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Disintegrating Behavior of A Rapidly Disintegrating Famotidine Tablet Formulation

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ABSTRACT – A rapidly disintegration famotidine tablet formulation in the oral cavity was developed using microcrystalline cellulose (MCC) and low-substituted hydroxypropyl cellulose (L-HPC), or additionally cropovidone as an internal disintegrant. Effects of disintegrants on the disintegration time in vitro and hardness were evaluated. Average wetting time of the tablets prepared in scale-up manufacturing process was less than 15 sec. Among the formulations tested, the tablet prepared with crospovidone as an internal disintegrant and Emcocel 90M® as an external disintegrant showed fastest disintegration. These results may suggest that crospovidone and Emcocel 90M® possessed excellent wetting nature, which result in the rapid disintegration of tablet.

Key words – Rapidly disintegrating tablets, Crospovidone, Emcocel 90M®, Famotidine

As a result of increased life expectancy, the elderly constitute a large portion of the worldwide population today. Many older patients have difficulty in swallowing tablets or capsules and yet the vast majority of dosage forms administered to the elderly are tablets or capsules. Therefore, fast dispersible tablets were developed to facilitate the administration of tablets for patients with esophageal problems. For example, jelly preparations were developed as oral dosage forms for the elderly.[1,2] However, tablets were most favorite and popular among the currently used dosage forms, and efficacy of this type of tablets have been clinically evaluated.[3-5]

Recent developments in technology have presented viable dosage alternatives for patients who may have difficulty swallowing tablets or liquid. Traditional tablets and capsules administered with a 100-mL glass of water may be inconvenient or impractical for some patients. For example, a very elderly patient may not be able to swallow a daily dose of antidepressant. An eight-year-old with allergies would use a more convenient dosage form than antihistamine syrup. A schizophrenic patient in the institutional setting can hide a conventional tablet under his or her tongue to avoid their daily dose of an atypical antipsychotic. A middle-aged woman undergoing radiation therapy for breast cancer may be too nauseous to swallow her H2-blocker. Rapidly disintegrating/dissolving tablets are a perfect fit for all of these patients.

Ideal rapidly disintegrating tablet is a preparation which is ready to disintegrate within 10 sec without need for water. Moreover, the tablet manufacturing should be simple with good hardness, friability and weight variation. In this study, we developed rapidly disintegrating tablets containing famotidine as a model drug..

Famotidine is most stable in pH 6.5-7.0, and is decomposed in acid or basic solution.[6] Since famotidine is water-insoluble and has low bioavailability, many complexations have been reported to overcome the problems with xilytol,[7] β-cyclodextrin[8] and hydroxyl-β-cyclodextrin.[9,10] In addition, famotidine tastes bitter and need the addition of sweetener.

To satisfy the rationale of rapidly disintegrating tablets, we formulated the rapidly disintegrating famotidine tablet with disintegrant, excipient, binder and sweetener, and evaluated the tablet properties, e.g. hardness, disintegration, friability, wetting time and wettability.

Experimental Methods

Materials

Famotidine was kindly provided by Sam-A Pharmaceutical Co. Ltd., (Seoul, Korea). Crospovidone (Polyplasdone, XL-10, I.S.P. Technologies Inc., USA), low-substituted hydroxypropylcellulose (L-HPC, LH-21, Shin-Etsu Chemical Co. Ltd., Japan), cromscarmellose sodium (Ac-Di-Sol®, Asahi Kasei Co. Ltd., Japan), microcrystalline cellulose (Emcocel 90M®, JRS Pharma, USA) and sodium starch glycolate (Primojel®, Avebe, Netherlands) were used as disintegrants. WowTab® (Yamanouch Pharma Technologies, Inc., Japan) was used as a reference.

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Preparation of Tablets

The granules were prepared by kneading the intragranular disintegrants and excipients, and adding water as a binder. Granules screened with an 18 mesh sieve were dried and mixed with excipients. Some disintegrants such as crospovidone could also be added to the granules in some cases as extragranular disintegrants, and then the blend was directly compressed into tablets using a conventional tablet machine (TRB 16, Erweka, Germany).

