# Investigation of the Dissolution Difference between Acidic and Neutral Media of Acetaminophen Tablets Containing a Super Disintegrant and a Soluble Excipient

Chun-Ren CHEN,*[,a] Yaw-Hung LIN,[b] Shu-Ling CHO,[b] Shu-Yang YEN,[a] and Hsueh-Ling S. WU[c]

*Chia Nan College of Pharmacy and Science,[a] 60, Sec. 1, Erh-Jen Road, Jen-Te Hsiang, Tainan Hsien 71710, Taiwan, Chen-Ho Pharmaceutical Co., Ltd.,[b] 23, Hsinkung Road, Hsinging Industrial Dist., Hsin Ying City, Tainan Hsien 73023, Taiwan and Block Drug Company, Inc.,[c] Jersey City, NJ 07302, U.S.A.*

Received August 19, 1996; accepted November 12, 1996

**This study used acetaminophen as a model drug and investigated the effect of soluble excipients and super disintegrants on the dissolution difference between acidic and neutral media. Tablets with various formulas were prepared and their disintegration and dissolution in both acidic and neutral media were studied. A formula containing acetaminophen and crospovidone (Polyplasdone XL), with or without sucrose, did not show a big dissolution difference between acidic and neutral media, which correlates well with the disintegration study. In contrast, a formula containing acetaminophen, sucrose and croscarmellose sodium (Ac-Di-Sol) caused longer disintegration and slower dissolution in the acidic medium than those in the neutral medium. The difference of disintegration and dissolution in both media might be due to the interaction among ingredients.**

**Key words** super disintegrant; acetaminophen; dissolution; excipient; pH; disintegration

Super disintegrants are often incorporated into tablets to enhance the dissolution of the active ingredient in the tablet. The effect of a super disintegrant is generally attributed to its swelling and wicking actions.[1] However, the effect of pH on the efficiency of the super disintegrant in terms of dissolution has seldom been studied. It was first reported by Gordon *et al.*[2] that the dissolution of *p*-aminobenzoic acid within 15 min from a tablet using lactose or dibasic calcium phosphate as the excipient, without super disintegrants, was not affected by the pH (pH 2.0 or 7.4) of the medium used. However, when the super disintegrant was incorporated into the tablet, the dissolution of a *p*-aminobenzoic acid tablet within 15 min in the acidic medium was slower than that in the neutral medium regardless of whether crospovidone (Polyplasdone XL, GAF Corp., U.S.A.), croscarmellose sodium (Ac-Di-Sol, FMC Corp., U.S.A.), or sodium starch glycolate (Explotab, Edward Mendell Co., U.S.A.) was used. Furthermore, Polyplasdone XL incorporated intragranularly caused the greatest decrease in dissolution among these three super disintegrants in the acidic medium within 15 min when lactose was used as the excipient. Ac-Di-Sol incorporated intragranularly caused the greatest decrease in the acidic medium within 15 min when dibasic calcium phosphate was used as the excipient. Dahl *et al.*[3] also pointed out that in a capsule formula (acetaminophen + dibasic calcium phosphate + magnesium stearate), the dissolution was faster in 0.1 N HCl than in deionized water due to the excipient dibasic calcium phosphate. In 0.1 N HCl there is almost no $HPO_4^{2-}$ species available, thus allowing more calcium ion to be solubilized.[4] Therefore, both the super disintegrant and the excipient may cause the dissolution difference between acidic and neutral media.

No systemic studies have been done regarding the effect of a super disintegrant or an excipient on the dissolution difference between acidic and neutral media. It has been known that tablets with a large amount of soluble excipient such as lactose tend to dissolve, while tablets with an insoluble excipient such as dibasic calcium phosphate tend to disintegrate.[5] Therefore, the study was divided into two parts with this first part emphasizing investigation of the dissolution difference between acidic and neutral media of acetaminophen tablets containing a super disintegrant and a soluble excipient.

