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

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**The disintegration and dissolution of acetaminophen tablets containing sucrose and Ac-Di-Sol/Primojel was significantly different between acidic and neutral media. The purpose of this study was to investigate the mechanism of this phenomenon and to propose a way of reducing the dissolution difference between the two media. Tablets of different combinations of active ingredient, sucrose, and Ac-Di-Sol/Primojel were prepared and their dissolution in various media was evaluated. The dissolution differences were found to be largely related to the hydrophobicity of the active ingredient and pH difference of the two media. This difference was even more evident under the condition where acetaminophen, sucrose, and Primojel were combined. The dissolution difference was therefore attributed to the depressed function of Primojel in the acidic medium, the stronger binding of sucrose, the hydrophobicity of the active ingredient and pH difference of the two media. Increasing the concentration of Primojel or incorporating the surfactant in the tablet can thus greatly decrease the dissolution difference between acidic and neutral media.**

**Key words** dissolution; Primojel; Ac-Di-Sol; pH; acetaminophen

In our previous investigation[1] it was found that the dissolution (DR) of acetaminophen tablet, incorporated with sucrose as excipient and croscarmellose sodium (Ac-Di-Sol, FMC Corp., U.S.A.) or sodium starch glycolate (Primojel, Avebe, Holland) as disintegrant, is significantly decreased in acidic medium compared with that in neutral medium. We hypothesized that Ac-Di-Sol in the tablet matrix may lose part of its wicking efficiency in the acidic medium, and the rate of fluid diffusion inside the tablet matrix may become worse when a hydrophobic drug or a strong binder is present.[1] The interaction among acetaminophen, sucrose, and Ac-Di-Sol to which this phenomenon is attributed has been described.[1]

In this study the DR difference of the formula containing acetaminophen, sucrose, and Primojel will be discussed. Meanwhile, a very slightly soluble[2] drug, allopurinol, and a freely soluble[2] drug, chlorpheniramine maleate were chosen to study the effect of the hydrophobicity of the active ingredient on the DR difference between the two media. Similarly, the effect of the ionic strength (NaCl) and pH of the DR medium on this DR difference were also investigated. Finally, the acetaminophen tablet, incorporated with sucrose and Primojel, which caused the greatest decrease in the acidic medium in our previous investigation[1] was used as a model to study how to decrease the DR difference between the acidic and neutral environment. Since decreased DR in the acidic stomach environment which the tablet will first encounter may cause reduced *in vivo* bioavailability, it is essential that this difference in DR be prevented.

## Materials and Methods

**Materials** Acetaminophen (Seven Stars Chem. Corp., Taiwan), allopurinol (Siegfried Chemie, Switzerland), chlorpheniramine maleate (Kowa, Japan), sucrose (Taiwan Sucrose Corp., Taiwan), sodium lauryl sulfate (E. Merck, Germany), magnesium stearate (Akcros Corp., Holland), croscarmellose sodium (Ac-Di-Sol, FMC Corp., U.S.A.) and sodium starch glycolate (Primojel, Avebe, Holland) were all of USP/NF grade. All reagents used were of analytical grade.

**Tablet Preparation, Disintegration (DT) and DR Tests** The preparation of acetaminophen tablets, DT and DR tests were similar to part I[1] Allopurinol and chlorpheniramine maleate tablets were compressed into round tablets (diameter 12.2 mm) with a targeted weight of 620 mg. The ingredients of each formula are listed in Table 1. The weight variation of all the tablets was within ±5%. Tablets of closely similar weight were chosen for all comparative studies. The hardness of the tablets was measured by a hardness tester made by Imada Seisakusyo. Although the hardness might vary by 15% RSD (relative standard deviation), it did not significantly affect the DR as the standard deviation of six determinations of DR in most cases was within 3 percent.

## Results and Discussion

**Effect of Different Ingredient Combinations (Acetaminophen, Sucrose, and Primojel) on DR and DT Difference between Acidic and Neutral Media** Acetaminophen has a p*K*a of 9.5[3] and its solubility is not affected by pH of the medium used in this study (pH 1.3 or 6.3).[4] Therefore, pH related solubility factor does not cause the DT or DR difference between the two media.