Measurement of Wetting Time and Water Absorption Ratio of Tablet

Wetting time of tablets prepared with disintegrants was measured using the method reported by Bi et al.[11] Brifely, a piece of tissue paper folded twice was kept in a culture dish (internal diameter 8.5 cm) containing ~6 mL of purified water. A tablet having a small amount of amaranth powder on the upper surface was placed on the tissue paper. The time required to develop a red color on the upper surface of the tablet was recorded as the wetting time. The same procedure without amaranth was followed for determining the water absorption ratio, R, was determined according to the following equation.

$$R = \frac{(W_a - W_b)}{W_b} \times 100 \quad (1)$$

where W_a and W_b were the weights before and after water absorption, respectively.

Evaluation of the Produced Tablets

The obtained tablets of the rapidly disintegrating famotidine were evaluated with regard to tablet hardness and friability. The hardness of each tablet was measured with a tablet hardness tester (TBH 28, Erweka, Germany). Each hardness value reported is average of six measurements. The average tablet weight was determined by weighing 20 tablets individually using an analytical balance. Tablet friability was calculated as the percentage weight loss of 20 tablets after rotation at 30 rpm for 4 min in a friability tester (TAR x20, Erweka, Germany).[12]

***In Vitro* Disintegration Time**

Disintegration tests were carried out in distilled water at 37°C using a KP disintegration apparatus. Each value represents the mean ± S.D. for six tablets.

***In Vivo* Disintegration Time**

The time required for the complete disintegration in the oral cavity was collected from five health male volunteers, who were randomly administered each tablet at designated time intervals.[13]

Table I–*Formula Sheet and Manufacturing Procedure of Famotidine Tablets*

Formula	Amount (mg) per tablet			
	A1	A2	A3	A4
Mixing				
Famotidine	20	20	20	20
Emcocel 90M	120	120	120	120
L-HPC	30	30	30	30
Kneading (Binder)				
H_2O	45	45	45	45
Mixing				
Emcocel 90M	28	-	-	-
Ac-Di-Sol	-	28	-	-
Primojel	-	-	28	-
Crospovidone	-	-	-	28
Mg. stearate	2	2	2	2
Total	200	200	200	200
Batch size	500 T	500 T	500 T	500 T

Results and Discussion

Effect of Emcocel 90M® and L-HPC as Intragranular Disintegrant

To investigate the effect of excipient for direct tabletting, Emcocel 90M® on disintegration, tablets were prepared by using Emcocel 90M® and L-HPC as intragranular disintegrant and excipient at the ratio of 4:1 as shown in Table I. After preparation of granules by using water as a binder, each tablet was prepared by using extragranular excipients such as Emcocel 90M®, Ac-Di-Sol®, Primojel® and crospovidone (Table I) and characterized. As shown in Figure 1a, the disintegration times of the tablet containing Primojel® or Ac-Di-Sol® were more than 20 sec and the tablets containing Emcocel 90M® and crospovidone showed the disintegration time about 5 sec. Bi et al.[11] and Watanabe et al.[14] used microcrystalline cellulose (MCC) and low-substituted hydroxypropyl cellulose (L-HPC) as disintegrants to prepare rapidly disintegrating tablet by direct compression. According to the authors the ratios of these two disintegrants MCC/L-HPC in the range of 8:2-9:1 resulted in tablets with the shortest disintegration times, while we prepared the tablets with the ratio of MCC/L-HPC in 4:1. Emcocel 90M®-containing tablet showed fastest disintegration among the four disintegrants used, and the disintegration time was not affected by the tablet hardness. Although the disintegration time in oral cavity of the tablet containing Emcocel 90M® and crospovidone was very short, they showed a pattern to be rapidly degraded by absorbing the saliva in oral cavity due to the strong hygroscopicity. Therefore, it is supposed that

