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Original research paper

Tablet characteristics and pharmacokinetics of orally disintegrating tablets containing coenzyme Q10 granules prepared by different methods

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ABSTRACT

This study aimed to elucidate the characteristics and pharmacokinetics of orally disintegrating tablets (ODTs) containing coenzyme Q10 (CoQ10) granules prepared by spray drying, hot-melting, and wet granulation. The hardness and disintegration times of CoQ10-ODTs containing 5 % crospovidone were 61.6–81.8 N and < 30 s, respectively; these values indicate that the as-prepared ODTs were adequate for clinical use. The hardness and disintegration times of all ODTs did not change significantly after a 28-day storage period at 30 °C/10 % relative humidity (RH), but storage under high temperature and humidity affected their characteristics. The dissolution and pharmacokinetics of CoQ10-ODTs showed that ODTs prepared using the spray-drying method had the highest dissolution and absorbability among the CoQ10-ODTs tested. These results provide useful information for the preparation of ODTs using CoQ10.

Keywords: coenzyme Q10, orally disintegrating tablets, granules, spray drying, tablet characteristics, pharmacokinetics

Coenzyme Q10 (CoQ10) is widely used as a prescribed medicine for heart disease and as a supplement (1–3). CoQ10, a fat-soluble vitamin-like substance with a low melting point (48 °C), is a crystalline powder (4). It has an extremely low water solubility (4 ng mL^{-1} at 25 °C) (5) and low membrane permeability; therefore, it is classified as a biopharmaceutical classification system (BCS) class IV drug (6). Soft capsules and tablets are often used for the administration of CoQ10 (5, 7). In general, soft capsules may soften and become deformed, leading to leakage of their contents and adhesion to the patient's throat during oral administration. In addition, capsules and tablets sometimes present swallowing difficulties in patients (including the elderly and small children), which may lead to extremely poor drug adherence (8, 9). Orally disintegrating tablets (ODTs) have emerged as a dosage form that

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overcomes these problems (10–12). ODTs disintegrate quickly and are easily swallowed with a small amount of water in the oral cavity. Therefore, ODTs containing CoQ10 (CoQ10-ODTs) could be favoured among the various dosage forms as prescribed medicine and supplement.

There are certain technical difficulties related to the preparation of ODTs containing oily pharmaceuticals, such as CoQ10. Oily pharmaceuticals with low melting points frequently melt during tablet compression, which results in sticking. This property also causes defects in the external appearance of tablets, such as surface spotting caused by the melted pharmaceutical substance (12, 13). Granulated designs obtained from powder processing could be utilized as a solution to the problems related to the preparation of ODTs from oily pharmaceuticals. In addition, the physical properties of CoQ10 could be controlled using granules in ODTs since the original properties of CoQ10 are masked in the granules. Prevention of sticking by preparation of tablets using granulated fat-soluble drugs has been reported (14, 15). Thus, granulation could be useful in the preparation of CoQ10-ODTs.

Appropriate tablet characteristics (disintegration properties and hardness) of ODTs are necessary for drug administration and tablet handling in clinical settings. The stability of these properties of ODTs is important for storage in patients' homes lacking control of temperature and humidity. However, the effects of the typical physical properties of CoQ10, such as high lipophilicity and low melting point, on these tablet characteristics and stability of CoQ10-ODTs are unclear. In addition, the pharmacokinetics of CoQ10 following oral administration is a crucial property of ODTs because the bioavailability of CoQ10 has been reported to be extremely low (16, 17).

Therefore, the objective of this study was to elucidate the characteristics and pharmacokinetics of ODTs containing CoQ10 granules prepared by three particle preparation methods: spray drying (SD) (18, 19), hot-melting (HM) (20, 21), and wet granulation (WG) (22). SD and WG methods are the most common techniques used in preparing particles for several drugs. HM methods, in which the pharmaceutical is combined with a binder at a relatively low temperature, are beneficial for oily pharmaceuticals with a low melting point. In the present study, we prepared ODTs containing SD-G (SD-ODTs), HM-G (HM-ODTs), and WG-G (WG-ODTs).

