撹拌造粒による新規口腔内崩壊錠に関する研究［Ⅲ］

Studies on orally disintegrating tablets manufacturing by agitation granulation［Ⅲ］

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概要

今回我々は、新たに開発した口腔内崩壊錠の、製剤処方に伴う許容性を検証することを目的に、プラセボ製剤を用い、本製剤の添加剤(賦形剤、結合剤、崩壊剤)を種々選択して配合した錠剤について、それぞれ錠剤物性の評価を行った。その結果、本製剤技術を基に、水溶性結合剤であるポビドン又はヒドロキシプロピルセルロースと、矯味剤として知られるタンニン酸とを添加することにより、本製剤の構成成分を種々変更した錠剤において、崩壊性及び吸水性に対する優れた改善効果が認められた。

Introduction

The dosage forms of oral solid preparations including tablets, capsules, granules, powders and the like are generally known in the field of pharmaceuticals. However, there is a big problem in terms of patient compliance and adherence that it is difficult for elderly people and children, patients with dysphagia, bedridden patients or patients whose water intake has been limited to take medicines because each of these dosage forms is required water at the use of them. In recent years, to improve patient compliance and adherence, orally disintegrating tablets which can disintegrate with saliva in the oral cavity or a small amount of water have been developed as tablets which can be taken easily and safely.

According to the classification of Masuda *et al.*[1], orally disintegrating tablets can fall into 3 categories based on technology concept: molded tablet preparation, wet type tablet preparation and ordinary tablet preparation. Moreover, ordinary tablet preparation can fall into 3 categories: preparation with additives having high formability, creative preparation of decay mechanism, porous molding preparation. There have been many problems to be solved in terms of versatility because they are required specific manufacturing method and complicated manufacturing process to improve moldability, disintegration and water absorption[2),3)]. However, we already have discovered oral disintegrating tablets having excellent moldability, disintegration and water absorption, produced through the agitation granulation, used as the general-purpose manufacturing methods, added povidone or hydroxypropylcellulose used as

water-soluble binder together with tannic acid used as a taste masking agent in the formulation[4),5)]. In addition, it was confirmed that each of tablet properties remains even under severe conditions when temporal stability of orally disintegrating tablets prepared according to the formulation were examined[6),7)].

In the study, the excellent disintegration and fast water absorption was found when the impact on tablet properties with tannic acid was examined about tablets which consist of various additives (excipient, binder and disintegrator).

Method

1. Sample

The list of equipment used in the study is shown in table 1.

Table 1. Sample

Application	Compounding sample	Manufacturer
Water-soluble binder	Povidone	ISP (Japan) Co., Ltd.
	Hydroxypropylcellulose	Nippon Soda Co., Ltd.
Excipient	D-Mannitol	Roquette (Japan) Co., Ltd. Mitsubishi Shoji Foodtech Co., Ltd.
	Lactose hydrate	DMV-Fonterra Excipients Co., Ltd.
Binder	Magnesium aluminometasilicate	Fuji Chemical Industry Co., Ltd.
	Synthetic aluminum silicate	Kyowa Chemical Industry Co., Ltd.
	Light anhydrous silicic acid	Fuji Silysia Chemical Co., Ltd.
	Calcium silicate	Tomita Pharmaceutical Co., Ltd.
Disintegrator	Crospovidone	BASF (Japan) Co., Ltd.
	Croscarmellose sodium	Asahi Kasei Chemicals Corporation
	Carmellose calcium	Nichirin Chemical Industries Co., Ltd.
	Carmellose	Nichirin Chemical Industries Co., Ltd.
Algefacient	l-Menthol	Koshiro Co., Ltd.
High-sweetness sweetener	Aspartame	Ajinomoto Co., Ltd.
Taste masking agent	Citric acid hydrate	Satuma Kako Co., Ltd.
	Tannic acid	Fuji Chemical Industry Co., Ltd.
Lubricant	Magnesium stearate	Taihei Chemical Industrial Co., Ltd.

2. Equipment

The list of equipment used in the study is shown in table 1.

Table 2. Equipment

Name	Manufacturer	Model
Agitation granulator	Okada Seiko Co., Ltd.	Mechanomill MM-20N
Shelf dryer	Kimura Kagaku Kikai Co., Ltd.	Fast dryer
Rotary Tablet Press	Kikusui Seisakusho Co., Ltd.	VELA5
Tablets Hardness Tester	Toyama Sangyo Co., Ltd.	TH-303MP
Disintegration tester	Toyama Sangyo Co., Ltd.	NT-40H

3. Formulation and preparation method (Placebo)

Based on the component of preparation formulation shown in Table 3-7, after povidone or hydroxypropylcellulose and D-mannitol or lactose hydrate were mixed in the agitation granulator, the mixture was granulated by adding gradually a solution dissolving tannic acid in an adequate anhydrous ethanol or an adequate anhydrous ethanol. After drying the granule in a shelf dryer, it was subjected to particle size regulation. After other additives were added and mixed, tablets having 8.5 mm of tablet diameter and 240 mg of tablet weight were obtained by using a rotary

tablet press at about 8 kN of tableting pressure.

