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Quality Evaluation of Carnitine for Proper Use of Supplement

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Abstract

In recent years, consumers are becoming more health-conscious. Supplements are becoming popular as they can be purchased easily. In Japan, the "Food with Function Claims" system began in 2015; the market for supplements is expected to continue to expand. However, the use of some supplements has not been supported with sufficient scientific evidence; some products have even caused health problems. In addition, consumers may not be able to make correct decisions based on the information from the Internet. Unlike medicine, the instruction on the usage of supplements is not precise. Therefore, improving the quality of the information on the supplements will become more necessary in the future. This study aims to improve the quality of the information on supplements by surveying the disintegration and dissolution behavior of the carnitine-containing supplements and evaluated their quality. The products tested here were supplements containing commercial carnitine. Disintegration test and dissolution test were conducted according to the Japanese Pharmacopoeia. Carnitine was quantified by high-performance liquid chromatography. The disintegration tests revealed that the products had different disintegration times, varying from 35 to 100 minutes; some products took more than 5 hours to disintegrate. Thus, some products had a slow rise in their dissolution rate. These results suggest that the carnitine-containing supplements used in this study may affect the absorption process. Therefore, in the case of oral administration, the expected effect might not be achieved depending on the product.

Keywords

Supplement, Disintegration Test, Dissolution Test, Carnitine

1. Introduction

The concept of self-medication has permeated public consciousness in recent years. With the consumers' increasing health awareness, supplements have become an attractive option as they can be purchased and utilized easily by themselves. In 2015, "Foods with Function Claims" has been launched based on the Food Labeling Act. The system of "Foods with Function Claims" provides "opportunities for consumers to make voluntary and reasonable product choices." Supplements and functional foods are quickly forming a new food system. Food business operators are responsible for providing consumers with accurate information to help them understand the new system. By October 2020, about 3500 functional labeled foods have been reported, and the number of registered items is increasing [1]. In 2012, "Survey on the Use of Supplements" by the Consumer Committee of the Cabinet Office, about 25% of 10,000 consumers age 20 - 79 used supplements every day to "maintain health and promote health." If the occasional users are included, about 60% of the consumers have reported using supplements [2]. With the increasing prevalence of the Internet and smartphones, consumers have easy access to domestic and international products. The supplement market is expected to expand further in the future.

On the other hand, there have been cases of health hazards related to supplements. For example, 4 of 796 health claims against Chinese diet supplements were reported to be fatal [3]. In addition, much uncertain information from the Internet and television has significantly impacted food safety [4]. While the Internet allows instantaneous access to a vast amount of information, it is challenging for consumers to identify the correct information.

Moreover, supplements are different from medicines due to the lack of standardization in their quality control and usage [5]. First, supplements are sold by different companies. Also, the scientific evidence supporting their usage is not always sufficient. Even if the products have the same ingredients, they may significantly different compositions of the ingredients, resulting in variations in quality and safety. In addition, it has been reported that there are many cases of health claims caused by the use of products of deteriorated quality and overdose [6]. Kawamura *et al.* conducted disintegration tests on functional food products and found that they did not disintegrate within the specified time, indicating a clear difference in quality compared to medicines [7]. The National Consumer Affairs Center also conducted disintegration tests on popular health foods and found that in 42 out of 100 cases, the products did not disintegrate within the specified time [8]. Accurate information on supplements is necessary to the consumers to avoid the adverse events related to incorrect consumption. Therefore, there is a need for full disclosure of product quality information for medicine and supplements.

Carnitine, an ingredient of supplements, is thought to help control body weight and reduce body fat. Carnitine is a type of free amino acid found in living organisms and essential for lipid metabolism. It is touted as a "burning fat" etc.,

because it produces acyl-CoA from fatty acids in the body and uses it as energy [9] [10]. We have previously enhanced the quality of the information on supplements containing chondroitin sulfate, hyaluronic acid, and collagen by conducting disintegration and dissolution tests [11].