EXPERIMENTAL

Materials

CoQ10 (pure grade, 99.8 %) was obtained from Nisshin Seifun Co. Ltd. (Japan). Dextrin (Pinedex #1, Matsutani Chemical Industry Co., Ltd., Japan) was used as a support agent, and gum arabic (San-ei Yakuhin Boeki Co., Ltd., Japan) and alginic acid propylene glycol ester (KIMICA Corp., Japan) were used as emulsifying agents to prepare SD-G granules.

Porous dextrin (Pineflow S, Matsutani Chemical Industry Co., Ltd.) was used as an adsorption carrier for CoQ10 in the preparation of HM-G granules. D-Mannitol (Mannit P, Mitsubishi Corporation Life Sciences Co., Ltd., Japan; mean particle size, 52 μm diameter) was used as an excipient and crospovidone (PVP K-30, ISP Technologies Inc., USA) as a

disintegrant to prepare WG-G granules. D-Mannitol (Mannit Q, Mitsubishi Corporation Life Sciences Co., Ltd., mean particle size of 37 μm diameter) was used as an excipient and crospovidone (Kollidon CL-SF, BASF Kapan Ltd., Japan.) as a disintegrant to prepare the various CoQ10-ODTs. All other chemicals used were of commercial grade.

Preparation of SD-Gs using spray drying method

The components used to prepare SD-Gs are listed in Table I. First, gum arabic and propylene glycol alginate were added to purified water in a 60 °C water bath, and the solution was agitated at 10,000 rpm using a T.K. Homo Mixer (Primix Corp., Japan) to dissolve the components. CoQ10 was then gradually added to the homomixer and agitated for 20 min. Pinedex #1 was added, and the resulting mixture was agitated at 10,000 rpm for 10 min. The CoQ10 emulsion was maintained in a water bath at 60 °C and spray dried using a spray-dryer with an M-type rotary disk with 0.7 mm nozzles (OC-16, Ohkawara Kakohki Co., Ltd., Japan). SD-G was then obtained by sieving the spray-dried granules through a 1.0 mm sieve. For spray drying, the inlet air temperature was set at 180 °C, while the outlet temperature was approximately 95 °C. The disk rotation speed and the feeding rates were 20,000 rpm and 50 mL min^{-1}, respectively.

Preparation of HM-Gs using the hot-melting method

The components used to prepare the HM-Gs are shown in Table I. CoQ10 and Pineflow S were placed in a high-speed agitating and granulating machine (Super Mixer SMV-20, Kawata Mfg. Co., Ltd., Japan) and mixed for 5 min at 500 rpm. Next, the mixture that had been preheated to 95 °C was mixed at 400 rpm for 25 min to allow CoQ10 to reach an oily consistency and adhere to the micropores of the Pineflow S. Water at 25 °C was then circulated at 400 rpm through the machine jacket to fix the CoQ10 inside the micropores of the Pineflow S. HM-Gs were obtained by sieving the dried granules through a 1.0 mm sieve.

Table I. Formulation of coenzyme Q10 (CoQ10) in granules

Component (g)	Granules (Content of CoQ10)		
	SD-G (50 %)	HM-G (33 %)	WG-G (50 %)
CoQ10	500	500	150
Gum arabic	250	–	–
Propylene glycol alginate	10	–	–
Maltodextrin (Pinedex #1)	240	–	–
Maltodextrin (Pineflow)	–	1000	–
D-Mannitol (Mannit P)	–	–	144
Polyvinylpyrrolidone (PVP K-30)	–	–	6
Total	1000	1500	300

SD-G (50 %) – granules prepared by spray drying, containing 50 % (*m*/*m*) of CoQ10; HM-G (33 %) – granules prepared by hot-melting, containing 33 % (*m*/*m*) of CoQ10; WG-G (50 %) – granules prepared by wet granulation, containing 50 % (*m*/*m*) of CoQ10

Preparation of WG-Gs using wet granulation method

The method used to prepare the WG-Gs is shown in Table I. Mannit P and PVP K-30 were placed within the VG-01, and the main plate was agitated for 3 min at 300 rpm. After CoQ10 was added, the main plate was agitated at 300 rpm, and the cross-screw was agitated at 1,500 rpm for 5 min. Purified water was then added, the main plate was agitated at 250 rpm, and the cross-screw was agitated at 1,500 rpm for 7 min. Purified water was added and the mixture was agitated for an additional 11 min. The granules obtained were dried in a DAE-100 at 40 °C for 10 h. The dried granules were sieved through a 1.0 mm sieve to obtain WG-Gs.