Table 3. Placebo formulation (A)

Formulation No.	1	2	3	4	5	6	7	8
Povidone	12.0	12.0	12.0	12.0	—	—	—	—
Hydroxypropylcellulose	—	—	—	—	12.0	12.0	12.0	12.0
Tannic acid	6.0	—	6.0	—	6.0	—	6.0	—
D-Mannitol	510.6	516.6	—	—	510.6	516.6	—	—
Lactose hydrate	—	—	510.6	516.6	—	—	510.6	516.6
Magnesium aluminometasilicate	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Crospovidone	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Aspartame	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
l-Menthol	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Citric acid hydrate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total weight (g)	576.0	576.0	576.0	576.0	576.0	576.0	576.0	576.0

Table 4. Placebo formulation (B)

Formulation No.	1	2	9	10	11	12	13	14
Povidone	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Tannic acid	6.0	—	6.0	—	6.0	—	6.0	—
D-Mannitol	510.6	516.6	510.6	516.6	510.6	516.6	510.6	516.6
Magnesium aluminometasilicate	9.0	9.0	—	—	—	—	—	
Synthetic aluminum silicate	—	—	9.0	9.0	—	—	—	—
Light anhydrous silicic acid	—	—	—	—	9.0	9.0	—	—
Calcium silicate	—	—	—	—	—	—	9.0	9.0
Crospovidone	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Aspartame	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
l-Menthol	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Citric acid hydrate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total weight (g)	576.0	576.0	576.0	576.0	576.0	576.0	576.0	576.0

Table 5. Placebo formulation (C)

Formulation No.	5	6	15	16	17	18	19	20
Hydroxypropylcellulose	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Tannic acid	6.0	—	6.0	—	6.0	—	6.0	—
D-Mannitol	510.6	516.6	510.6	516.6	510.6	516.6	510.6	516.6
Magnesium aluminometasilicate	9.0	9.0	—	—	—	—	—	
Synthetic aluminum silicate	—	—	9.0	9.0	—	—	—	—
Light anhydrous silicic acid	—	—	—	—	9.0	9.0	—	—
Calcium silicate	—	—	—	—	—	—	9.0	9.0
Crospovidone	30.0	30.0	30.0	30.0	30.0	30.0	30.0	30.0
Aspartame	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
l-Menthol	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Citric acid hydrate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total weight (g)	576.0	576.0	576.0	576.0	576.0	576.0	576.0	576.0

Table 6. Placebo formulation (D)

Formulation No.	1	2	21	22	23	24	25	26
Povidone	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Tannic acid	6.0	—	6.0	—	6.0	—	6.0	—
D-Mannitol	510.6	516.6	510.6	516.6	510.6	516.6	510.6	516.6
Magnesium aluminometasilicate	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Crospovidone	30.0	30.0	—	—	—	—	—	—
Croscarmellose sodium	—	—	30.0	30.0	—	—	—	—
Carmellose calcium	—	—	—	—	30.0	30.0	—	—
Carmellose	—	—	—	—	—	—	30.0	30.0
Aspartame	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
l-Menthol	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Citric acid hydrate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total weight (g)	576.0	576.0	576.0	576.0	576.0	576.0	576.0	576.0

Table 7. Placebo formulation (E)

Formulation No.	5	6	27	28	29	30	31	32
Hydroxypropylcellulose	12.0	12.0	12.0	12.0	12.0	12.0	12.0	12.0
Tannic acid	6.0	—	6.0	—	6.0	—	6.0	—
D-Mannitol	510.6	516.6	510.6	516.6	510.6	516.6	510.6	516.6
Magnesium aluminometasilicate	9.0	9.0	9.0	9.0	9.0	9.0	9.0	9.0
Crospovidone	30.0	30.0	—	—	—	—	—	—
Croscarmellose sodium	—	—	30.0	30.0	—	—	—	—
Carmellose calcium	—	—	—	—	30.0	30.0	—	—
Carmellose	—	—	—	—	—	—	30.0	30.0
Aspartame	1.8	1.8	1.8	1.8	1.8	1.8	1.8	1.8
l-Menthol	0.6	0.6	0.6	0.6	0.6	0.6	0.6	0.6
Citric acid hydrate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Magnesium stearate	3.0	3.0	3.0	3.0	3.0	3.0	3.0	3.0
Total weight (g)	576.0	576.0	576.0	576.0	576.0	576.0	576.0	576.0

4. Measurement method

1) Hardness test

The tablet hardness was determined by using tablets hardness tester (n = 10).