This study aims to improve the quality of the information on carnitine-containing supplements. The disintegration and dissolution behavior of the various carnitine-containing supplements were evaluated based on the quality of the supplements.

2. Method

2.1. Test Products

The commercially available supplements (C1-C3) were selected for analysis. The ethical medication (M1) was used for comparison to the supplements. The content and additives of each supplement are shown (**Table 1**, **Table 2**). The reagents and solvents used in the experiment were reagent grade or high-performance liquid chromatography grade.

2.2. Disintegration Test [12] [13]

The disintegration test was conducted following the Japanese Pharmacopoeia 14th edition (JP14) and 16th edition (JP16). A bath of purified water at 37˚C ± 2˚C with the shaking speed of 29 - 32 shakes per minute and the shaking width of 53 - 57 mm, and the disintegration tester HC-1 (Yazawa Science Co., Ltd.) were used. In JP14, auxiliary disks are always used (disk-method). In JP16, the use of auxiliary disks is permitted only where specified or allowed, and the disks are not used normally (no disk-method). The time from the start of the test to the tablet's disintegration was observed visually to determine the end of disintegration.

Table 1. Carnitine containing products.

Type	Product name	Recommended dose	characteristics
Supplement	C1	5 tablets/day (750 mg)	Coating tablet
	C2	4 tablets/day (432 mg)	Tablet
	C3	6 tablets/day (200 mg)	Coating tablet
Medicine	M1	—	Tablet

Table 2. Additives agent.

C1	cellulose, calcium stearate, starch (hydroxypropyl cellulose), tocotrienol, silicon dioxide, and vitamin B_1
C2	powdered reduced maltose, cellulose, calcium stearate, hydroxypropyl cellulose, shellac
C3	piper longum powder, starch, reduced maltose, starch degradation product, green tea extract, cellulose, cyclodextrin, sucrose ester, fine silicon dioxide, hydrochloride, hydroxypropyl methylcellulose, shellac, glycerol, wax
M1	hydroxypropyl cellulose, cellulose, light anhydrous silicic acid, magnesium stearate, hypromellose, macrogol 6000, talk, and titanium oxide

2.3. Dissolution Test [12] [14]

The dissolution test was conducted according to the method 2 (the paddle method), of the JP16. The dissolution tester TMB-81 NTR-1000 (Toyama Sangyo Co., Ltd.) was used. A bath of purified water at 37˚C ± 0.5˚C with the paddle's rotational speed of 60 rpm was used. The samples were eluted, collected, and passed through a 0.45-μm membrane filter. Lastly, because some products did not increase the elution rate, an additional test using a stirrer at a rotation of about 100 rpm was conducted instead of the paddle method (Figure 1).

2.4. Quantification of Carnitine [12] [14]

The amount of carnitine was measured using high-performance liquid chromatography (SHIMADZU CORPORATION) according to the JP16. The COSMOSIL5C 18-MS-II 4.6 × 150 mm column (NACALAITESQUE, INC.) was used at 40˚C at a flow speed of 1.0 mL/min and the wavelength 220 nm. Acetonitrile/pH2.5 and 0.05 mol/L phosphate buffer at the ratio of 1:19 were used for the mobile phase.

3. Result

3.1. Disintegration Test

The disintegration times of carnitine-containing products were determined (Table 3). JP stipulates that "tablets will disintegrate within 30 minutes, and coated tablets will disintegrate within 60 minutes." C1 was found to disintegrate in 52.4 minutes and C2 in 35.6 minutes using no disk-method. JP's stipulation concerns the regulation of clinical medicine. However, C1 and C2 were found to conform to the criterion. C3 had a sturdy film coating that did not break during the disintegration test; in fact, it did not disintegrate for more than 300 hours. Assayed by disk-method, all supplements were found to meet the standards of the JP. Assayed by the no disk-method, the supplements' disintegration times were found to be longer than that of the medicine.