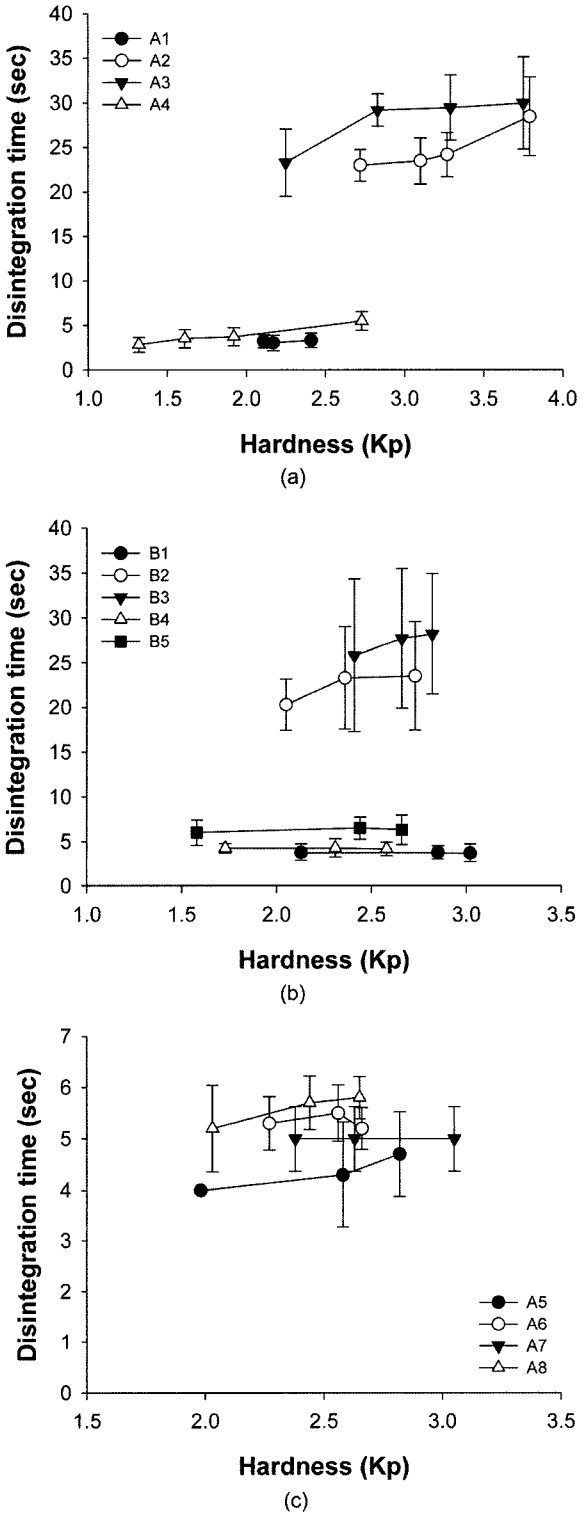

Figure 1—Effect of disintegrants on disintegration time in vitro. (a) Effect of extragranular disintegrants types. A1, Emcocel 90M®; A2, Ac-Di-Sol®; A3, Primojel®; A4, crospovidone. (b) Effect of intragranular crospovidone. B1, Emcocel 90M®; B2, Ac-Di-Sol®; B3, Primojel®; B4, crospovidone; B5, calcium CMC. (c) Effect of Emcocel series. A5, Emcocel 50M®; A6, Emcocel LM50®; A7, Emcocel XLM90®; A8, Emcocel LP200® (n=6).

Table II—*Formula Sheet and Manufacturing Procedure of Famotidine Tablets*

Formula	Amount (mg) per tablet				
	B1	B2	B3	B4	B5
Mixing					
Famotidine	20	20	20	20	20
Emcocel 90M	100	100	100	100	100
L-HPC	30	30	30	30	30
Crospovidone	20	20	20	20	20
Kneading (Binder)					
Maltodextrin	2	2	2	2	2
H_2O	45	45	45	45	45
Mixing					
Emcocel 90M	28	-	-		
Ac-Di-Sol	-	28	-		
Primojel	-	-	28		
Crospovidone	-	-	-	28	
Calcium CMC	-	-	-	-	28
Mg. stearate	2	2	2	2	2
Total	202	202	202	202	202
Batch size	500 T	500 T	500 T	500 T	500 T

Emcocel 90M® and L-HPC are good candidates as intragranular excipients in rapidly disintegration tablets.

