Functionality Comparison of 3 Classes of Superdisintegrants in Promoting Aspirin Tablet Disintegration and Dissolution

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ABSTRACT

The aims of this study are (1) to compare the disintegration efficiency, and (2) to develop a discriminating test model for the 3 classes of superdisintegrants represented by Ac-Di-Sol, Primojel, and Polyplasdone XL10. Using a digital video camera to examine the disintegration process of tablets containing the same wt/wt percentage concentration of the disintegrants, Ac-Di-Sol was found to disintegrate tablets rapidly into apparently primary particles; Primojel also apparently disintegrated tablets into primary particles but more slowly; Polyplasdone XL10 disintegrated tablets rapidly but into larger masses of aggregated particles. The differences in the size distribution generated in the disintegrated tablets likely contribute to the drug dissolution rate differences found for aspirin tablets with similar disintegration rates. The aspirin tablet matrix is proposed as a model formulation for disintegrant efficiency comparison and performance consistency testing for quality control purposes.

KEYWORDS: Superdisintegrants, aspirin tablet, disintegration, dissolution test.

INTRODUCTION

Despite increasing interest in controlled-release drug delivery systems, the most common tablets are those intended to be swallowed whole and to disintegrate and release their medicaments rapidly in the gastrointestinal tract (GIT). The proper choice of disintegrant and its consistency of performance are of critical importance to the formulation development of such tablets. In more recent years, increasing attention has been paid to formulating not only fast dissolving and/or disintegrating tablets that are swallowed, but also orally disintegrating tablets that are intended to dissolve and/or disintegrate rapidly in the mouth.[1-3]

Most prior studies have focused on the function-related properties of superdisintegrants with special emphasis on correlating these functional properties to disintegrant efficiency and drug release rate. Water penetration rate and rate of disintegration force development are generally positively related to disintegrant efficiency in nonsoluble matrices.[4,5] However, such a positive correlation is not always observed between tablet disintegration time and drug dissolution rate.[6-8] This lack of correlation can be attributed to many factors. One factor is the disintegration test itself. The *United States Pharmacopeia (USP)* disintegration apparatus is not intended to accurately measure the disintegration time. Furthermore, agitation is likely to be more vigorous in the disintegration test compared with dissolution testing. The different pH media specified by the dissolution test also can contribute to lack of correlation since medium pH is reported to influence the efficiency of several tablet disintegrants.[9-11] In addition, this lack of correlation can also in part be attributed to the specific design of the *USP* disintegration apparatus. According to the *USP* specification, "complete disintegration is defined as that state in which any residue of the unit, except fragments of insoluble coating or capsule shell, remaining on the screen of the test apparatus is a soft mass having no palpably firm core."[12] For an uncoated tablet, the disintegrated fragments need only be small enough to pass through the screen of the disintegration apparatus. Thus, this apparatus provides no discrimination of the size distribution of the disintegrated tablets beyond the size needed to just pass through the screen.

The objectives of this study were thus to provide a closer look at the functionality of superdisintegrants in promoting tablet disintegration and to develop a model formulation for discriminating super disintegrant functionality. To those ends, the size distribution of disintegrated dicalcium phosphate-based fast disintegrating tablets was examined with the help of videography and dissolution profiles of aspirin were compared for tablets containing different superdisintegrants at varied levels of addition. Aspirin has been successfully applied by many investigators in studying the mechanisms of tablet disintegrants[13-15] and was selected in this study because of its good compactibility and moderately low solubility in water.

MATERIALS AND METHODS

Materials

Acetylsalicylic acid (aspirin) was obtained from AnMar International (Bridgeport, CT). Dicalcium phosphate dihydrate,

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unmilled, *USP*/FCC (Emcompress) was obtained from JRS Pharma (Patterson, NY). Lactose monohydrate (spray-dried NF Fast Flo) was obtained from Foremost Farms USA (Baraboo, WI). The 3 superdisintegrants studied were croscarmellose sodium (Ac-Di-Sol, FMC BioPolymer, Philadelphia, PA), sodium starch glycolate (Primojel, DMV International, Veghel, The Netherlands), and crospovidone NF (Polyplasdone XL and Polyplasdone XL10, ISP Technologies, Ashland, KY). Magnesium stearate (Mallinckrodt, St Louis, MO) was used as the internal lubricant. Dicalcium phosphate and magnesium stearate were sieved through screen No. 45 (354 μm), and aspirin was sieved through screen No. 60 (250 μm) before use. Superdisintegrants were used as received.