Table 1. Ingredients of Each Formula

| Formula | Ingredients |
|---|---|
| F | Acetaminophen 500 mg, sucrose 500 mg, Primojel 40 mg |
| G | Acetaminophen 500 mg, sucrose 500 mg |
| J | Sucrose 500 mg, Primojel 40 mg |
| K | Acetaminophen 500 mg, Primojel 40 mg |
| L | Allopurinol 300 mg, sucrose 300 mg |
| M | Allopurinol 300 mg, sucrose 300 mg, Ac-Di-Sol 24 mg |
| N | Chlorpheniramine maleate 300 mg, sucrose 300 mg, Ac-Di-Sol 24 mg |
| O | Acetaminophen 500 mg, sucrose 500 mg, Primojel 80 mg |
| P | Acetaminophen 500 mg, sucrose 500 mg, Primojel 40 mg, SLS 6 mg |

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Table 2. Interaction Effect on % DR Difference and DT between Acidic and Neutral Media

| Formula | % DR difference[a] | | | | | | | DT | |
|---|---|---|---|---|---|---|---|---|---|
| | 5′ | 10′ | 15′ | 25′ | 35′ | 45′ | 55′ | DW | SGF |
| F | 29 | 53 | 85 | 79 | 73 | 66 | 62 | 13′15″—13′44″ | 49′48″—51′48″ |
| G | −1 | 0 | 1 | 3 | 3 | 5 | 7 | 85′20″—89′10″ | 72′40″—76′21″ |
| J | | | | N/A | | | | 5′01″— 6′50″ | 5′10″— 7′07″ |
| K | 42 | 13 | 4 | −1 | 0 | 0 | 0 | 1′30″— 4′53″ | 1′52″— 4′22″ |

*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.

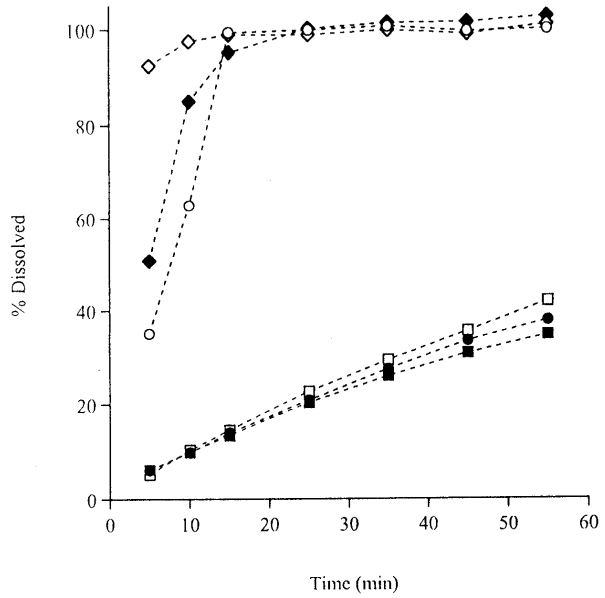


Fig. 1. Interaction Effect on % Dissolved in Acidic and Neutral Media

◇, acetaminophen and Primojel (DW); ◆, acetaminophen and Primojel (SGF) (formula K); ○, acetaminophen, sucrose, and Primojel (DW); ●, acetaminophen, sucrose, and Primojel (SGF) (formula F); □, acetaminophen and sucrose (DW); ■, acetaminophen and sucrose (SGF) (formula G). Each point represents the mean of six determinations. All standard deviations were within 5%.