Preparation of CoQ10-ODTs

Using the CoQ10 bulk powder and the three types of granules (SD-G, HM-G, and WG-G), we pressed the following tablets: P-ODTs, SD-ODTs, HM-ODTs, and WG-ODTs, respectively (Table II). We prepared the ODTs using granules containing the greatest amount of the drug. SD-G and WG-G could be prepared for 50 % (*m*/*m*) of CoQ10 content by SD and WG methods, respectively, whereas the content in the case of the HM method was 33 % (*m*/*m*). Each ODT contained 10 mg CoQ10. The CoQ10 bulk powder or granule was mixed with Kollidon CL-SF (0, 1, 3, 5, or 10 %), sodium stearyl fumarate (2 %), and mannitol (Mannit Q). Each tablet weighed 280 mg. Using a manual tablet compressor (Handtab 200, Ichihashi Seiki, Co., Ltd., Japan), to which a 9.0 mm diameter mortar and pestle were attached, we pressed the tablets at a fixed pressure of 5 kN.

Assessment of the SD-G, HM-G, and WG-G particle diameter

We assessed the mean particle diameter (D_{50}) and particle size distribution using a laser scattering particle measurement device (LA-910 Particle Analyzer, Horiba Ltd., Japan).

Assessment of the tablet characteristics of the CoQ10-ODTs

The hardness of the CoQ10-ODTs. – The hardness of the CoQ10-ODTs was measured using a load-cell-type tablet hardness tester (PC-30, Okada Seiko Co., Ltd., Japan). The hardness of 10 tablets from each preparation was measured, and the mean values were calculated.

Disintegration time of the CoQ10-ODTs. – The disintegration time of the CoQ10-ODTs was measured using a Tricorptester (Okada Seiko Co., Ltd., Japan). A test solution (1.44 g L^{-1} NaCl, 1.47 g L^{-1} KCl, 0.3 % Tween 80) heated to 37 °C was dropped onto the tablets at a flow rate of 6.0 mL min^{-1}. A load of 40 g was applied to the upper mesh. The disintegration time of 10 tablets from each preparation was measured, and the mean values were calculated.

Dissolution of the CoQ10-ODTs. – Dissolution tests were performed in accordance with the paddle dissolution method in the 17th Revised Japanese Pharmacopoeia Dissolution Test Protocol, using a dissolution tester (PJ-6S, Miyamoto Riken Ind. Co., Ltd., Japan). The

Table II. Formulation of orally disintegrating tablets (ODTs) containing coenzyme Q10 (CoQ10)

Component (mg)	P-ODT	SD-ODT	HM-ODT	WG-ODT
Powder CoQ10	10.0	–	–	–
SD-G (50 %)	–	20.0	–	–
HM-G (33 %)	–	–	30.0	–
WG-G (50 %)	–	–	–	20.0
D-mannitol (Mannit Q)	250.4	240.4	230.4	240.4
Kollidon® CL-SF	14.0	14.0	14.0	14.0
Sodium stearyl fumarate	5.6	5.6	5.6	5.6
Total	280.0	280.0	280.0	280.0

P-ODTs – ODTs containing CoQ10 powder; SD-ODTs – ODTs containing CoQ10 produced by spray drying (SD-G, 50 %); HM-ODTs – ODTs containing CoQ10 produced by a hot-melting (HM-G, 33 %); WG-ODTs: ODTs containing CoQ10 produced by wet granulation (WG- G, 50 %)

test conditions were: rotation, 100 rpm; test solution volume (1.0 % Tween 80), 900 mL; and temperature of test solution, 37 ± 0.5 °C. One CoQ10-ODT was placed in the vessel and 12 mL of the solution was removed at 3, 5, 10, 15, 30, and 60 min after the start of the test. Immediately after the solution was removed, an equal volume of solution at the same temperature was added to the vessel.