2) Disintegration test

According to “the disintegration testing method” stipulated in the Japanese Pharmacopoeia 16th edition, the tablet disintegration time was determined by using disintegration tester. Water was used as a test solution and the tablet disintegration time was determined without disk (n = 6).

3) Absorption test

As shown figure 1, after fully soaking an insoluble paper folded in four with 6 mL of water in 6.5 cm of petri dish, one tablet was put on the paper and the time taken to wet whole tablet was measured (n = 3)[8].

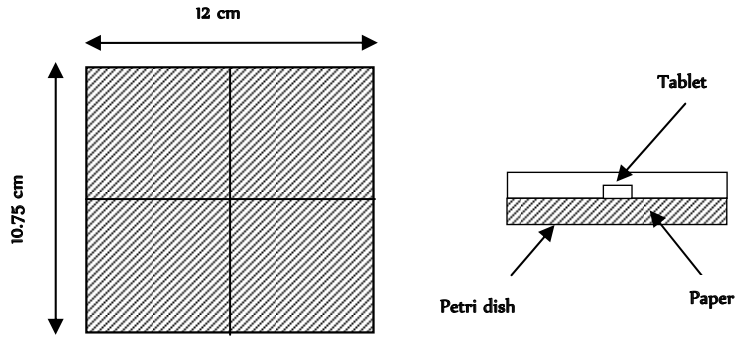

Fig. 1. Absorption test method

Results and Discussion

Various additives such as povidone and hydroxypropylcellulose which are water-soluble binder, D-mannitol or lactose hydrate which are excipients, magnesium aluminometasilicate, synthetic aluminum silicate, light anhydrous silicic acid or calcium silicate which are binders, crospovidone, croscarmellose sodium, carmellose calcium or carmellose which are disintegrators were added in the placebo formulations, and the effects on the tablet properties with tannic acid were evaluated.

1. The effect on physical properties resulting from the change of excipient

Table 8 and figures 2-4 showed physical properties when povidone was used as water-soluble binder and D-mannitol as excipient. As for No. 1 formulation, the result showed 8 seconds for disintegration time, 9 seconds for absorption time and 53 N for hardness. On the other hand, as for No. 2 formulation which contained no tannic acid, the result showed 40 seconds for disintegration time and 32 seconds for absorption time. The same table and figures showed physical properties when lactose hydrate is used as excipient. As for No. 3 formulation, the result showed 14 seconds for disintegration time, 15 seconds for absorption time and 53 N for hardness. On the other hand, as for No. 4 formulation which contained no tannic acid, the result showed 46 seconds for disintegration time and 44 seconds for absorption time.

The same table and figures showed physical properties when hydroxypropylcellulose was used as water-soluble binder and D-mannitol as excipient. As for No. 5 formulation, the result showed 8 seconds for disintegration time, 11 seconds for absorption time and 51 N for hardness. On the other hand, as for No. 6 formulation which contained no tannic acid, the result showed 19 seconds for disintegration time and 307 seconds for absorption time. The same table and figures showed physical properties when lactose hydrate was used as excipient. As for No. 7 formulation, the result shows 8 seconds for disintegration time, 11 seconds for absorption time and 59 N for hardness. On the other hand, as for No. 8 formulation which contained no tannic acid, the result showed 48 seconds for disintegration time and 169 seconds for absorption time.

Table 8. Physical properties of placebo formulation (A)

Formulation No.	1	2	3	4	5	6	7	8
Hardness (N) (Average)	53	63	53	62	51	64	59	57
Disintegration time (Sec.) (Average)	8	40	14	46	8	19	8	48
Absorption time (Sec.) (Average)	9	32	25	44	11	307	11	169

■ : Tannic acid (1.0%)

□ : No tannic acid

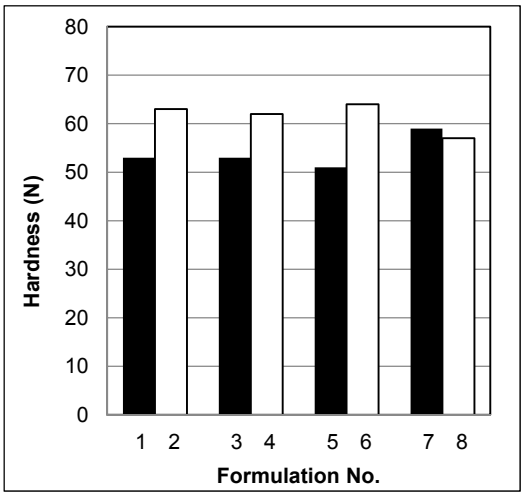

Fig. 2. Hardness test (A)