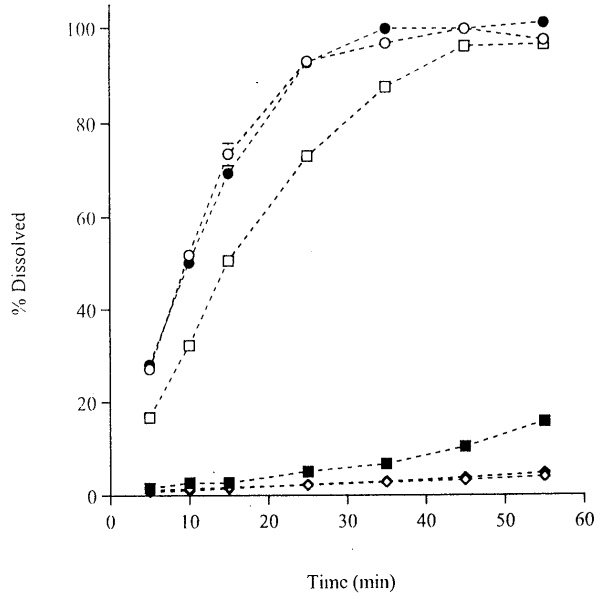


Fig. 2. Effect of Hydrophobicity of Active Ingredient on % Dissolved of Tablets in Acidic and Neutral Media

○, chlorpheniramine maleate, sucrose, and Ac-Di-Sol (DW); ●, chlorpheniramine maleate, sucrose, and Ac-Di-Sol (SGF) (formula N); □, allopurinol, sucrose, and Ac-Di-Sol (DW); ■, allopurinol, sucrose, and Ac-Di-Sol (SGF) (formula M); ◇, allopurinol and sucrose (DW); ◆, allopurinol and sucrose (SGF) (formula L). Each point represents the mean of six determinations. All standard deviations were within 5%.

Both DR and DT of formulas containing different combinations of acetaminophen, Primojel and sucrose (formulas F, G, J, and K) were conducted, and the results are shown in Table 2 and Fig. 1. DR of a tablet containing acetaminophen and sucrose (formula G) showed little difference in acidic and neutral media.

The DR of tablet containing acetaminophen and Primojel (formula K) in the acidic medium showed decreased DR at the very early stage (5 min) but the difference disappeared after 15 min. However, similar short DT of formula K was observed in both media. This might be related with the initially decreased rate of liquid uptake of Primojel in the acidic medium.[5] However, the difference of liquid uptake between the two media became smaller after the tablet broke into particles.

Although the DT difference between acidic and neutral media for the tablet containing sucrose and Primojel (formula J) is not evident, formula F, containing acetaminophen, sucrose, and Primojel showed very large DR and DT difference between the two media. In the acidic medium, the tablet containing the three components had a very long DT time, perhaps due to the dramatically depressed swelling function of Primojel in the acidic medium.[6] In addition, the strong binding of sucrose and probable interaction among the three ingredients may also result in longer DT time of the tablet. However, in the neutral media, the tablet quickly disintegrates to many small particles and results in faster DR.

**Effect of Hydrophobicity of the Active Ingredient on the DR Difference between Acidic and Neutral Media** A very slightly soluble drug, allopurinol, and a freely soluble drug, chlorpheniramine maleate, were chosen to compare DR behavior in the media. The two drugs have a p*K*a of 9.4 and 9.1, respectively,[3] so pH related solubility factor does not cause a DR difference between two media. When allopurinol was combined with sucrose alone (formula L), its DR in the acidic and neutral media was almost the same as shown in Fig. 2 and Table 3. However, when Ac-Di-Sol was incorporated (becoming formula M), DR in the acidic medium was greatly decreased as that of the acetaminophen tablets (formula F). This agrees with our previous hypothesis[1] that the combination of Ac-Di-Sol, sucrose and a hydrophobic drug caused DR decrease in acidic medium. To further confirm the hypothesis that the hydrophobic drug and strong binder decreased DR, chlorpheniramine maleate was used in place of allopurinol

Table 3. Effect of Hydrophobicity of Active Ingredient on % DR Difference between Neutral and Acidic Media

| Formula | % DR difference[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5′ | 10′ | 15′ | 25′ | 35′ | 45′ | 55′ |
| L | 0 | 0 | 0 | 0 | 0 | −1 | −1 |
| M | 15 | 30 | 48 | 68 | 81 | 86 | 81 |
| N | −1 | 2 | 4 | 0 | −3 | 0 | −4 |

*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.