Effect of storage on CoQ10-ODTs. – Four Petri dishes containing 24 CoQ10-ODTs were stored for 28 days at each of the following conditions: 30 °C/10 % RH; 30 °C/75 % RH; 50 °C/10 % RH; and 50 °C/75 % RH. One Petri dish was removed after 28 days of storage, and tablet hardness, disintegration time, and external appearance were assessed.

Assessment of pharmacokinetics of CoQ10 following oral administration of the ODTs

Animals. – Male Sprague-Dawley rats, 8–10 weeks old (Japan SLC Inc., Japan), were housed under a 12 h light/dark cycle at a controlled temperature (24 ± 2 °C) and humidity (55 ± 5 %). Food and water were provided *ad libitum*. All animal experiments were approved by the Institutional Animal Care and Use Committee of the University of Shizuoka (approval number: 156166) and adhered to the Japanese Guidelines for Proper Conduct of Animal Experiments.

Pharmacokinetics following oral administration of CoQ10-ODTs to rats. – The rats were fasted for 16–18 h before administration. One tablet of each CoQ10-ODT was suspended in water (5 mL) and the suspended solution was administered orally at a dose of 16 mg kg^{-1} CoQ10. Blood (0.2 mL) was collected from the jugular veins 1, 3, 6, 10, and 24 h after administration. Plasma was collected by centrifugation at 10,000 ×g for 5 min and stored at –20 °C until analysis by HPLC.

Pharmacokinetic analysis. – The pharmacokinetic parameters of CoQ10 were estimated by non-compartmental analysis. The maximum concentration in plasma (C_{max}) and time to reach C_{max} (T_{max}) were used as observed data. The elimination half-life ($t_{1/2}$) was calculated from the slope of the elimination phase. The area under the plasma concentration--time curve ($AUC_{0\text{-}24}$) was obtained by the trapezoidal rule up to 24 h.

Measurement of CoQ10 concentration

Sample preparation. – Plasma samples (100 μL) of rats were diluted with distilled water (900 μL) before sample preparation. Samples (1 mL) from the dissolution test or diluted plasma samples (1 mL) were mixed with CoQ9 (1 μg mL^{-1}, 100 μL) as the internal standard, ethanol (2 mL), and hexane (5 mL) and centrifuged at 3,000 rpm for 10 min. The organic solvent phase was dried under a nitrogen stream. The obtained dry residues were dissolved in 50 μL of ethanol, filtered through a 0.2 μm membrane filter (4 mm, Millex-LG, Millipore), and injected into the HPLC.

HPLC Measurement Conditions. – The amount of CoQ10 was determined by an HPLC system (Shimadzu Corporation, Japan), which consisted of an online degassing unit (DGU-20A3), solution sending unit (LC-20AD), column oven (CTO-20AC), autosampler (SIL-20AC), photodiode array UV visible detector (SPD-M20A), and system controller (CBM-20A). The column used was Inertsil® ODS-3 column (2.1 × 50 mm, 2.0 μm, GL Sciences Inc., Japan). In the dissolution test, the column temperature was set at 60 °C and a mixture of ethanol and acetonitrile (10/90) was used. In the pharmacokinetics test, the column temperature was set at 40 °C and a mixture of ethanol and acetonitrile (5/95) was used. The flow rate was set at 0.5 mL min^{-1} and the detection was based on UV absorbance at 275 nm. The analysis software used was the LC solution (version 1.25; Shimadzu Corporation).

Data analysis

The measured data are displayed as the mean ± standard deviation. Statistical analysis was performed using statistical analysis software (GraphPad Prism ver. 5.02, GraphPad Software, Inc., USA). Statistically significant differences in the dissolution test and pharmacokinetic analyses were determined using Dunnett's test. Statistically significant differences in pharmacokinetic parameters were determined using Tukey's multiple comparison test. In all cases, $p < 0.05$ were considered significant.

