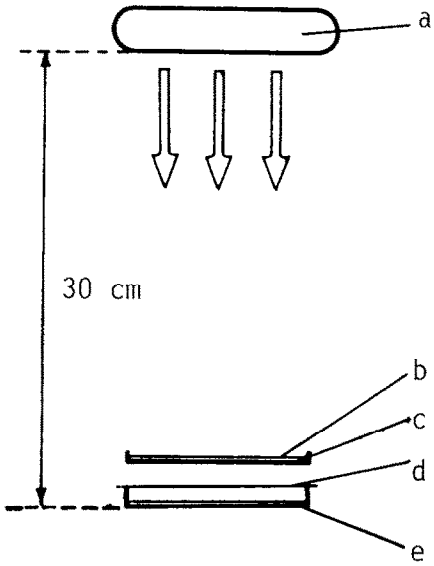

Fig. 1. Illustration of the system used for the photostability test: (a) UV light source, (b) excipient layer, (c) quartz glass plate, (d) polyvinylidene chloride film, (e) sample (oily solution of drug or dry emulsion).

Tests were carried out in a dark room by using a chemical lamp (FL 20SNBL-B, Matsushita Electric Co.; wavelength, 300–420 nm; maximum, 357 nm; intensity, 0.34 mW cm^{-2}) as a UV irradiation source. For the oily solution of drug with and without colorants, 1 g of the oily solution was spread at the bottom of a Petri dish (4 cm diameter) and then covered with a piece of polyvinylidene chloride film. To examine the effect of excipient, an excipient layer formed on a circular quartz plate (4 cm diameter) was placed on the Petri dish to screen the UV radiation. In the case of dry emulsion particles, the desired amount of particles (2.5–10 mg on drug basis) was dispersed on the Petri dish and covered with a piece of polyvinylidene chloride film. These samples were positioned 30 cm below the UV light source and exposed to UV irradiation for 0–24 h at room temperature. The whole system for the test is illustrated in Fig. 1.

After UV irradiation, the oily sample was dissolved in a methanol-chloroform mixture (2:1) in order to determine the amount of drug remaining unchanged. The drug content remaining in the

dry emulsion was determined in the same manner as that described above.

Results and Discussion

Micromeritic and oil releasing properties of dry emulsion

Various kinds of oily carriers, such as natural oils (castor oil and olive oil), medium-chain triglycerides (Panasate 810 and Triester F-810) and medium-chain fatty acid-polyalcohol esters (Sefsols 220, 228 and 668) were examined with respect to being suitable as drug carriers. Drug dissolution in the oils was determined over the range of 1.2–7.0% at room temperature. It was found that the drug was completely dissolved in Panasate 810, Triester F-810 and Sefsols 220 and 228 within the above drug concentration range (Table 1). In the case of Sefsol 668, part of the drug was precipitated at a concentration of 7.0%. Based on the test, a 4.8% drug solution was used to prepare dry emulsion particles with medium-chain triglycerides and medium-chain fatty acid-polyalcohol esters. Drug concentrations of 1.2 and 2.4% were used for castor oil and olive oil, respectively, since drug solubility was low in the case of the natural oils.

The dry emulsion particles were formulated such that each preparation had a composition that conformed with that of the following typical formulation (designated as formulation 1): ubidecarenone, 1.0 g; oil, 20.0 g; Pluronic F-68, 2.0 g; Aerosil 200, 10.0 g. Irrespective of the type of oily carrier, the emulsions were convertible into powdered forms. The drug-containing oily droplets were embedded into a colloidal silica matrix in the particles (Takeuchi et al., 1991a). Inspection under a microscope showed that each of the resulting types of dry emulsion particles was spherically shaped with an average diameter of 10–40 μm. The angle of repose of the particles was found to be within the range 44.0–51.8°. The