In the first part of the study, the soluble excipients, including lactose, mannitol, and sucrose, were evaluated. Three common super disintegrants, Ac-Di-Sol, sodium starch glycolate (Primojel, Avebe, Holland), and Polyplasdone XL, were also chosen for the study. Acetaminophen, which has been widely used in dissolution studies, was selected as a model drug. The purpose of this study was to identify the soluble ingredient which is likely to cause the greatest dissolution difference. The selected soluble ingredient which caused the greatest dissolution difference was further studied with different super disintegrants to find out the super disintegrant likely to cause the greatest dissolution difference. Finally, the dissolution and the disintegration of different combinations of the selected soluble excipient, super disintegrant and acetaminophen were evaluated to determine whether there is an interaction effect.

## Materials and Methods

**Materials** The acetaminophen (Seven Stars Chem. Corp., Taiwan), sucrose (Taiwan Sucrose Corp., Taiwan), lactose (HMS, Holland), mannitol (Getec, Brazil), magnesium stearate (Akcros Corp., Holland), sodium starch glycolate (Primojel, Avebe, Holland), croscarmellose sodium (Ac-Di-Sol, FMC Corp., U.S.A.), and crospovidone (Polyplasdone XL, GAF Corp., U.S.A.) were all of USP/NF grade. All reagents used were of analytical grade.

**Tablet Preparation** The ingredients were passed through an 80-mesh screen and then mixed in a tumbling mixer (YM-500 Yuyama, Japan). Deionized water (formulas containing sucrose or mannitol) or starch paste (all other formulas) was added to the mixture and the mixture was kneaded to a suitable condition. Next, it was passed through a 24-mesh

* To whom correspondence should be addressed.

screen to form granules and dried in an oven at 50 °C to the desirable moisture content. The granules were passed through a 24-mesh screen again. One percent of magnesium stearate, which had been passed through an 80-mesh screen, was added to granules in the same tumbling mixer to mix slowly for 3 min. The granules were compressed into capsule-shaped tablets (length 19.45 mm, width 8.2 mm) by a rotary tableting machine (Jenn Chiang Machinery Co., Ltd., Taiwan, type JC/RT/15H) with a targeted hardness of 7 kg, a targeted weight and thickness of 1050 mg and 6.8 mm for formulas A, B, C, D, F and G and 545 mg and 3.5 mm for other formulas. Tablets with almost the same weight were chosen for all dissolution and disintegration studies used for the comparison. The ingredients of each formula are listed in Table 1.

**Disintegrating (DT) Test** The disintegration of tablets was studied using the USP XXI method with 900 ml deionized water (DW, pH 6.25) or simulated gastric fluid without enzyme (SGF, pH 1.25) as the medium. Each of six tablets was put into one tube of the disintegration tester (Shin Guan, Taiwan) and the disintegration time was measured. The temperature of the medium was maintained at 37 °C.

**Dissolution (DR)** The dissolution of tablets was studied using the USP XXI basket method with 900 ml DW or SGF as the medium. Every time, each of six tablets was put inside one flask of the automatic dissolution tester (Toyama, Japan). Five ml of solution was automatically sampled at 5, 10, 15, 25, 35, 45, and 55 min, and was replaced with an equivalent amount of fresh DW or SGF. The rotating speed was 50 rpm and the temperature of the medium was 37 °C. The sample was automatically filtered (Toyama, Japan) and assayed by UV at 235 nm.