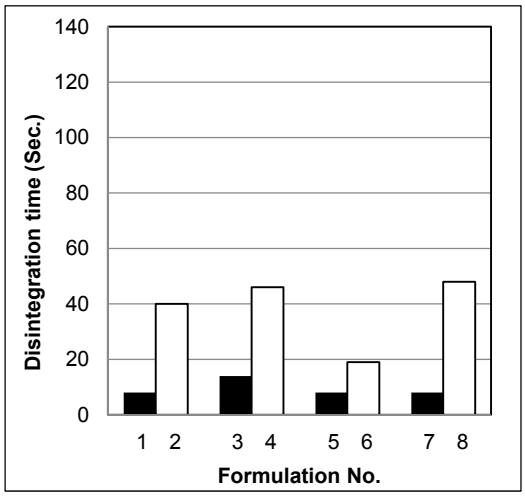

Fig. 3. Disintegration test (A)

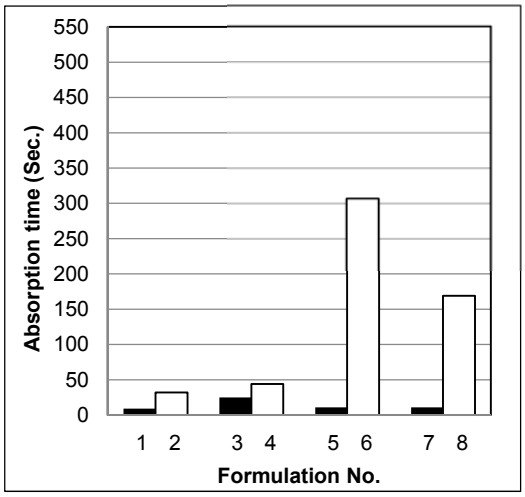

Fig. 4. Absorption test (A)

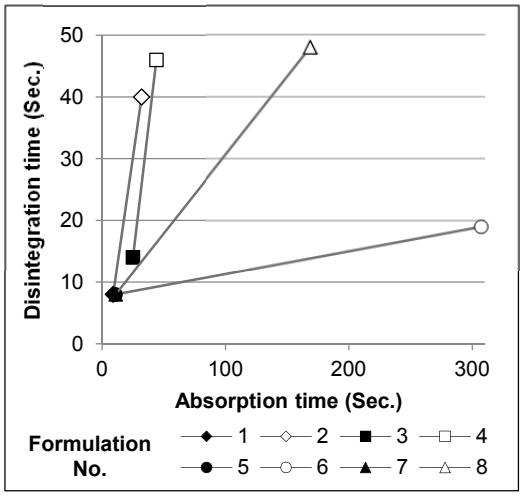

Fig. 5. Property correlation of disintegration time and absorption time (A)

From the result, even if D-mannitol which is sugar alcohol or lactose hydrate which is sugar was added as excipient, it was implied that disintegration time and absorption time were shortened and had good disintegration property and fast water absorption by adding povidone or hydroxypropylcellulose which is water-soluble binder and tannic acid.

2. The effect on physical properties resulting from the change of binder

Table 9 (including the result of formulation No. 1 and No. 2) and figures 6-8 show physical properties when povidone is used as water-soluble binder. As for formulation No. 9, No. 11 and No. 13, the result showed 11 seconds, 12 seconds and 11 seconds for disintegration time, 9 seconds, 12 seconds and 11 seconds for absorption time and 68 N, 63 N and 63 N for hardness respectively. On the other hand, as for formulation No. 10, No. 12 and No. 14 which contain no tannic acid, the result showed 39 seconds, 40 seconds and 42 seconds for disintegration time and 46 seconds, 40 seconds and 43 seconds for absorption time respectively. It turned out that they had bad disintegration and water absorption compared to the formulations which contain tannic acid.

Table 9. Physical properties of placebo formulation (B)

Formulation No.	1	2	9	10	11	12	13	14
Hardness (N) (Average)	53	63	68	74	63	72	63	64
Disintegration time (Sec.) (Average)	8	40	11	39	12	40	11	42
Absorption time (Sec.) (Average)	9	32	9	46	12	40	11	43

■ : Tannic acid (1.0%)

□ : No tannic acid

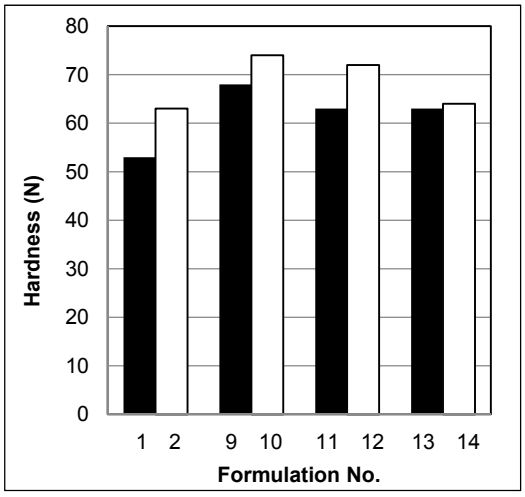

Fig. 6. Hardness test (B)