RESULTS AND DISCUSSION

Tablet characteristics and dissolution of CoQ10-ODTs

We assessed the hardness and disintegration time of four types of CoQ10-ODTs (P-ODTs, SD-ODTs, HM-ODTs, and WG-ODTs) containing 0, 1, 3, 5 and 10 % Kollidon CL-SF (Table III). The hardness values ranged from 61.6 to 81.8 N. Hardness and friability are used as indicators of tablet strength. It has been shown that the ODTs with ≥ 40 N hardness could prevent problems caused by lower strength and be clinically acceptable (12). In addition, both parameters showed a good correlation in our preliminary tests. The prepared ODTs in this study would be adequate for clinical use (23). The disintegration time tended to be shortened as the Kollidon CL-SF content increased. SD-ODTs had the longest disintegration time, but it was less than 30 s when the Kollidon CL-SF content was 5 or 10 %. The United States Food and Drug Administration (USFDA) guidelines indicate a desirable disintegration time of less than 30 s (24). Therefore, based on the results for hardness and disintegration time, 5 % Kollidon CL-SF was added to all CoQ10-ODTs.

Table III. Hardness and disintegration time of orally disintegrating tablets (ODTs) containing coenzyme Q10 (CoQ10) with different concentrations (%) of Kollidon CL-SF

CoQ10-ODTs	Kollidon CL-SF concentration				
	0 %	1 %	3 %	5 %	10 %
Hardness (N)					
P-ODTs	71.0 ± 3.5	80.6 ± 3.6	81.8 ± 2.3	67.6 ± 3.3	77.0 ± 3.9
SD-ODTs	74.0 ± 3.5	75.8 ± 2.3	73.6 ± 3.2	61.6 ± 2.8	70.4 ± 5.8
HM-ODTs	73.2 ± 1.8	80.4 ± 2.5	76.8 ± 3.0	74.6 ± 4.2	69.4 ± 4.8
WG-ODTs	75.6 ± 3.0	74.4 ± 4.3	71.6 ± 3.4	67.8 ± 4.9	72.6 ± 2.6
Disintegration time (s)					
P-ODTs	115.6 ± 4.4	33.5 ± 2.0	12.9 ± 0.4	11.7 ± 0.5	10.8 ± 0.2
SD-ODTs	> 250	> 250	29.2 ± 0.9	21.9 ± 1.2	20.2 ± 0.8
HM-ODTs	> 250	129.8 ± 10.9	16.9 ± 0.3	14.9 ± 0.7	13.8 ± 0.5
WG-ODTs	125.3 ± 3.8	26.2 ± 1.1	13.1 ± 0.7	11.9 ± 0.4	10.9 ± 0.3

P-ODTs – ODTs containing CoQ10 powder; SD-ODTs – ODTs containing CoQ10 produced by spray drying; HM-ODTs – ODTs containing CoQ10 produced by hot melting; WG-ODTs: ODTs containing CoQ10 produced by wet granulation. The data represent the mean ± SD (n = 5).

Dissolution tests were performed on the four CoQ10-ODTs. Tween 80 solution (1 %) was selected as the test solution because CoQ10 has poor solubility in this substance. The SD-ODTs showed the highest dissolution rate among all CoQ10-ODTs, and the dissolution rate at all sampling points was significantly higher than that of P-ODTs (Fig. 1). There were no significant differences in dissolution rate among P-ODTs, HM-ODTs, and WG-ODTs.

Storage properties of CoQ10-ODTs

We subjected the four types of CoQ10-ODTs to different storage conditions: 1, 30 °C/10 % RH; 2, 30 °C/75 % RH; 3 50 °C/10 % RH; and 4, 50 °C/75 % RH. The effects of the four storage conditions were assessed on hardness, disintegration time (Fig. 2), and the external appearance of the CoQ10-ODTs.