Table 1. Ingredients of Each Formula

| Formula | Ingredients |
|---|---|
| A | Acetaminophen 500 mg, lactose 500 mg, Ac-Di-Sol 40 mg |
| B | Acetaminophen 500 mg, sucrose 500 mg, Ac-Di-Sol 40 mg |
| C | Acetaminophen 500 mg, mannitol 500 mg, Ac-Di-Sol 40 mg |
| D | Acetaminophen 500 mg, sucrose 500 mg, Polyplasdone XL 40 mg |
| E | Acetaminophen 500 mg, Polyplasdone XL 40 mg |
| F | Acetaminophen 500 mg, sucrose 500 mg, Primojel 40 mg |
| G | Acetaminophen 500 mg, sucrose 500 mg |
| H | Acetaminophen 500 mg, Ac-Di-Sol 40 mg |
| I | Sucrose 500 mg, Ac-Di-Sol 40 mg |

## Results and Discussion

**The Pattern of DR Difference *versus* Time** The pattern of DR difference *versus* time varied in our data. For example, type I showed the maximum difference early, then the difference decreased such as in formula H in Table 2. This type of formula usually completes a high percentage of DR in the early period of time, both in the acidic and neutral media, so that the difference of two close values, both of them approaching 100% DR in the later period, becomes small, as shown in Fig. 1. Type II shows a maximum difference in the middle period of time, with less DR difference on either side, such as in formula F in Table 3. This type results from different DR rates in the acidic and neutral media, as shown in Fig. 2. Type III is the opposite of type I, with the maximum difference appearing late, such as in formula D in Table 3. This type results from slow DR in the acidic and neutral media, as shown in Fig 2. Type IV has an almost insignificant DR difference, such as in formula A in Table 4. The formula of this type has nearly equal DR rates in the acidic and neutral media, as shown in Fig. 3.

For type I, type II, and type IV, the DR difference within 15 min was taken as representative of the DR difference in the following discussion. Caution should be taken regarding type III, for its DR difference can be observed only at a late period of time, and comparison within 15 min may not distinguish the DR difference.

**Effect of Soluble Excipient on DR Difference and DT Difference between Acidic and Neutral Media** The DR and DT of formulas containing lactose, sucrose, or mannitol, respectively, were conducted in both acidic and neutral media. The results are shown in Fig. 3 and Table 4. When lactose, sucrose, or mannitol was mixed with Ac-Di-Sol and acetaminophen (formula A, B, or C), it was found that formula B (sucrose) causes a much greater DR difference between the two media than formula A (lactose) or C (mannitol). Acetaminophen solubility was not affected by pH.[3] This is not related to the hardness

Table 2. Interaction Effect on % Dissolution Difference and Disintegration between Neutral and Acidic Media

| Formula | Ingredients | % dissolution difference[a] | | | | | | | DT | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 25 | 35 | 45 | 55 min | DW | SGF |
| B | Acetaminophen, sucrose, Ac-Di-Sol | 40 | 55 | 57 | 35 | 17 | 3 | 0 | 10′20″—11′27″ | 20′50″—22′20″ |
| G | Acetaminophen, sucrose | −1 | 0 | 1 | 3 | 3 | 5 | 7 | 85′20″—89′10″ | 72′40″—76′21″ |
| H | Acetaminophen, Ac-Di-Sol | 22 | 21 | 17 | 13 | 9 | 3 | 2 | 1′20″—1′50″ | 13″—33″ |
| I | Sucrose, Ac-Di-Sol | | | | N/A | | | | 11′45″—12′40″ | 12′50″—15′10″ |

a) % dissolved of the mean of six tablets in neutral medium minus % dissolved of the mean of six tablets in acidic medium. The symbol inside the parenthesis (′) is used to represent minutes and (″) is used to represent seconds.

Table 3. Effect of Super Disintegrants on % Dissolution Difference and Disintegration between Neutral and Acidic Media

| Formula | Super disintegrant | % dissolution difference[a] | | | | | | | DT | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 25 | 35 | 45 | 55 min | DW | SGF |
| B | Ac-Di-Sol | 40 | 55 | 57 | 35 | 17 | 3 | 0 | 10′20″—11′27″ | 20′50″—22′20″ |
| D | Polyplasdone XL | 1 | 2 | 2 | 5 | 9 | 12 | 13 | 47′25″—49′9″ | 50′15″—54′8″ |
| F | Primojel | 29 | 53 | 85 | 79 | 73 | 66 | 62 | 13′15″—13′44″ | 49′48″—51′48″ |

a) % dissolved of the mean of six tablets in neutral medium minus % dissolved of the mean of six tablets in acidic medium. The symbol inside the parenthesis (′) is used to represent minutes and (″) is used to represent seconds.