TABLE 1

Dissolution behavior of ubidecarenone in various oily carriers

Oil	Concentration of ubidecarenone (%)			
	1.2	2.4	4.8	7.0
Panasate 810	S	S	S	S
Triester F-810	S	S	S	S
Sefsol 228	S	S	S	S
Sefsol 220	S	S	S	S
Sefsol 668	S	S	S	P
Castor oil	S	P	P	P
Olive oil	S	S	P	P

S, soluble; P, precipitated or insoluble

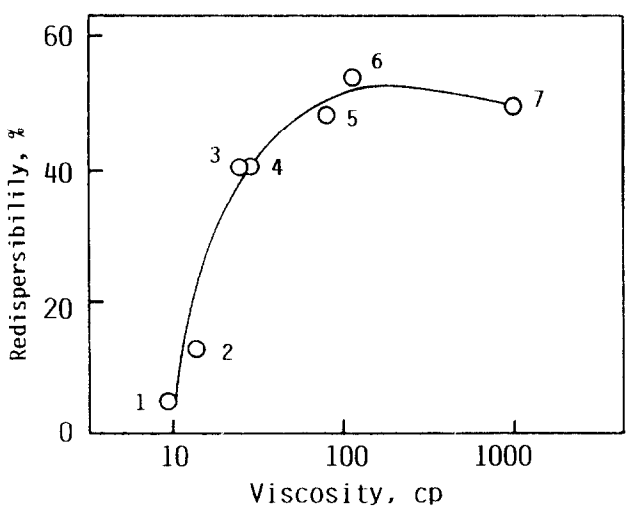

Fig. 2. Relationship between viscosity of oily carriers and redispersibility of the corresponding dry emulsion system. (1) Sefsol 228, (2) Sefsol 220, (3) Panasate 810, (4) Triester F-810, (5) olive oil, (6) Sefsol 668, (7) castor oil.

flowability of the particles was greatly improved on increasing the Aerosil content of the formulation. The variations in this property of particle flow behavior as a function of Aerosil content are listed in Table 2 for the dry emulsion with Sefsol 668. In the case where the amount of Aerosil was reduced to 5 g, the particles became sticky, suggesting that Aerosil was unable to form a matrix structure. The formulation with an Aerosil content of 20 g was observed to contain freely flowing particles.

It is important for the dry emulsion to release the oily droplets and re-form the original emulsion under mild rehydration conditions. The redispersibility, which is defined as the percentage of oily droplets released from the particles, was influenced by the type of oily carrier. The use of a more viscous carrier up to 100 cP led to higher redispersibility. The relationship between the viscosity of the oily carrier and the percentage released is shown in Fig. 2.

The release behavior of oily droplets from the dry emulsion particles may be correlated with the structure of the particles. Oily droplets in the dry emulsion particles would need to be embedded within the colloidal silica matrix as a droplet form in order for sufficient redispersibility to be attained, since the conditions for redispersion in the present study are too mild to convert the oily mass released into the form of small droplets and also since this formulation cannot be expected to achieve self-emulsification. The oily droplets with higher viscosity appear to maintain their shape in the silica matrix during the drying process due to their greater resistance against deformation forces. From this point of view, highly viscous oils are considered to be suitable for the formulation of dry emulsions. On the other hand, measurements of the contact angles showed that the oils with higher viscosity possessed relatively lower affinity for the silica surface coated with the surfactant (Table 3). It appears that the oils must attain a sufficiently strong affinity for the silica particles in order to avoid separation of the silica particles from the surface of the oily droplets, which may lead to the coagulation of oily droplets. Owing to such effects, an appropriate viscosity of oil is required for good redispersibility. Based on the above results, Sefsol 668, Panasate 810 and Triester F-810 were selected as oily carriers of ubidecarenone for the following photostability study.