After a 28-day storage period at 30°C/10 % RH, the hardness and disintegration times of SD-ODTs, HM-ODTs, and WG-ODTs did not significantly change (Fig. 2). In contrast, after storage at 50 °C/10 % RH, the hardness in all CoQ10-ODTs decreased and disintegration times increased (Fig. 2). As the melting point of CoQ10 is approximately 48 °C (4), it was inferred that CoQ10 melted under the storage conditions of 50 °C, resulting in loss of appropriate tablet characteristics such as sufficient hardness and rapid disintegration. All CoQ10-ODTs showed an overall change toward the characteristic yellow colour of CoQ10 after storage at 50 °C in 10 % RH and 75 % RH, suggesting that CoQ10 had melted on the surface of tablets. Under storage at 75 % RH (30 °C and 50 °C) for 28 days, the hardness was reduced and disintegration times were shorter in all ODTs compared with the initial values (Fig. 2). It was speculated that the characteristic hygroscopicity of ODTs was enhanced in the high-humidity environment, which reduced their hardness and shortened their disintegration time (25, 26).

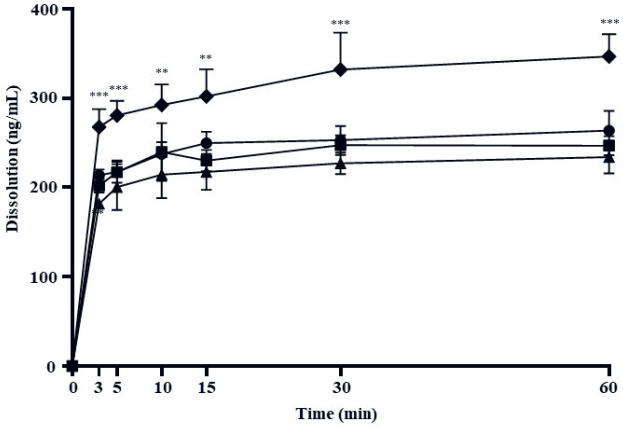

Fig. 1. Dissolution profiles of CoQ10 from P-ODTs, SD-ODTs, HM-ODTs, and WG-ODTs in 1.0 % Tween 80 solution. Each point represents the mean ± SD (n = 5). ●, ODTs containing powdered CoQ10 (P-ODTs); ◆, ODTs containing CoQ10 granules prepared by spray drying (SD-ODT); ■, ODTs containing CoQ10 granules prepared by hot-melting (HM-ODTs); ▲, ODTs containing CoQ10 granules prepared by wet granulation (WG-ODTs). $^{**}p < 0.01$, $^{***}p < 0.001$, significant difference compared with the values of P-ODTs using Dunnett's multiple comparison test.