Effect of Crospovidone as Intragranular Disintegrant

To investigate the effect of crospovidone as intragranular disintergrant, the granules were prepared by addition of crospovidone to the mixture of Emcocel 90M® and L-HPC (Table II). As shown in Figure 1b, the integration time of the tablet containing Emcocel 90M®, crospovidone and calcium CMC as extragranular disintegrant was about 3.8, 3.4 and 6.5 sec, respectively. On the other hands, Ac-Di-Sol® and Primojel® showed the prolonged disintegration time about 20-24 and 25-29 sec, respectively. From the results, the disintegration enhancing effect of extragranular disintegrants was in order of Emcocel 90M®, crospovidone, calcium CMC, Ac-Di-Sol® and Primojel®. Therefore, as intragranular disintegrants, the mixture of Emcocel 90M® and L-HPC or the addition of crospovidone to the mixture was most compatible for the preparation of rapidly disintegration tablet. For extragranular disinterant, Emcocel 90M® or crospovidone was favorable.

Effect of Emcocel Types on Disintegration Time

Among the formulations, because the disintegration and hardness of A1, B1 and B4 tablets were very excellent in rapidly disintegration property, the extragranular disintegrant of tablet formulations was varied by using the different types of Emcocel; Emcocel 50M, Emcocel LM50, Emcocel XLM90 and Emcocel LP200 (Table III). All the types of Emcocel were good disintegrants and the disintegration time of four tablets

Table III–*Formula Sheet and Manufacturing Procedure of Famotidine Tablets*

Formula	Amount (mg) per tablet			
	A5	A6	A7	A8
Mixing				
Famotidine	20	20	20	20
Emcocel 90M	120	120	120	120
L-HPC	30	30	30	30
Kneading (Binder)				
H_2O	80	80	80	80
Mixing				
Emcocel 50M	28	-	-	
Emcocel LM50	-	28	-	
Emcocel XLM90	-	-	28	
Emcocel LP200	-	-	-	28
Mg. stearate	2	2	2	2
Total	200	200	200	200
Batch size	500 T	500 T	500 T	500 T

(A5-A8) was within 6.5 sec (Figure 1c). However, Emcocel 90M®-containing tablet showed fastest disintegration about 3.5 sec among the five Emcocel series used, and the disintegration time of the tablets containing Emcocel 50M®, Emcocel XLM90®, Emcocel LM50® and Emcocel LP 120® was about 4-4.7, 5, 5.5 and 5.8 sec, respectively.

The disintegration time of the tablet containing Emcocel series was within 10 sec, which is satisfactory for the rapidly disintegration tablets. Actually, the disintegration in oral cavity of the tablets was carried out within 10-20 sec by absorbing saliva. However, it needs a lot of saliva to dissolve completely this rapidly disintegration tablet and there is some feeling of foreign substance in oral cavity. In particular, the patient feeling a strong thirst may have a trouble to administer this type of table. Therefore, a good rapidly disintegration tablet should be formulated to be rapidly dissolved in oral cavity, not to cause an unpleasant feeling in the mouth and to be easily disintegrated with small amount of saliva.

Scale-up of Tablet Manufacturing

Up to now, batch size of 100-500 tablets was prepared by manual direct die filling and compression. However, a continuous compression with regular rate is preferable to manual compression in order to validate tablet formulation parameters such as flowability, friability, weight variation and so on. Hence, we scaled-up the tablet manufacturing with automatic filling and compression. From the results of intra- and extra-granular disintegrants test, we selected two formulations, A1 and B4, which showed most satisfactory disintegration time, and scaled-up with slight modification (Table IV). Formulations C and E were based on formulation A1, containing Emcocel 90M® and L-HPC, while formulations D and F were based on formulation B4 containing Emcocel 90M®, L-HPC and crospovidone in granules. In addition, formulations E1, E2 and F were compressed with decrease in the weight as 151.5 mg per one tablet.