TABLE 2

Flow properties of dry emulsion particles with different Aerosil contents

Aerosil formulated (g)	20	10	5
Angle of repose (°)	36	51	60
Bulk density (g cm^{-3})			
before tapping (ρ_0)	0.29	0.35	
after tapping (ρ_f)	0.36	0.44	
Compressibility $[(\rho_f - \rho_0)/\rho_f]$ [a]	0.19	0.20	

[a] Carr's index for powder flow (Carr, 1965).

TABLE 3

Contact angle of oils to colloidal silica coated with Pluronic F-68

Oil	Viscosity (cP)	Contact angle (°)
Panasate 810	24.2	13.6
Triester F-810	28.3	15.0
Sefsol 220	13.4	11.4
Sefsol 228	9.4	10.0
Sefsol 668	110.7	20.0
Castor oil	987.6	36.6
Olive oil	80.0	17.6

Photostability of ubidecarenone in the oily solution

Ubidecarenone is more photolabile in oily solution than in the solid form, since a greater proportion of the drug molecules are exposed to light in the transparent oily solution. As the drug would be dissolved in an oily carrier in the dry emulsion particles, the evaluation of photostability was carried out first for the oily solution. UV irradiation of the solution in a Petri dish was performed for 24 h and the percentage of drug remaining ($R(24)$) was measured. Irrespective of the type of oily carrier, the $R(24)$ value for the oily solution of the drug was determined to be $67 \pm 3\%$ at 4.8% w/w drug concentration.

To improve the photostability of the drug in the oily solution, the effect of co-formulation with

oil-soluble colorants was examined. Colorants that result in high levels of UV absorption would be expected to be the most suitable for protecting the drug against photodegradation. Fig. 3 shows typical absorption spectra obtained through UV analysis of chloroform solutions of the various colorants at a fixed concentration (10 ppm) over the wavelength range 300–400 nm. No detectable UV absorption was observed for the natural colorant capsanthin at the same concentration. Oily solutions of the drug containing a fixed concentration (0.5%) of the colorants were evaluated with respect to photostability. Although β-carotene demonstrated the highest degree of UV absorption in chloroform solution we found it to be inadequate in Sefsol 668 as a result of its relatively low solubility in the latter. Y-3 and R-5 were confirmed to be the most effective, as concluded on the basis of the photostability data listed in Table 4. In contrast, riboflavin butylate (RB) accelerated the photolytic decomposition of

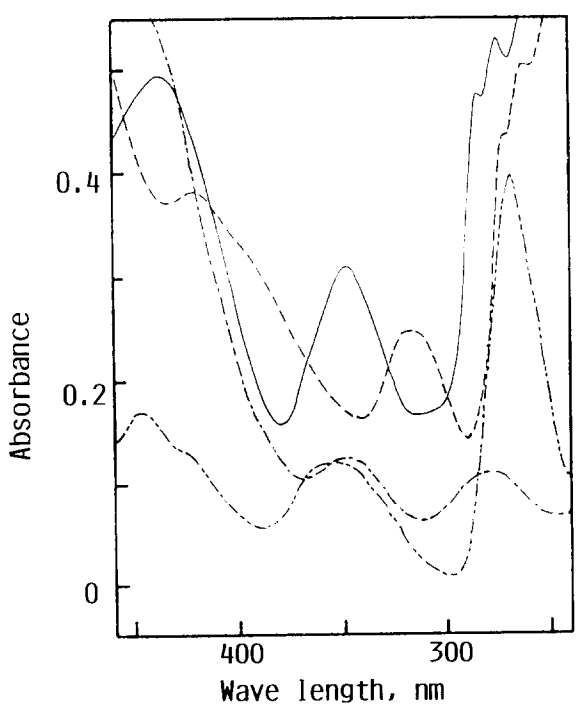

Fig. 3. UV absorption spectra of colorants in chloroform solution: (———) Y-3, (- - - - -) R-5, (— — —) β-carotene, (· — · — ·) RB.