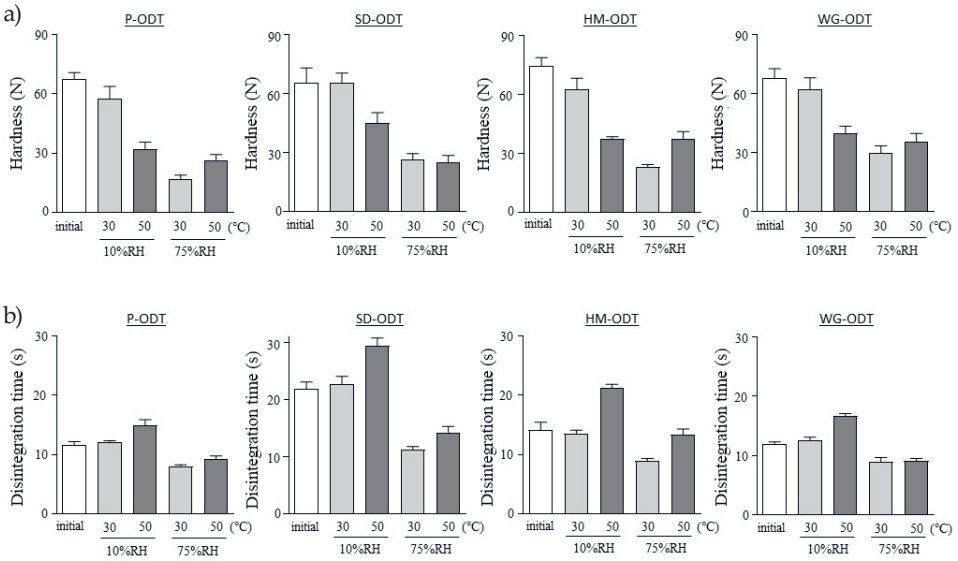

Fig. 2. a) Hardness and b) disintegration time of P-ODTs, SD-ODTs, HM-ODTs, and WG-ODTs after preparation (initial) and 28-day storage in various preservation conditions (30 or 50 °C /10 %RH and 30 or 50 °C/75 %RH). Each column represents the mean ± SD (n = 5). ODTs containing powdered CoQ10 (P-ODTs), ODTs containing CoQ10 granules prepared by spray drying (SD-ODTs), hot-melting (HM-ODTs), and wet granulation (WG-ODTs).

Particle preparation could be useful for avoiding the problems of manufacturing CoQ10-ODTs, such as sticking and surface spotting, and could be beneficial for the storage of ODTs. We had no compression trouble when preparing ODTs using three different particles in this study and the tablets had a good appearance. The powder flowability was not evaluated in this study, although the flow properties are one of the most important powder characteristics. Every CoQ10-ODTs was prepared using a single-punch tablet press, after precisely weighing the powder mixture. Thus, we believe that the mass and drug uniformity of the CoQ10-ODTs can be assured, and the powder flowability test was not evaluated in this study. Further evaluation including manufacturing difficulties of the rotary tabletting machine, flowability of the granules, and uniformity of tablets are necessary.

The results of this study indicated that the tablet characteristics of each CoQ10-ODT--containing particles prepared *via* the three methods were negatively affected by the storage in the high-humidity and high-temperature environment. Appropriate packages such as a blister or press-through pack (PTP) package could effectively prevent moisture damage. From a clinical point of view, temperature and humidity for the storage of tablets are not often controlled in patients' homes. Thus, patients should be advised to avoid high temperatures and humidity for the storage of CoQ10-ODTs.

Pharmacokinetics following oral administration of CoQ10-ODTs in rats

We evaluated the pharmacokinetics of CoQ10 following oral administration of the four CoQ10-ODTs to rats. The plasma drug concentration-time profiles are shown in Fig. 3, and the pharmacokinetic parameters are listed in Table IV. No significant differences in $t_{1/2}$ and T_{max} were observed for any of the ODTs. The C_{max} and $AUC_{0\text{-}24}$ for SD-ODTs were

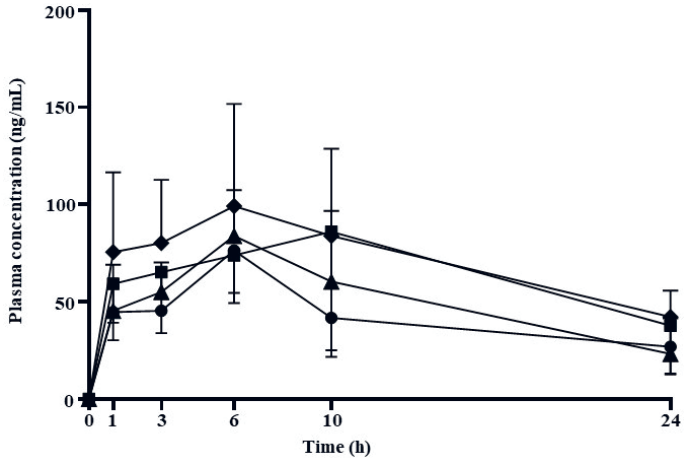

Fig. 3. Plasma concentration profiles of CoQ10 after oral administration of P-ODTs, SD-ODTs, HM-ODTs, and WG-ODTs to rats. Each point represents the mean ± SD (n = 6–7). ●, ODTs containing powdered CoQ10 (P-ODTs); ◆, ODTs containing CoQ10 granules prepared by spray drying (SD-ODTs); ▲, ODTs containing CoQ10 granules prepared by hot-melting (HM-ODTs); ■, ODTs containing CoQ10 granules prepared by wet granulation (WG-ODTs).