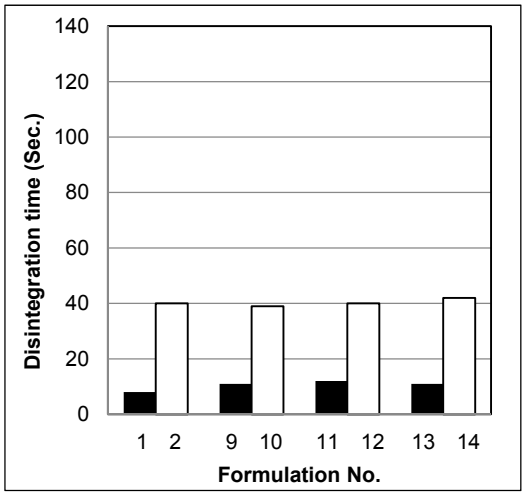

Fig. 7. Disintegration test (B)

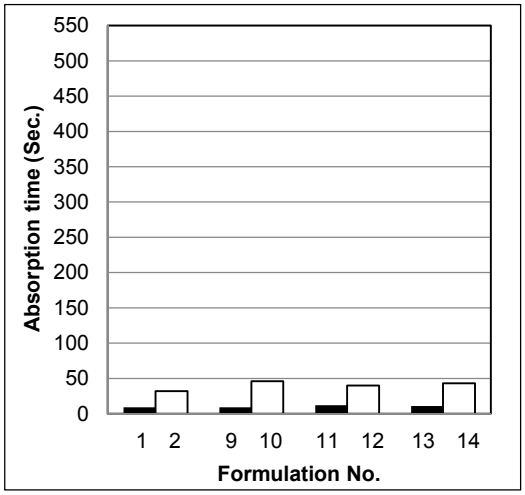

Fig. 8. Absorption test (B)

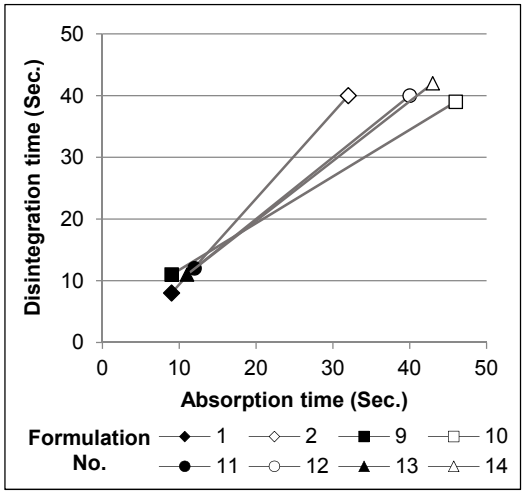

Fig. 9. Property correlation of disintegration time and absorption time (B)

Table 10 (including the result of formulation No. 5 and No. 6) and figures 10-12 show physical properties when hydroxypropylcellulose is used as water-soluble binder. As for formulation No. 15, No. 17 and No. 19, the result showed 9 seconds, 9 seconds and 11 seconds for disintegration time, 9 seconds, 11 seconds and 12 seconds for absorption time and 68 N, 67 N and 61 N for hardness respectively. On the other hand, as for formulation No. 16, No. 18 and No. 20 which contain no tannic acid, the result showed 20, 18 and 19 seconds for disintegration time and 203 seconds, 209 seconds and 182 seconds for absorption time respectively. It turned out that they had bad disintegration and water absorption compared to the formulations which contain tannic acid.

Table 10. Physical properties of placebo formulation (C)

Formulation No.	5	6	15	16	17	18	19	20
Hardness (N) (Average)	51	64	68	66	67	69	61	63
Disintegration time (Sec.) (Average)	8	19	9	20	9	18	11	19
Absorption time (Sec.) (Average)	11	307	9	203	11	209	12	182

■ : Tannic acid (1.0%)