TABLE 4

Effect of colorants on the photostability of ubidecarenone in the oily solution

Colorant	Percentage of drug remaining after UV irradiation for 24 h
Oil yellow OB (Y-3)	92.3
Oil red XO (R-5)	90.3
Riboflavin butylate	55.3
No colorant	65.7

Oily solution: Sefsol 668.

the drug. The cause of this phenomenon was ascribed as being due to the excitation of molecules of RB to higher energy levels by UV irradiation, thereby promoting the decomposition of the drug via the process of fluorescence emission.

In the dry emulsion particles, the excipients were assumed to play the important role of protecting the drug against photolytic decomposition. In order to verify the validity of this assumption, UV irradiation of the drug solution on a Petri dish was performed through an excipient bed of constant thickness (approx. 0.8 mm) formed upon a quartz plate. In addition to colloidal silica (Aerosil 200), tests were also conducted on monodispersed spherical silica (MSS) and silica-titanium dioxide-zirconium composite particles (ZS-5000IT). The new type of complexed particles designated as ZS-5000IT are a recent development for use in the field of cosmetics. These particles provide protection by the reflection of a proportion of the UV radiation as a result of the zirconium adhering to the particle surface and by the absorption of the remaining UV radiation by the titanium dioxide deposited within the particles. MSS and ZS-5000IT were observed to function well as UV protectants, as indicated by the data in Table 5. However, these excipients were found to be unsuitable for the dry emulsion preparation. 100 g of excipient was required to convert 20 g of oil to the dry emulsion form (see composition of formulation 1; preceding section) whilst the resultant particles released no oily droplets on redispersion. These phenomena were attributed to the relatively larger particle size

TABLE 5

Effect of the type of excipients on the photostability of ubidecarenone in the oily solution

Excipient	Percentage of drug remaining after UV irradiation for 24 h
MSS [a]	95.4
ZS-5000IT [b]	96.2
Aerosil 200	84.2
No excipient	65.7

[a] Monodispersed spherical silica.
[b] Silica-titanium dioxide-zirconium composite particle.
Oily solution: Sefsol 668.

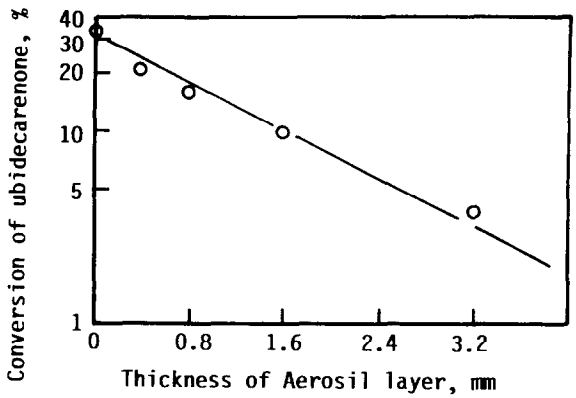

Fig. 4. Effect of the thickness of Aerosil layer on the photostability of ubidecarenone dissolved in Sefsol 668.

(spherical silica, 1.3 μm; ZS-5000IT, 5 μm) as compared to that of Aerosil (12 nm). In order to maintain the droplet shape of the oily carrier in the dry emulsion particles, the excipient should be employed in a colloidal form.

The weight of Aerosil used for the test was 1/10 of that of the excipients owing to its bulk density being very low (0.04–0.06 g cm^{-3}). The $R(24)$ values increased with increase in the amount of Aerosil, i.e., with the thickness of the Aerosil layer (Fig. 4). The semilogarithmic plot of the extent of conversion of ubidecarenone in the oily solution due to photodecomposition against the thickness of the Aerosil layer demonstrates a straight line. This confirms that the change in UV intensity on passing through the Aerosil layer follows Lambert's law, assuming that the rate of photodecomposition of ubidecarenone in the oily solution is proportional to the intensity of the UV radiation. Therefore, Aerosil was expected to be effective in the protection of ubidecarenone against photodecomposition in the dry emulsion particles depending on amount present in the formulation.