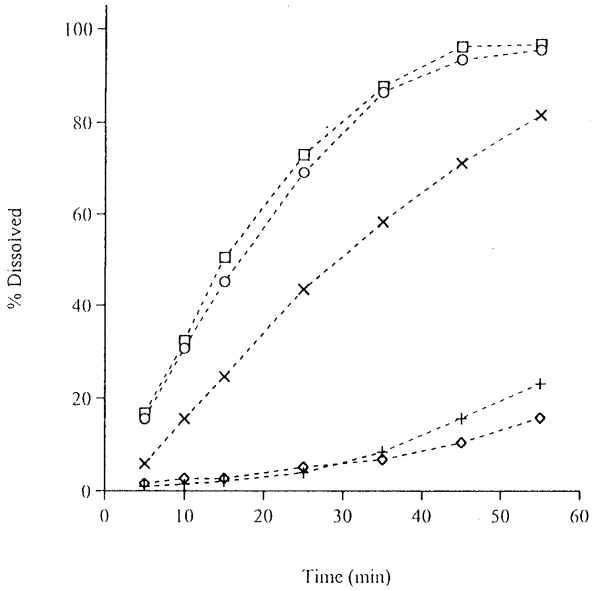


Fig. 3. Effect of Dissolution Medium on % Dissolved of Tablets Containing Allopurinol, Sucrose, and Ac-Di-Sol (formula M) in Acidic and Neutral Media

□, (DW); ○, pH 3.0 HCl solution; × pH 2.0 HCl solution; +, pH 1.3 HCl solution; ◇, SGF. Each point represents the mean of six determinations. All standard deviations were within 5%.

Table 4. Effect of Ionic Strength (NaCl) and pH Values of DR Medium on % DR Difference of Allopurinol Tablets (Formula M) between Neutral and Acidic Media

| Dissolution | Medium % DR difference[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5′ | 10′ | 15′ | 25′ | 35′ | 45′ | 55′ |
| pH 1.3 SGF | 15 | 30 | 48 | 68 | 81 | 86 | 81 |
| pH 1.3 HCl solution | 16 | 31 | 49 | 69 | 79 | 81 | 74 |
| pH 2.0 HCl solution | 11 | 17 | 26 | 30 | 29 | 25 | 15 |
| pH 3.0 HCl solution | 1 | 2 | 5 | 4 | 1 | 3 | 1 |

*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.

(becoming formula N), and the DR difference between the two media disappeared.

**Effect of Ionic Strength (NaCl) and pH Value of the DR Medium on the DR Difference between Acidic and Neutral Media** The difference between two DR media, deionized water (DW) and simulated gastric fluid without enzyme (SGF) is pH and ionic strength (the incorporation of sodium chloride in the SGF). The DR difference of allopurinol tablets (formula M) was affected by pH of the

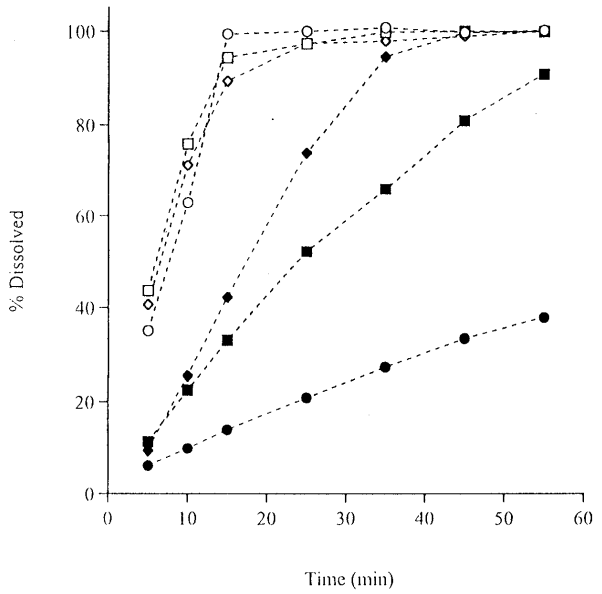


Fig. 4. Effect of Increasing Primojel Concentration or Incorporating SLS on % Dissolved of Tablet Containing Acetaminophen, Sucrose and Primojel in Acidic and Neutral Media

○, 40 mg Primojel (DW); ●, 40 mg Primojel (SGF) (formula F); ◇, 80 mg Primojel (DW); ◆, 80 mg Primojel (SGF) (formula O); □, Incorporating 6 mg SLS (DW); ■, Incorporating 6 mg SLS (SGF) (formula P). Each point represents the mean of six determinations. All standard deviations were within 5%.