□ : No tannic acid

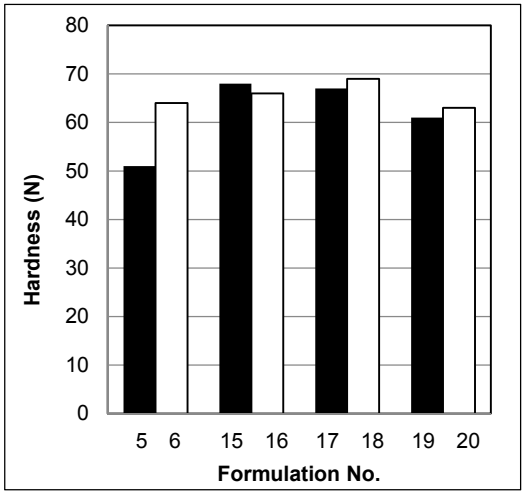

Fig. 10. Hardness test (C)

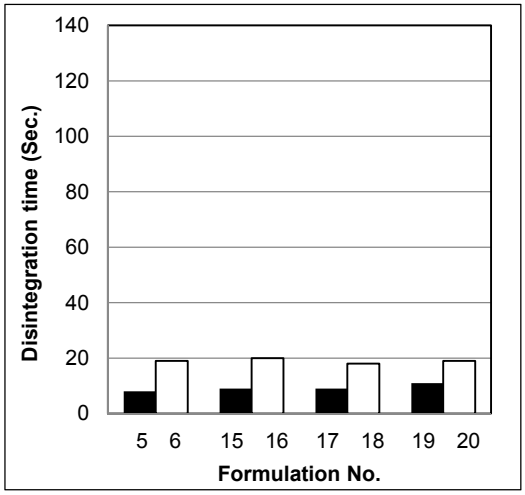

Fig. 11. Disintegration test (C)

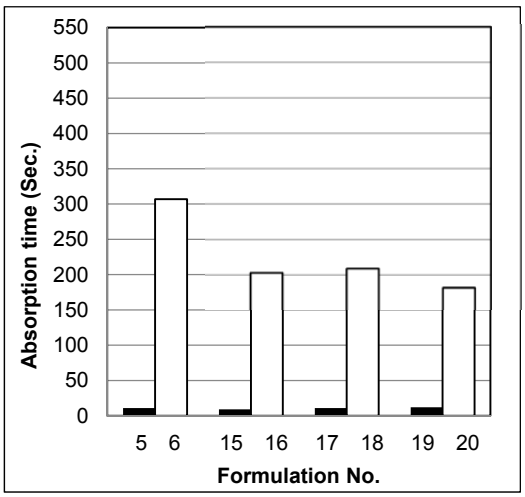

Fig. 12. Absorption time (C)

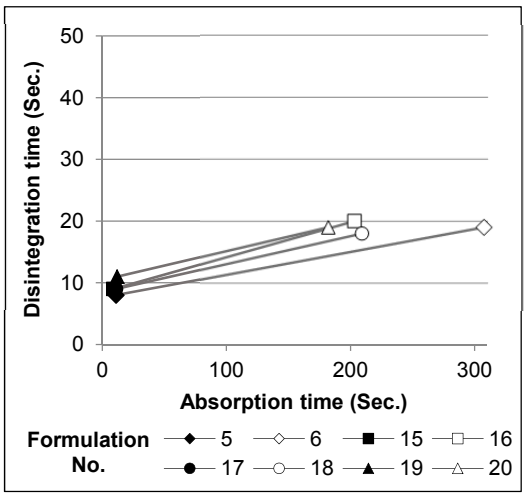

Fig. 13. Property correlation of disintegration time and absorption time (C)

From the result, even if any of magnesium aluminometasilicate, synthetic aluminum silicate, light anhydrous silicic acid and calcium silicate was added as binder, it was implied that disintegration time and absorption time were shortened and had better disintegration and water absorption by adding povidone or hydroxypropylcellulose which is water-soluble binder and tannic acid, shown in figures 9 and 13.

3. The effect on physical properties resulting from the change of disintegrator

Table 11 (including the result of formulation No. 1 and No. 2) and figure 14-16 show physical properties when povidone is used as water-soluble binder. As for formulation No. 21, No. 23 and No. 25, the result showed 16 seconds, 28 seconds and 20 seconds for disintegration time, 22 seconds, 63 seconds and 37 seconds for absorption time and 59 N, 54 N and 52 N for hardness respectively. On the other hand, as for formulation No. 22, No. 24 and No. 26 which contain no tannic acid, the result showed 65 seconds, 121 seconds and 86 seconds for disintegration time and 98 seconds, 120 seconds and 66 seconds for absorption time respectively. It turned out that they had bad disintegration and water absorption compared to the formulations which contain tannic acid.