Table IV. Pharmacokinetic parameters of coenzyme Q10 (CoQ10) following the oral administration of P-ODTs, SD-ODTs, HM-ODTs, and WG-ODTs in rats

	P-ODTs	WG-ODTs	HM-ODTs	SD-ODTs
$t_{1/2}$ (h)	24.3 ± 23.5	15.7 ± 14.5	19.4 ± 14.3	17.6 ± 8.0
T_{max} (h)	6.67 ± 1.63	7.33 ± 2.07	6.33 ± 3.14	5.14 ± 3.18
C_{max} (ng mL^{-1})	77.2 ± 19.7	91.1 ± 27.2	109 ± 49	130 ± 44*
$AUC_{0\text{-}24}$ (h μg mL^{-1})	1.01 ± 0.14	1.21 ± 0.43	1.55 ± 0.71	1.71 ± 0.60*

P-ODTs – Orally disintegrating tablets (ODTs) containing CoQ10 powder; SD-ODTs – ODTs containing CoQ10 produced by spray drying; HM-ODTs – ODTs containing CoQ10 produced by a hot-melting; WG-ODTs – ODTs containing CoQ10 produced by wet granulation; $t_{1/2}$ – elimination half-life; T_{max} – time to reach C_{max}; C_{max} – maximum concentration in plasma; $AUC_{0\text{-}24}$ – area under the curve of plasma concentration *vs.* time up to 24 h. The data represent the mean ± SD (n = 6–7). * $p < 0.05$, a significant difference compared with the values of P-ODT using Tukey's multiple comparison test.

significantly higher (1.7-fold) than those for P-ODTs. There were no statistically significant differences between the P-ODTs, WG-ODTs, and HM-ODTs in the values of C_{max} and $AUC_{0\text{-}24}$, but those for SD-ODTs were the highest of all ODTs. This agrees with the results of the dissolution test, which suggests that SD-ODTs may be the most appropriate ODTs from the perspective of absorbability.

It has been reported that the solubility and oral bioavailability of poorly water-soluble drugs are improved by granulation using the SD method. Griseofulvin particles containing a hydrophilic surfactant (poloxamer 407) produced by the SD method showed a significant increase in dissolution rate and absolute oral bioavailability compared to crystalline griseofulvin (27). Thus, it is likely that SD methods in the presence of other hydrophilic surfactants (gum arabic) in this study could play an important role in increasing the absorbability of SD-ODTs.

CoQ10 is a typical BCS class IV drug with low bioavailability (0.66 % in humans and 0.22 % in rats) (28, 29). Some formulations of CoQ10 have been reported to improve its absorption and bioavailability. Hatanaka *et al.* indicated that both *AUC* and C_{max} of liquid nano-emulsion formulations of CoQ10 were 1.7-fold higher than those of crystalline CoQ10 in correlation with the particle size after dissolution (30). Other components, such as liposomes, cyclodextrin complexes, and self-emulsifying drug delivery systems, have also been reported to improve the absorption of CoQ10 (31). These methods have been applied to solid pharmaceutical formulations, such as soft gel, suspension, syrup, and capsules. However, there are currently no reports of the development of CoQ10 tablets. Our CoQ10-ODT with improved bioavailability of CoQ10 could provide a new option for solid formulations.

CONCLUSIONS

In this study, we prepared and evaluated the tablet characteristics and pharmacokinetics of CoQ10-ODTs containing CoQ10 granules prepared by the SD, HM, and WG methods. The hardness and disintegration times of CoQ10-ODTs containing 5 % Kollidon CL-SF were 61.6–81.8 N and < 30 s, respectively, suggesting sufficient values for clinical use of ODTs. The hardness and disintegration times of all ODTs were not significantly changed

after a 28-day storage period at 30 °C/10 % RH, but storage under high temperature and humidity affected their tablet characteristics. No differences in the results based on the particle preparation of CoQ10 in ODTs were observed. The dissolution test and pharmacokinetics of CoQ10-ODTs showed that SD-ODTs had the highest dissolution and absorbability among the CoQ10-ODTs tested. Our results provide useful information for the preparation of CoQ10-ODTs avoiding technical difficulties related to their manufacture.

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