Table 5. Effect of Increasing Primojel Concentration or Incorporating SLS on % DR Difference between Acidic and Neutral Media

| Formula | % DR difference[a] | | | | | | |
|---|---|---|---|---|---|---|---|
| | 5′ | 10′ | 15′ | 25′ | 35′ | 45′ | 55′ |
| F | 29 | 53 | 85 | 79 | 73 | 66 | 62 |
| O | 31 | 46 | 47 | 23 | 3 | −1 | 0 |
| P | 32 | 53 | 61 | 45 | 34 | 19 | 9 |

*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.

DR medium but not by the sodium chloride content (Fig. 3 and Table 4). The DR difference of allopurinol tablets (formula M) between DW (pH 6.3) and various HCl solutions (pH = 1.3, 2.0, 3.0) was compared. The greatest difference of DR was observed between medium at pH 1.3 (HCl solution) and medium at pH 6.3 (DW). The DR difference decreased when pH of the HCl solution increased. Consequently, no difference of DR between DW at pH 6.3 and HCl solution at pH 3.0 was observed. This also agrees with our previous hypothesis[1] that Ac-Di-Sol in the tablet matrix may lose part of its wicking efficiency in acidic medium.

Two approaches were made to decrease the DR difference between two media. The first was to increase the concentration of Primojel in a tablet and the second was to incorporate a surface active agent.

**Effect of Increasing Primojel Concentration on the DR Difference between Acidic and Neutral Media** The commonly used concentration of Primojel as disintegrant is 2 to 8%.[7] A higher concentration was used in this study due to the acidic condition and possible interference with other ingredients.

In Fig. 4 and Table 5, the DR of formula F containing

acetaminophen, sucrose, and Primojel (40 mg) was less in the acidic medium. However, this DR difference was significantly decreased when Primojel concentration was increased to 80 mg (becoming formula O) due to the significant increase of DR of formula O in the acidic medium. This might be explained by the Primojel function being partially destroyed in the acidic medium and a higher concentration of compensating the loss.

**Effect of Sodium Lauryl Sulfate (SLS) on the DR Difference between Acidic and Neutral Media** A surfactant has been incorporated into the tablet to increase its DR rate. Its action is often associated with the increase of liquid penetration by lowering the surface tension and contact angle,[8] or the producing of finer disintegrated particles with correspondingly larger surface area.[9-11] Ganderton[12] reported that the addition of SLS broke and improved the DR of phenindione tablets. SLS is also added in the DR medium of water or 0.1 N HCl for medroxyprogesterone acetate tablets to meet the DR tolerance limits.[13] Therefore, SLS was chosen to be incorporated into the tablets and the results are shown in Fig. 4 and Table 5.

When SLS was incorporated into formula F (becoming formula P), the DR in the acidic medium was greatly increased and the DR difference was consequently significantly decreased.

## Conclusion

The DR difference of the tablet containing acetaminophen, sucrose, and a super disintegrant Primojel between acidic and neutral media was investigated. The tablets fail to disintegrate in the acidic medium and the interaction among ingredients are the causes of this DR difference between the two media.

The large DR difference of the tablet containing a very hydrophobic drug, allopurinol, sucrose, and Ac-Di-Sol is consistent with our previous hypothesis. The difference disappeared when allopurinol was replaced with the hydrophilic drug, chlorpheniramine maleate.

The change of ionic strength by incorporation of NaCl in the DR medium does not significantly affect the DR difference. However, the lower the pH of the acidic medium, the greater the difference of DR between the two media.

Incorporation of a surfactant or addition of a large amount of super disintegrant can decrease the DR difference between two media. Decrease in the difference of DR between two media is mainly because of the enhancement of DR in the acidic medium.

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