行政院國家科學委員會專題研究計畫成果報告

酸鹼度對含超級崩散劑錠劑之溶離速率影響

計劃編號： NSC-87-2314-B-041-010
執行期限：86 年 8 月 1 日至 87 年 7 月 31 日
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含蔗糖及 Ac-Di-Sol/Primojel 之 Acetaminophen 錠劑之在酸性及中性媒液間之崩散與溶離有很大之差異。本計劃之目的即是在探討此一現象之機轉及尋求解決差異之方法。研究發現溶離差異原因與主成分之親水程度與溶離媒液之酸鹼值有關。這種差異在 Acetaminophen、Primojel 和蔗糖合用時更明顯，我們認為這與 Primojel 在酸性媒液之效率受抑制、蔗糖之強黏合性、主成分之厭水性，二個媒液間之酸鹼度差異有關。增加 Primojel 之用量或加入界面活性劑能大大地減低溶離差異。

關鍵字:溶離;超級崩散劑;酸鹼值

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. 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

Introduction

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]

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.

Results and Discussion

Acetaminophen has a pKa 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 DR difference between the two media. DR of formulas containing different combinations of acetaminophen, Primojel and sucrose (formulas F, G, and K) were conducted, and the results are shown in 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 minutes. However, similar short disintegration (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.

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

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 DR medium but not by the sodium chloride content (Fig. 3). 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. A higher concentration was used in this study due to the acidic condition and possible interference with other ingredients. In Fig. 4, 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 are shown in Fig. 4. 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.

References

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計劃成果自評：

本研究內容與原計劃相符，並且也達到預期目標，主要原因是因為預試驗皆試過。本研究成果在學術上適合發表，已獲日本藥學會 Chemical and Pharmaceutical Bulletin 之接受。主要發現可實際地供藥廠錠劑處方研發人員所使用。

Table I. 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

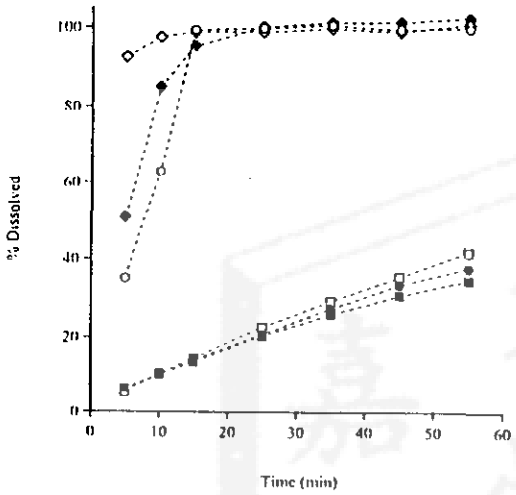

Fig. 1. Interaction Effect on % Dissolved in Acidic and Neutral Media

◇, 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%.

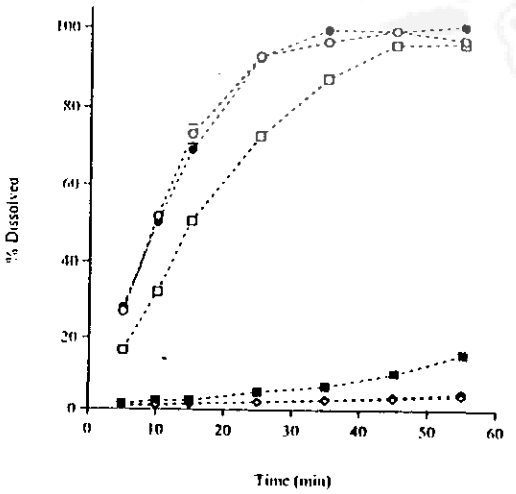

Fig. 2. Effect of Hydrophobicity of Active Ingredient on % Dissolved of Tablets in Acidic and Neutral Media

○, 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%.

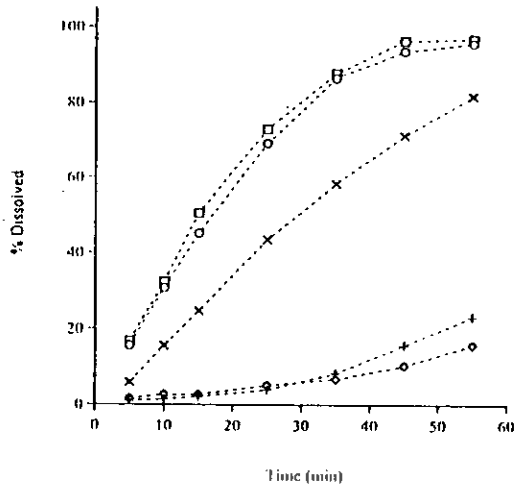

Fig. 3. Effect of Dissolution Medium on % Dissolved of Tablets Containing Allopurinol, Sucrose, and Ac-Di-Sol (formula M) in Acidic and Neutral Media

□, (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%.

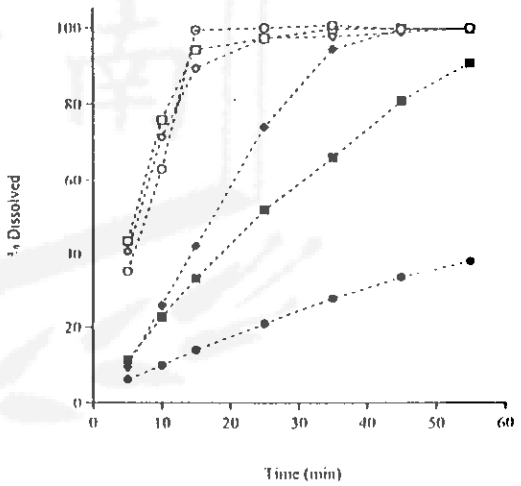

Fig. 4. Effect of Increasing Primojel Concentration or Incorporating SLS on % Dissolved of Tablet Containing Acetaminophen, Sucrose and Primojel in Acidic and Neutral Media

○, 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%.