Hardness of tablets was reduced in tablet weighing 151.5 mg (data not shown) due to the decrease in thickness of tablet. Both formulations C and D showed good disintegration time within 5 sec. Prolonged disintegration time was observed in

Table IV–*Formula Sheet and Manufacturing Procedure of Famotidine Tablets*

Formula	Amount (mg) per tablet						
	C1	C2	D1	D2	E1	E2	F
Mixing							
Famotidine	20	20	20	20	20	20	20
Emcocel 90M	120	120	100	100	103.5	103.5	86.5
L-HPC	30	30	30	30	25	25	20
Crospovidone	-	-	20	20	-	-	20
Aspartame	-	-	-	-	-	1.5	-
Kneading (Binder)							
Maltodextrin	-	-	2	2	-	-	2
Aspartame	1.5	1.5	2	2	1.5	-	-
H_2O	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.	q.s.
Mixing							
Emcocel 90M	28	-	28	-	-	-	-
Crospovidone	-	28	-	28	-	-	-
Mg. stearate	2	2	2	2	1.5	1.5	2
Total	201.5	201.5	204	204	151.5	151.5	151.5
Batch size	2000 T	2000 T	2000 T	2000 T	1000 T	1000 T	1000 T

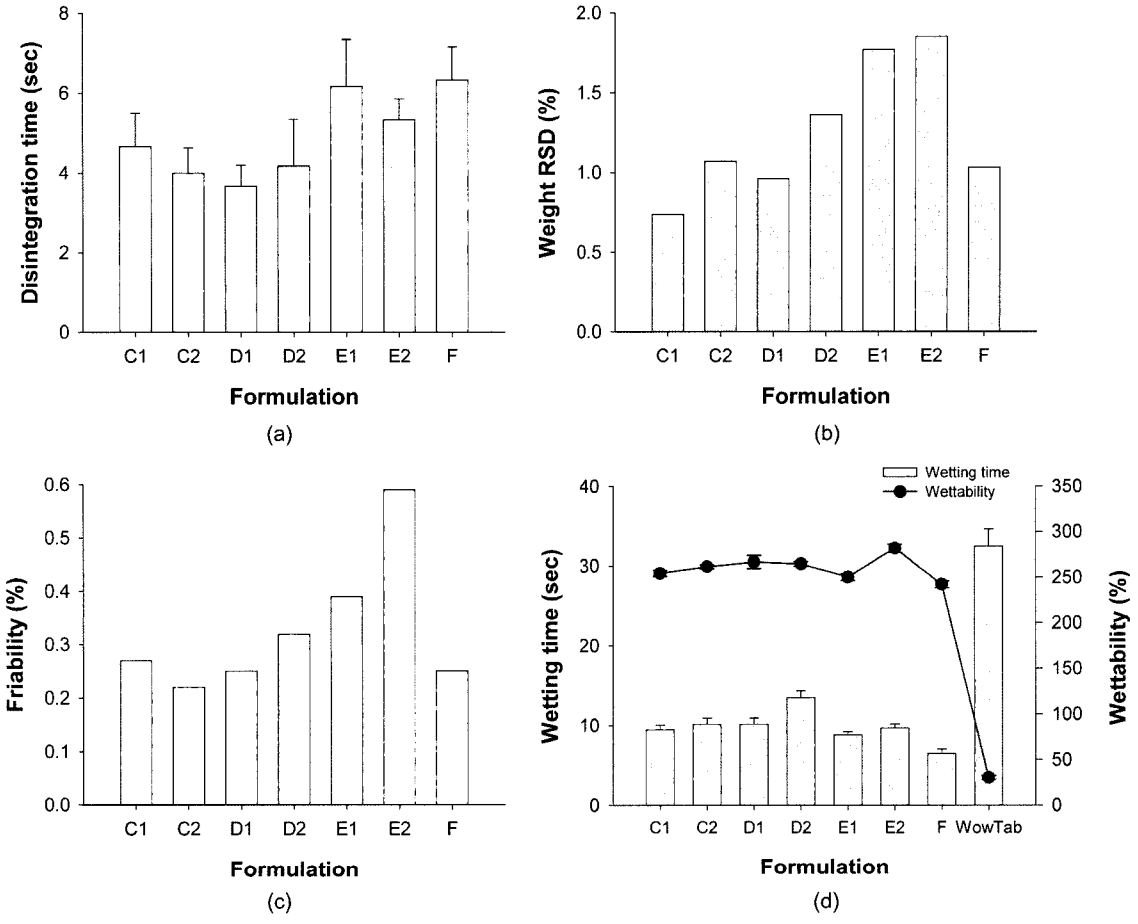

Figure 2–Characteristics of rapidly disintegration tablets. (a) Disintegration time; (b) Weight variation; (c) Friability; (d)Wetting time and wettability of tablets (n=6).

formulations E and F, whose weight was reduced into 151.5 mg. However, it is reasonable that the small amount of saliva in disintegration in oral cavity may be attributed to the reduced weight of tablet (151.5 mg). Moreover, the disintegration time of all formulations in scale-up was faster than that of commercial WowTab® (42 sec). Weight variation of tablets was also suitable for the Korean Pharmacopeia, but the variation was greater in the tablet D containing crospovidone as an intragranular disintegrants compared to tablet C. It is supposed that the specific volume of crospovidone is larger than that of Emcocel 90M®.

Tablet E1 was compressed with granules made from wet granulation and tablet E2 was directly compressed. Although the weight variation and friability of the tablets made by direct compression were increased as shown in Figures 2b and 2c, the extent of variation and friability was not significantly different and needed to be further investigated. Taken together, friability of all the tablets was less than 1% as shown in Figure 2c, but the friability of tablet E2 made by direct compression was greater than that of the tablet made by conventional wet granulation. Some researchers used a wet compression method where wet granules of α-lactose monohydrate were compressed, and then the formed wet tablets were dried at 60°C and kept in a desiccator for 12 h at room temperature.