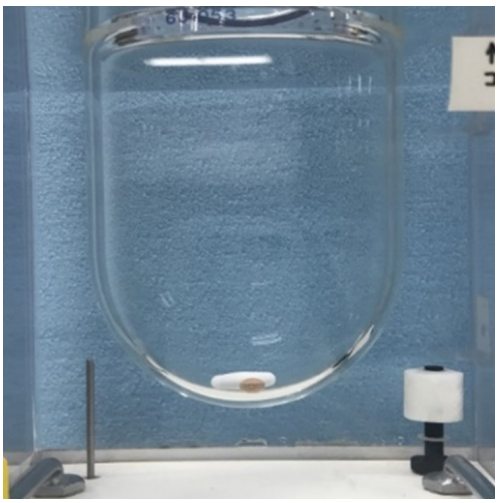

Figure 1. Dissolution test using stirrer.

3.2. Dissolution Test

The dissolution of carnitine-containing products was assayed by the paddle method (Figure 2). C1 and C2 dissolved more slowly than M1. However, the dissolution rate in C2 and C3 after 120 minutes was about 100%. On the other hand, C3 began to dissolve after 30 minutes, becoming 20% dissolved after 120 minutes. The dissolution behavior of carnitine-containing products using the stirrer was also examined (Figure 3). When the stirrer was used instead of the paddle method, all the products dissolved more quickly. C3 was dissolved more slowly than C1 and C2; it became 100% dissolved 120 minutes.

Table 3. Disintegration time of carnitine (min).

	C1	C2	C3	M1
no disk-method	52.4 ± 0.8	35.6 ± 1.4	300<	10.2
disk-method	32.8 ± 0.7	22.2 ± 1.3	42.1 ± 10.2	9.8 ± 1.8

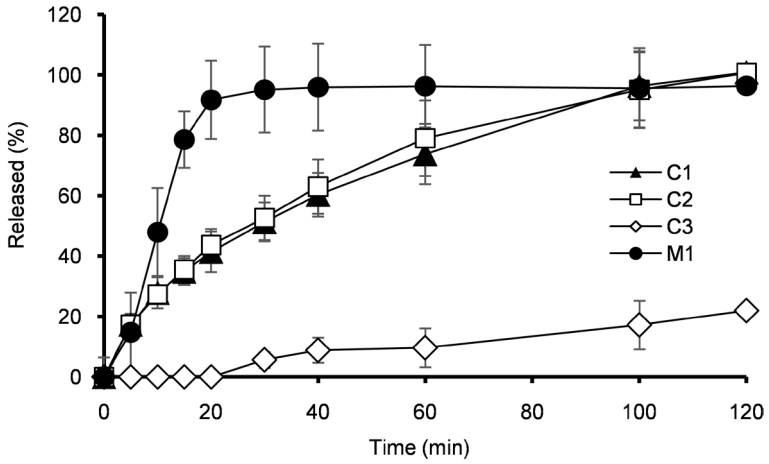

Figure 2. Dissolution behavior of paddle method. Mean ± SD (n = 6).

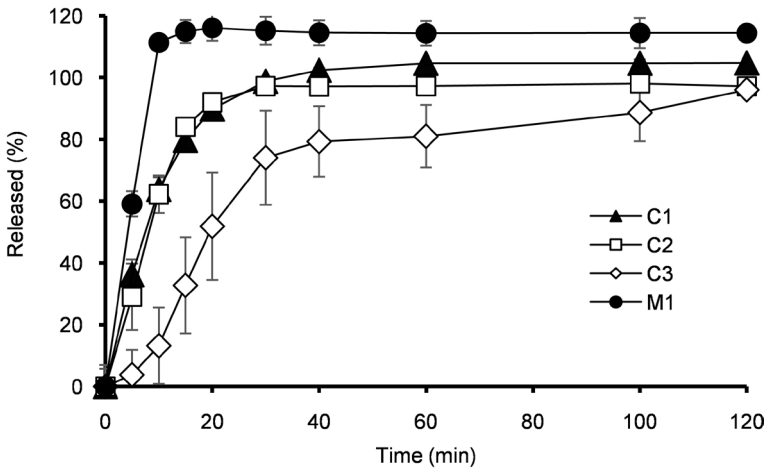

Figure 3. Dissolution behavior using stirrer. Mean ± SD (n = 6).