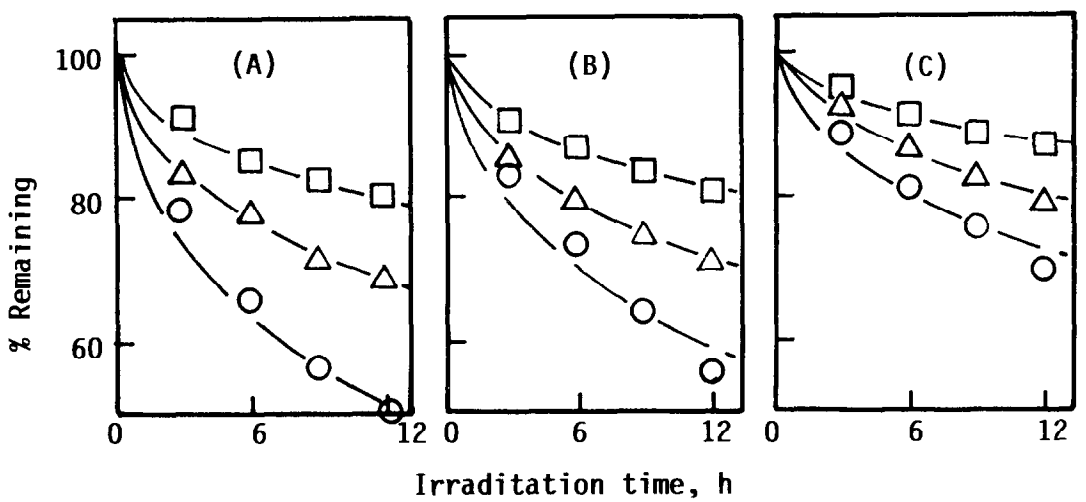

Fig. 5. Photodecomposition profile of ubidecarenone formulated into dry emulsion particles with various amounts of Aerosil and colorant (Y-3). Content of Aerosil in the formulation: (○) 5 g, (△) 10 g, (□) 20 g. Concentration of Y-3: (A) 0%, (B) 0.1 %, (C) 0.5%.

Kinetic analysis of photodecomposition of ubidecarenone in dry emulsion with Aerosil and oil yellow OB (Y-3)

The photodecomposition of ubidecarenone was evaluated in the dry emulsion form in the same manner as that above. Dry emulsions of ubidecarenone were prepared with Sefsol 668, Aerosil and Y-3. The percentage of drug remaining in the dry emulsion systems was measured as a function of time. As shown in Fig. 5A–C, improved photostability of the drug was achieved with increase in the amount of Aerosil formulated and the concentration of Y-3.

The decomposition profile of the drug in the dry emulsion particles in every case proved to be consistent with the expression reported by Jander (1927), viz., Eqn 1:

$$(1 - R^{1/3})^2 = k_1 t \tag{1}$$

where R, k_1 and t denote the remaining drug content, photodecomposition rate constant and duration of the UV irradiation, respectively. The broken lines in Fig. 5 show the results obtained on fitting the curves to Eqn 1. The difference between the data and the fitted curve was larger when 5 g of Aerosil was formulated than in the case of 10 or 20 g of Aerosil. This was considered to be attributable to the lack of matrix structure for silica particles containing 5 g of Aerosil.