Table 11. Physical properties of placebo formulation (D)

Formulation No.	1	2	21	22	23	24	25	26
Hardness (N) (Average)	53	64	59	74	54	67	52	69
Disintegration time (Sec.) (Average)	8	40	16	65	28	121	20	86
Absorption time (Sec.) (Average)	9	32	22	98	63	120	37	66

■ : Tannic acid (1.0%)

□ : No tannic acid

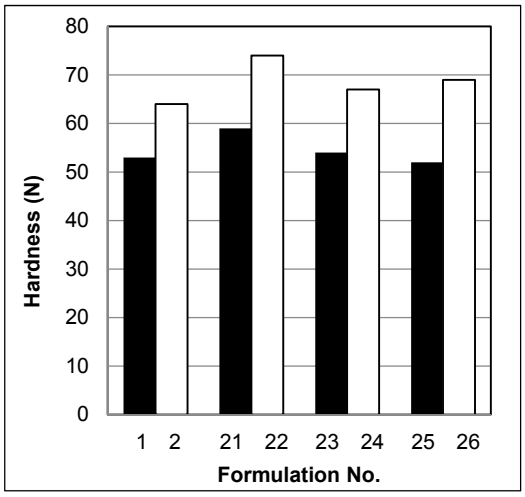

Fig. 14. Hardness test (D)

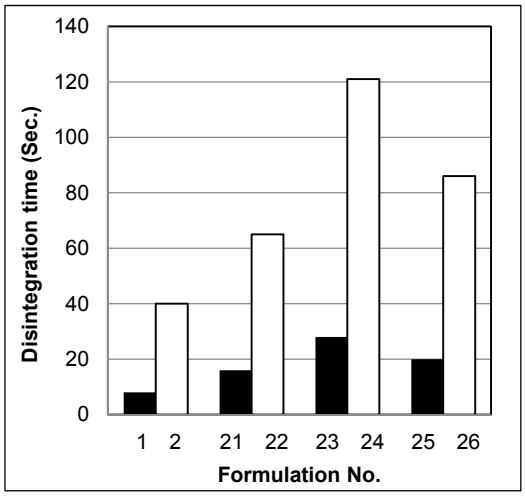

Fig. 15. Disintegration test (D)

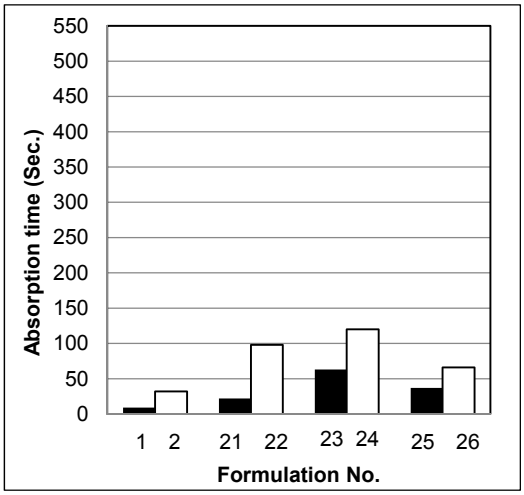

Fig. 16. Absorption test (D)

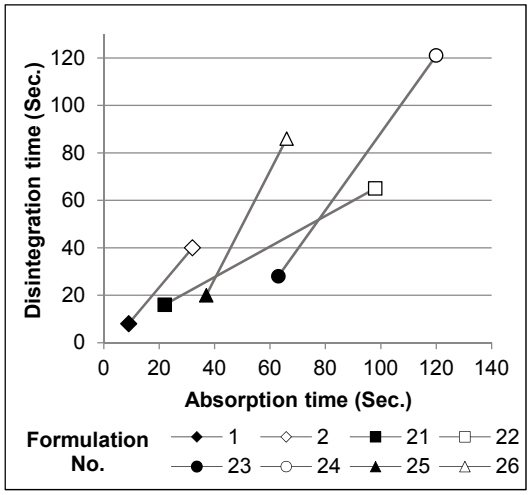

Fig. 17. Property correlation of disintegration time and absorption time (D)

Table 12 (including the result of formulation No. 5 and No. 6) and figures 17-19 show physical properties when hydroxypropylcellulose is used as water-soluble binder. As for formulation No. 27, No. 29 and No. 31, the result showed 14 seconds, 27 seconds and 21 seconds for disintegration time, 25 seconds, 73 seconds and 42 seconds for absorption time and 51 N, 55 N and 49 N for hardness respectively. On the other hand, as for formulation No. 28, No. 30 and No. 32 which contain no tannic acid, the result showed 31 seconds, 36 seconds and 27 seconds for disintegration time and 346 seconds, 538 seconds and 270 seconds for absorption time respectively. It turned out that they had bad disintegration and water absorption compared to the formulations which contain tannic acid.