4. Discussion

As consumers become more health-conscious and increasingly promote self-medication, it becomes necessary and urgent to collect product information on dietary supplements. In this study, disintegration tests and dissolution tests were conducted on carnitine-containing products to increase the understanding of these supplements.

According to the results from the disintegration test of no disk-method, C1 and C2 were compliant with the regulation, and they displayed relatively small variability. C3 had a longer disintegration time and displayed higher variability, suggesting that its coating tablet was less likely to break under stimulation in the disintegration test. In reports on disintegration studies of functional foods, the percentage of coated tablet that did not disintegrate within the specified time was higher than that of uncoated tablet and capsules, which was similar to this study [15]. M1 had the shortest disintegration time and the smallest variability compared to the supplements.

According to the results from disk-method, all supplements became compliant with the regulation, and they all had shorter disintegration time. The C3 tablets became disintegrated by the method using disks. It was presumed that the disks facilitated the disintegration of C3's coating tablet, thus shortening the disintegration time. The disintegration time of M1 was not changed by the use of the disks. These results suggest that medicine can be effective regardless of the condition of the stomach contents.

When the paddle method was used for the dissolution test, C1 and C2 were shown to become 100% dissolved after 2 hours. Meanwhile, the dissolution behavior of C3 increased more slowly than that of C1 and C2, becoming 20% dissolved within the same time frame. The dissolution of C3 was likely affected by the nature of the film coating, as with its results from the disintegration test.

On the other hand, the increase in dissolution behavior was accelerated for all products using a stirrer. The dissolution rate of C3 increased to nearly 100%. However, the rise in dissolution behavior was slower than that of the other products. C3's film coating might have taken some time to disintegrate; the physical stimulation by the stirrer might have accelerated the dissolution in all the products because of the fast start-up of dissolution.

According to the disintegration and dissolution tests, C1 had the shortest disintegration time and a dissolution rate of about 100%. Among the supplements tested in this study, C1 is likely to achieve the fastest absorption and efficacy. C3 was considered to be difficult to achieve the expected effect according to the test method of the JP16. Considering the fact that they are absorbed after being disintegrated after ingested into the body, it can be inferred that they may be discharged from the body without being disintegrated, which may have some effect on the absorption process. The difference between the time of disintegration and the dissolution behavior seemed to have been caused by the difference in viscosity and collapsibility of the additives contained in the products. Moreover, such a

difference may also affect the absorption process. In this study, some experiments were conducted with the additional stirrer, resulting in a reduction in the disintegration time and the increase of the dissolution rate. These data suggest that some products with film coating can have the expected effect with internal disintegration by the body, such as with or without food. In the case of insoluble coated tablets, it was not possible to evaluate according to the JP. Therefore, it is necessary to consider the body's stimulation and examine the experiment, such as physically destroying coating like this study.

The health support pharmacy system was started in April 2016. Health support pharmacies have the essential functions of the family pharmacist/pharmacy by proactively maintaining and promoting the health of community members [16]. Accordingly, pharmacists are required to be knowledgeable about pharmaceutical products as well as supplements [17]. Although the placebo effect may also be involved for supplements, it is thought that specific information needs to be provided so that formulation characteristics such as dissolution behavior and disintegration can be taken into account, just like for pharmaceuticals [18]. Therefore, it is necessary to present information on dosage and administration in consideration of formulation characteristics, such as dissolution behavior and disintegration. In the future, as a pharmacist, we must also educate consumers about supplements, recommend products that suit each consumer's needs, and contribute to the maintenance of health.

Conflicts of Interest

The authors declare no conflicts of interest regarding the publication of this paper.

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