To analyze quantitatively the influence of the amount of additives on the process of photolysis, a simple model was put forward in which the dry emulsion consisted of both the Aerosil and oily layers (Fig. 6). The rate constant k_1 in Eqn 1 is assumed to be proportional to the intensity of the UV radiation according to the expression:

$$k_1 = p_1 I \tag{2}$$

where p_1 is a constant determined by the experimental conditions. Based on the Beer-Lambert law, the intensity of the UV radiation is reduced in the presence of both layers as follows:

$$\ln I_0/I' = p_3 d \tag{4}$$

$$\ln I'/I = p_2 c \tag{5}$$

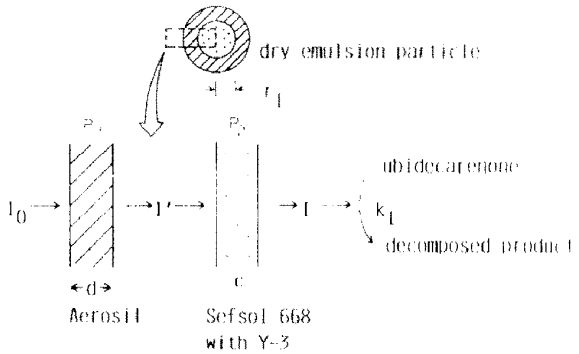

Fig. 6. A simple model for the photo-protection of ubidecarenone in the dry emulsion particles with excipient and colorant.

Thus,

$$I = I_0 \exp(-p_2 c - p_3 d) \tag{6}$$

where I_0 represents the initial intensity of the UV radiation, I' and I are the UV intensities after reduction due to the Aerosil and Y-3 layers, respectively, c (%) denotes the concentration of Y-3 and d (−) is the thickness of the Aerosil layer relative to that of the oily layer (r_1), which was calculated from the weight ratio of Aerosil and the oily solution of colorant during formulation by assuming that the apparent specific gravity of both layers is equivalent. Substitution of Eqn 6 into Eqn 2 yields:

$$\begin{aligned} &k_1 = p_1 I_0 \exp(-p_2 c - p_3 d) \\ &\text{or} \\ &\ln k_1 = \ln p_1 I_0 - p_2 c - p_3 d \end{aligned} \tag{7}$$

On carrying out regression analysis of the results, the constants p_1, p_2 and p_3 in Eqn 7 were evaluated as 4.68×10^{-7} ($m^2\ J^{-1}$), 1.00 ($\%^{-1}$) and 4.88 (−), respectively. Statistical confirmation of the validity of the analysis was provided by F-test: $F = 513.10 > F_7^1(0.01) = 12.2$, $r = 0.993$.

The level of agreement resulting from the analysis is sufficiently reliable to suggest that our simple model can help in the designing and regulation of the desired characteristics of the photostability function of the dry emulsion system. Such an analysis would also be applicable to other related particle types, for instance, microcapsules

or a colloidal particle matrix system for photolabile drugs.

Conclusion

The results of the present investigation have provided confirmation that the photostability of ubidecarenone in the dry emulsion particles can be enhanced considerably through the presence of colorants dissolved in the oily carrier. Although preparations of photolabile drugs can be protected against photo-induced degradation by suitable packaging, the conferral of the dosage form itself with a greater degree of resistance to photodecomposition would be desirable in order that preparations can be used more conveniently. Coloration of the oily drug carrier is one of the simplest means of achieving such protection for a drug in a formulation of dry emulsion particles. Despite the effectiveness demonstrated by the functional excipients such as MSS or ZS-5000IT in providing photoprotection, colloidal silica (Aerosil) represents the most appropriate excipient for dry emulsion particles, as concluded on the basis of the greater drug content and superior drug release behavior.

It has been found that several classes of drugs, e.g., oily, waxy or oil-soluble types, can be formulated as dry emulsion systems with or without oily carriers. From the viewpoint of pharmaceutics, the most important properties of dry emulsion particles, including the pattern of drug release, can be adjusted through the appropriate selection of oily carriers or excipients playing a variety of functional roles in the formulation. The desired powdered dosage forms of oily ingredients with various functions should thus be developed in combination with the basic examination of the oily formulation.

References

Bates, T.R. and Sequeira, J.A., Bioavailability of micronized griseofulvin from corn oil-in-water emulsion, aqueous suspension, and commercial tablet dosage forms in humans. *J. Pharm. Sci.*, 64 (1975) 793–797.