Table 12. Physical properties of placebo formulation (E)

Formulation No.	5	6	27	28	29	30	31	32
Hardness (N) (Average)	51	64	51	67	55	63	49	61
Disintegration time (Sec.) (Average)	8	19	14	31	27	36	21	27
Absorption time (Sec.) (Average)	11	307	25	346	73	538	42	270

■ : Tannic acid (1.0%)

□ : No tannic acid

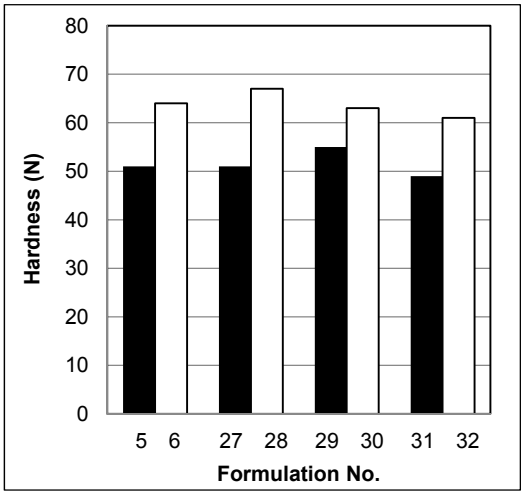

Fig. 18. Hardness test (E)

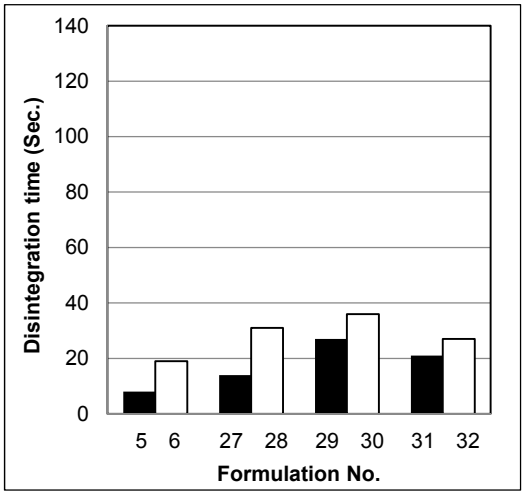

Fig. 19. Disintegration test (E)

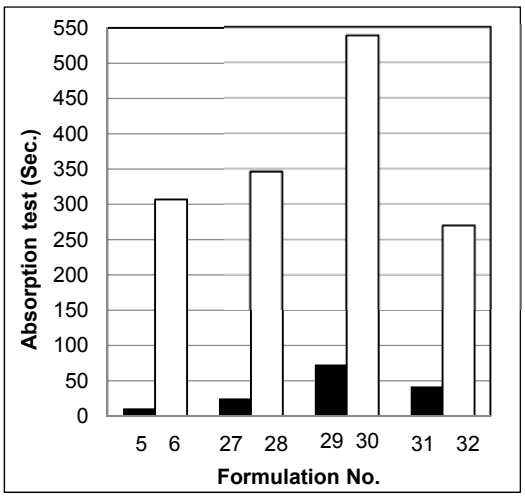

Fig. 20. Absorption test (E)

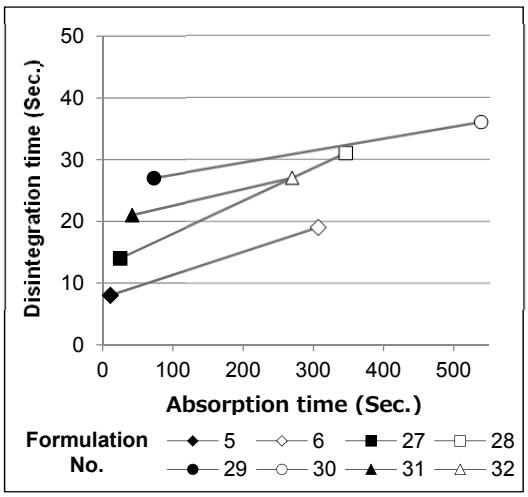

Fig. 21. Property correlation of disintegration time and absorption time (E)

From the result, even if any of crospovidone, croscarmellose sodium, carmellose calcium and carmellose was added as disintegrator, it was implied that disintegration time and absorption time were shortened and had better disintegration and water absorption by adding povidone or hydroxypropylcellulose which is water-soluble binder and tannic acid, shown in figures17 and 21.

Conclusion

In order to examine the tolerance of new orally disintegrating tablet, tablet properties were evaluated by using placebo tablets added various additives (excipient, binder and disintegrator).

As the result, excellent disintegration and fast water absorption was found about tablets added povidone or hydroxypropylcellulose which is a water-soluble binder together with tannic acid known as taste masking agent.

The technology for preparing the orally disintegrating tablet, as “howatt-technologies”, took Good Design Award (organized by Japan Institute of Design Promotion) and it was highly evaluated as the microlevel design which solved the trade-off between moldability (hardness) and disintegration (disintegration time). It is no doubt that establishing the basis of the new technology “howatt-technologies” will lead to the development of pharmaceutical fields.

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