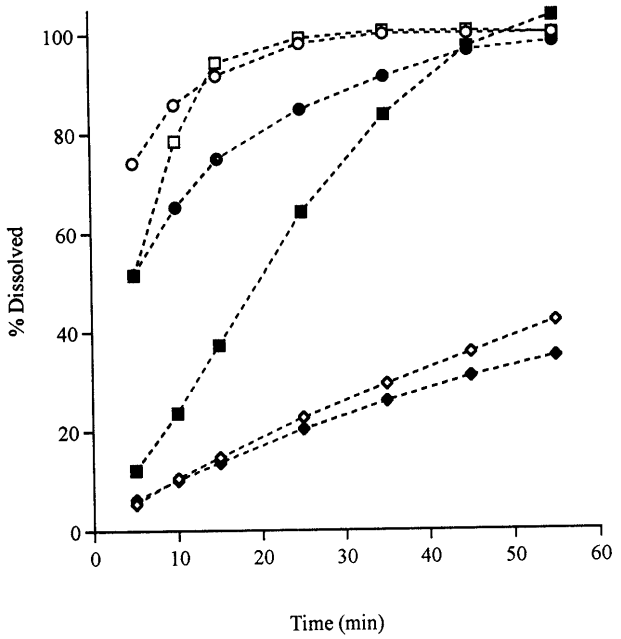


Fig. 1. Interaction Effect on % Dissolved in Acidic and Neutral Media

○, acetaminophen and Ac-Di-Sol (DW); ●, acetaminophen and Ac-Di-Sol (SGF) (formula H); □, acetaminophen, sucrose, and Ac-Di-Sol (DW); ■, acetaminophen, sucrose, and Ac-Di-Sol (SGF) (formula B); ◇, acetaminophen and sucrose (DW); ◆, acetaminophen and sucrose (SGF) (formula G). Each point represents the mean of six determinations. All standard deviations were within 5%.

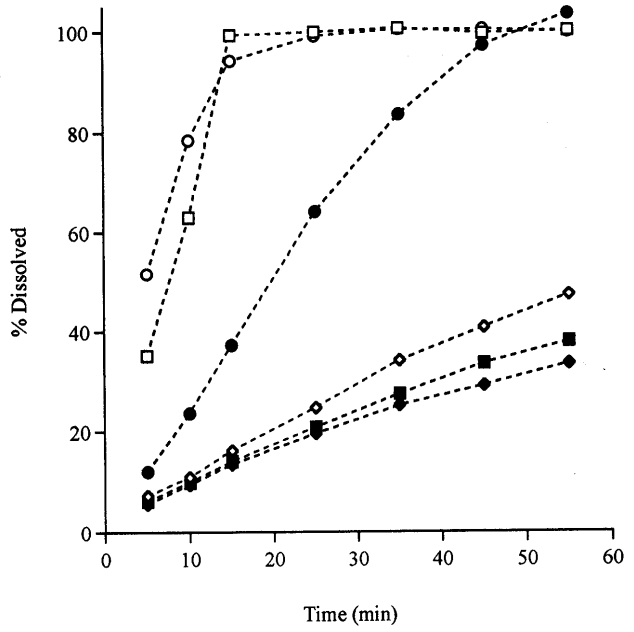


Fig. 2. Effect of Super Disintegrants on % Dissolved in Acidic and Neutral Media

○, Ac-Di-Sol (DW); ●, Ac-Di-Sol (SGF) (formula B); □, Primojel (DW); ■, Primojel (SGF) (formula F); ◇, Polyplasdone XL (DW); ◆, Polyplasdone XL (SGF) (formula D). Each point represents the mean of six determinations. All standard deviations were within 3%.

of the tablets either since all of them have an average hardness of $7 \pm 1$ kg.