[15,16] Formed rapidly disintegrating tablet showed a disintegration time of less than 30 sec and a hardness of 0.5 MPa.

To confirm that the rationale for the rapid disintegration of the tablet was brought to the wettability of the tablet, we investigated wetting time and wettability (water absorption ratio) of disintegrants. The Wowtab® fast-dissolving/disintegrating tablet formulation has been on the Japanese market for a number of years. The Wowtab® technology utilizes sugar and sugar-like (e.g., mannitol) excipients. The two different types of saccharides are combined to obtain a tablet formulation with adequate hardness and fast dissolution rate.[17] Due to its significant hardness, the Wowtab® formulation is a bit stable to the environment. The Wowtab® product dissolves quickly in 15 seconds or less.[18,19] Figure 2d shows the change in the appearance

of tablets preprared from various formulations by wetting. Tablets formulated in this study were dramatically swelled and collapsed within 10 sec, on the other hand, commercial Wowtab® needed longer disintegration time. However, the wettability of WowTab® was superior to those of formulation in the study (C, D, E and F; 240-280%), supposing that more water is necessary to disintegrate the formulated tablets.

Conclusion

We have prepared rapidly disintegrating famotidine tablets using Emcocel 90M® and L-HPC, and additionally crospovidone. The good disintegrating property of product was closely related to the excellent wetting nature of ingredients. The tablet formulated with Emcocel 90M®, L-HPC and crospovidone would be especially applicable to practically rapidly disintegration famotidine tablets. However, further investigations such as porosity, interaction among excipients, and developments of in vivo evaluation methods are required for its use in the development of rapidly disintegrating tablets.

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