Carr, R.L. Jr., Evaluating flow properties of solid. *Chem. Eng.*, 72 (1965) 163–168.

Carrigan, P.J. and Bates, T.R., Biopharmaceutics of drugs administered in lipid-containing dosage forms. I: GI absorption of griseofulvin from an oil-in-water emulsion in the rat. *J. Pharm. Sci.*, 62 (1973) 1476–1479.

Eisai Co. (Taki, K. and Takahira, H.), Formulations of ubidecarenone with good absorption characteristics. *Nippon Koukai Tokkyo Kouhou*, 56–18914 (1981)

Jander, W., Reaction in the solid state at high temperature. I: Rate of reaction for endothermic change. *Z. Anorg. Allgem. Chem.*, (1927) 1–30.

Kadir, S., Murakami, T., Higashi, Y. and Yata, N., Gastrointestinal absorption of griseofulvin from liquid organic acids and esters in rats. *Int. J. Pharm.*, 33 (1986) 235–342.

Katayama, K. and Fujita, T., Studies on lymphatic absorption of 1′,2′-[^{3}H]-coenzyme Q_{10} in rats. *Chem. Pharm. Bull.*, 20 (1972) 2585–2592.

Kawashima, Y., Takeuchi, H., Niwa, T., Sasaki, H., Miyake, Y., Kayano, M. and Uesugi, K., The effects of surfactants on the water dispersibility of spray dried vitamin-E powders. *J. Soc. Powder Technol. Jap.*, 25 (1988) 574–578.

Kishi, T., Okamoto, T., Kanamori, N., Yamagami, T., Kishi, H., Okada, A. and Folker, K., Estimation of plasma levels of coenzyme Q_{10} and relationship to oral dosage. In Folkers, K. and Yamaura, Y., (Eds), *Biomedical and Clinical Aspects of Coenzyme Q*, Elsevier, Amsterdam, 1981, pp. 67–78.

Takeuchi, H., Sasaki, H., Niwa, T., Hino, T., Kawashima, Y., Uesugi, K., Kayano, M. and Miyake, Y., Preparation of powdered redispersible vitamin E acetate emulsion by spray-drying technique. *Chem. Pharm. Bull.*, 39 (1991a) 1528–1531.

Takeuchi, H., Sasaki, H., Niwa, T., Hino, T., Kawashima, Y., Uesugi, K. and Ozawa, H., Redispersible dry emulsion system as novel oral dosage form of oily drugs: in vivo studies in beagle dogs. *Chem. Pharm. Bull.*, 39 (1991b) 3362–3364.

Takeuchi, H., Sasaki, H., Niwa, T., Hino, T., Kawashima, Y., Uesugi, K. and Ozawa, H., Design of redispersible dry emulsion as an advanced dosage form of oily drug (vitamin E nicotinate) by spray-drying technique. *Drug Dev. Ind. Pharm.*, 18 (1991c) 919–937.

Matsuda, Y. and Masahara, R., Photostability of solid-state ubidecarenone at ordinary and elevated temperatures under exaggerated UV irradiation. *J. Pharm. Sci.*, 72 (1983) 1198–1203.

Matsuda, Y. and Teraoka, R., Improvement of the photostability of ubidecarenone microcapsules by incorporating fat-soluble vitamins. *Int. J. Pharm.*, 26 (1985) 289–301.

Palin, K.J., Wilson, C.G., Davis, S.S. and Phillips, A.J., The effect of oils on the lymphatic absorption of DDT. *J. Pharm. Pharmacol.*, 34 (1982) 707–710.

Yatani, K., Shimizu, R., Ueno, S., Matsuo, K., Tsunakawa, F., Murayama, F. and Takada, K., Report on preliminary studies for the standard of photostability test of drugs (in Japanese). *Iyakuhin Kenkyu*, 19 (1988) 1028–1052.