It was reported that the differences between super disintegrants are greatly diminished with a fast dissolution lactose formulation.[5] The dissolution of formula A (lactose) and C (mannitol) is very fast, and consequently the DR difference between the two media is very small.

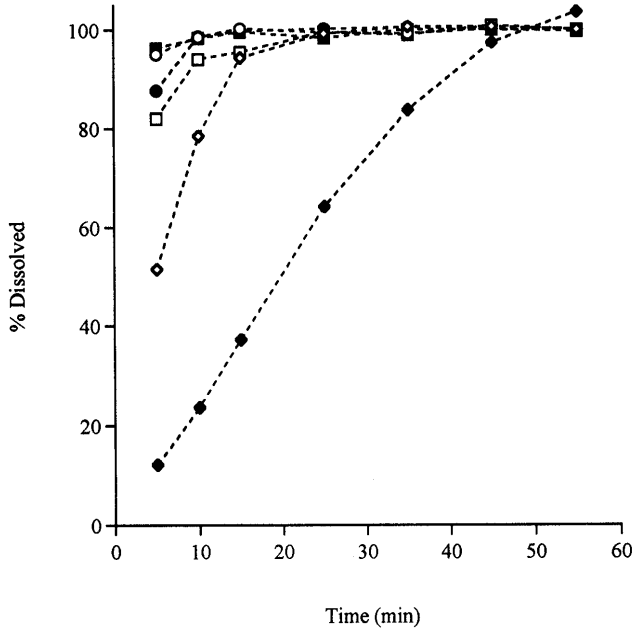


Fig. 3. Effect of Soluble Excipient on % Dissolved in Acidic and Neutral Media

○, lactose (DW); ●, lactose (SGF) (formula A); □, mannitol (DW); ■, mannitol (SGF) (formula C); ◇, sucrose (DW); ◆, sucrose (SGF) (formula B). Each point represents the mean of six determinations. All standard deviations were within 5%.

The DT time of formulas A and C in the two media is very short, which correlates well with the DR. Only the DT time of formula B showed a greater difference between the two media, which in turn caused the dissolution difference. Therefore, sucrose was chosen as a model water soluble excipient and was used in the further investigation of super disintegrants.

**Effect of Super Disintegrant on DR Difference and DT Difference between Acidic and Neutral Media** The DR and DT of sucrose formulas with Ac-Di-Sol, Polyplasdone XL, or Primojel (formulas B, D, or F), respectively, were conducted in both acidic and neutral media. The results are shown in Fig. 2 and Table 3. It was found that formula F (Primojel) caused the greatest DR difference between the two media, followed by formula B (Ac-Di-Sol) and formula D (Polyplasdone XL). This is consistent with the difference in DT time (Table 3). The DR of tablets containing acetaminophen and Polyplasdone XL (formula E) in both acidic and neutral media is also similar.

It was reported that for super disintegrant dispersions, the swelling of Polyplasdone XL in dilute hydrochloric acid (1 : 100) or water is the same, whereas the swelling of Primojel in dilute hydrochloric acid compared with that in water is dramatically depressed.[6] However, the same paper also reported that the swelling of Ac-Di-Sol in dilute hydrochloric acid compared with that in water is increased, which is inconsistent with the dissolution and disintegration results of formula B (Ac-Di-Sol).

The super disintegrant compacts were prepared and the pH effect on the rate of liquid uptake of super disintegrants, which in turn affects the rate of swelling, was studied.[7] It was found that pH does not affect the liquid uptake of Polyplasdone XL compact, but the liquid uptake into Primojel compact is significantly decreased with dilute

Table 4. Effect of Soluble Excipients on % Dissolution Difference and Disintegration between Neutral and Acidic Media

| Formula | Excipient | % dissolution difference[a] | | | | | | | DT | |
|---|---|---|---|---|---|---|---|---|---|---|
| | | 5 | 10 | 15 | 25 | 35 | 45 | 55 min | DW | SGF |
| A | Lactose | 7 | 0 | 0 | 0 | 0 | 0 | 0 | 37″—45″ | 26″—34″ |
| B | Sucrose | 40 | 55 | 57 | 35 | 17 | 3 | 0 | 10′20″—11′27″ | 20′50″—22′20″ |
| C | Mannitol | −14 | −4 | −4 | 1 | −1 | 1 | 0 | 52″—1′01″ | 16″—35″ |

a) % dissolved of the mean of six tablets in neutral medium minus % dissolved of the mean of six tablets in acidic medium. The symbol inside the parenthesis (′) is used to represent minutes and (″) is used to represent seconds.

hydrochloric acid than with water. This is again consistent with the dissolution and disintegration results for formulas D and F in Table 3. However, the same paper also reported that the liquid uptake into the Ac-Di-Sol compact was increased to a greater extent with dilute hydrochloric acid than with water, which is again inconsistent with the dissolution and disintegration results for formula B in Table 3.

Furthermore, Vadas *et al.*[8] reported that the disintegration of a tablet (lactose + Ac-Di-Sol + magnesium stearate) is insensitive to the pH (pH 1.5 or 6.0) of the medium. Caramella *et al.*[9] reported that the disintegration of a tablet (aspirin + Ac-Di-Sol + talc) behaves similarly in isotonic saline or 0.1 N HCl. Therefore, interaction among ingredients may affect the dissolution and disintegration and formula B was chosen for further interaction studies with other ingredients incorporated with the super disintegrant Ac-Di-Sol.

**Effect of Different Combinations of Acetaminophen, Sucrose, and Ac-Di-Sol on DR Difference and DT Difference between Acidic and Neutral Media** The DR and DT of formulas with different combinations of acetaminophen, sucrose, and Ac-Di-Sol (formulas B, G, H, or I) were conducted, and the results are shown in Fig. 1 and Table 2.

The DR and DT of formula G, which contains only acetaminophen and sucrose, do not show much difference between the two media. The DR of formula H, containing only acetaminophen and Ac-Di-Sol, shows some difference between the two media, but the difference is not as great as that of formula B containing acetaminophen, sucrose and Ac-Di-Sol. The DT of formula H in both acidic and neutral media is pretty fast, and the DT difference will probably not play an important role in the DR difference in two media. The DT difference between acidic and neutral media is not apparent for formula I, containing only sucrose and Ac-Di-Sol. Therefore, it seems that when acetaminophen, sucrose, and Ac-Di-Sol (formula B) are together, the DR and DT difference between the two media become more obvious. Interactions may exist among these three ingredients which causes the decrease in DR and DT, especially in the acidic medium, and results in DR and DT differences between the two media.

## Conclusions

Sucrose is the ingredient which causes the greatest DR difference between acidic and neutral media among lactose, mannitol, and sucrose. When a super disintegrant, Ac-Di-Sol, Primojel, or Polyplasdone XL, is incorporated into formulas with acetaminophen and sucrose, the effect of super disintegrants on the DR and DT differences between the two media is Primojel > Ac-Di-Sol > Polyplasdone XL.

When acetaminophen, sucrose, and Ac-Di-Sol are together, the DR and DT decreased, especially in the acidic medium, resulting in DR and DT differences between acidic and neutral media. Ac-Di-Sol in the tablet matrix of this study may lose part of its wicking efficiency in the acidic medium. Acetaminophen tablets with sucrose as an excipient tend to erode slowly rather than disintegrate. As the outer layer of the tablet matrix dissolves, the rate of fluid diffusion inside is retarded. It may become worse when a hydrophobic drug or a stronger binder is present.

Generally speaking, DT correlates well with the DR in this study. DT might still be valuable as a quick prediction tool if DR is not available.

**Acknowledgment** The authors would like to thank Cheng's Foundation for Pharmaceutical Sciences and Chen-Ho Pharmaceutical Co., Ltd. for the support of this study.

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