Methods

Blending and Tableting

Either dicalcium phosphate or aspirin was premixed with superdisintegrant for 15 minutes in a 500-mL twin shell blender (Patterson Kelly Twin Shell V-Blender, model LB-331, The Patterson-Kelly Co, East Stroudsburg, PA), and then lubricated with magnesium stearate for another 5 minutes. The magnesium stearate level was fixed at 0.5% for all formulations. Superdisintegrants were used at 1% and 2% in dicalcium phosphate tablets, and at 1%, 2%, and 5% in aspirin tablets. Round flat-faced tablets with diameter of 8.8 mm were prepared one at a time on an instrumented rotary press (Stokes B2, Stokes Engineering, Doylestown, PA). The weight of dicalcium phosphate tablets was 445 ± 5 mg, and the weight of aspirin tablets was 300 ± 5 mg. The tablet press setting was kept constant across all formulations. The resulting compression force was 5.1 ± 0.2 kN for dicalcium phosphate tablets and 3.9 ± 0.2 kN for aspirin tablets. Tablets were placed in scintillation vials and the vials were stored in a desiccator for at least 24 hours before testing.

Disintegration and Dissolution Test

Disintegration times were measured in 900 mL purified water according to the *USP* 24 method without disc at room temperature (20°C ± 2°C). Previous study showed that the tablet disintegration times were linearly increased by reducing the medium temperature from the 37°C required by the *USP* 24 method to room temperature, as were the differences between tablet disintegration times.[16] The disintegration times of 6 individual tablets were recorded and the average was reported.

Dissolution profiles of aspirin tablets were determined using the *USP* 24 Method II (Vankel VK7000, VanKel Industries, Edison, NJ) with paddle speed at 50 rpm. Dissolution was performed in 900 mL purified water at room temperature (20°C ± 2°C), the same medium as used in the disintegration test. A peristaltic pump (Rainin Instrument Co, Kent, WA) was coupled to a Shimadzu UV-160U UV/visible spectrophotometer (Shimadzu Corp, Tokyo, Japan) to provide a continuous flow of drug solution through the 1-mm cuvettes. The absorbance of aspirin solution at 229 nm was analyzed every 30 seconds for 45 minutes. The data given are the means of 6 individual determinations.

Video of the Tablet Disintegration Process

Despite the close disintegration times measured by the *USP* disintegration apparatus, superdisintegrants were observed to break tablets into particles of different sizes when disintegration took place with a low degree of agitation. A digital video camera (Nikon Coolpix 995, Nikon, Tokyo, Japan) was used to record the disintegration process when the tablet was dropped into a 140 × 20-mm Petri dish filled with 200 mL purified water at room temperature. The dynamic disintegration of dicalcium phosphate-based tablets with either 1% or 2% of superdisintegrants (Ac-Di-Sol, Primojel, Polyplasdone XL or XL10) is presented in the videos (Figures 1 and 2), respectively. Several attempts at direct measurement of the size distribution of the disintegrated fragments by either optical microscopy, laser scattering (Malvern Mastersizer, Malvern Instruments, Worcestershire, UK), or sieving (Sonic Sifter, ATM Corp, New Berlin, WI) were unsuccessful. Particle attrition during sifting or cycling inside the sample cell of the Mastersizer and particle hardening after drying due to the binding effect of the gelled Primojel were observed for some formulations.

To investigate the influence of temperature, tablets were disintegrated in 37ºC water following the same procedures. Limited sieve analysis did suggest that all superdisintegrants tended to break tablets into smaller fragments with an increase in medium temperature (data not presented).

Water Uptake Study by Aspirin Tablets

A modified gravimetric liquid uptake apparatus[17] previously developed in our laboratory was used to measure water uptake by the aspirin tablets. The apparatus consists of a sample holder and a liquid holding vessel that is set on an electronic balance. These 2 parts of the apparatus are adjusted to the same horizontal level and connected by a plastic tube so that water can flow freely from one side to the other. When a tablet was placed onto the sample holder, water was then passively withdrawn into the tablet from the feeder. The loss of weight from the

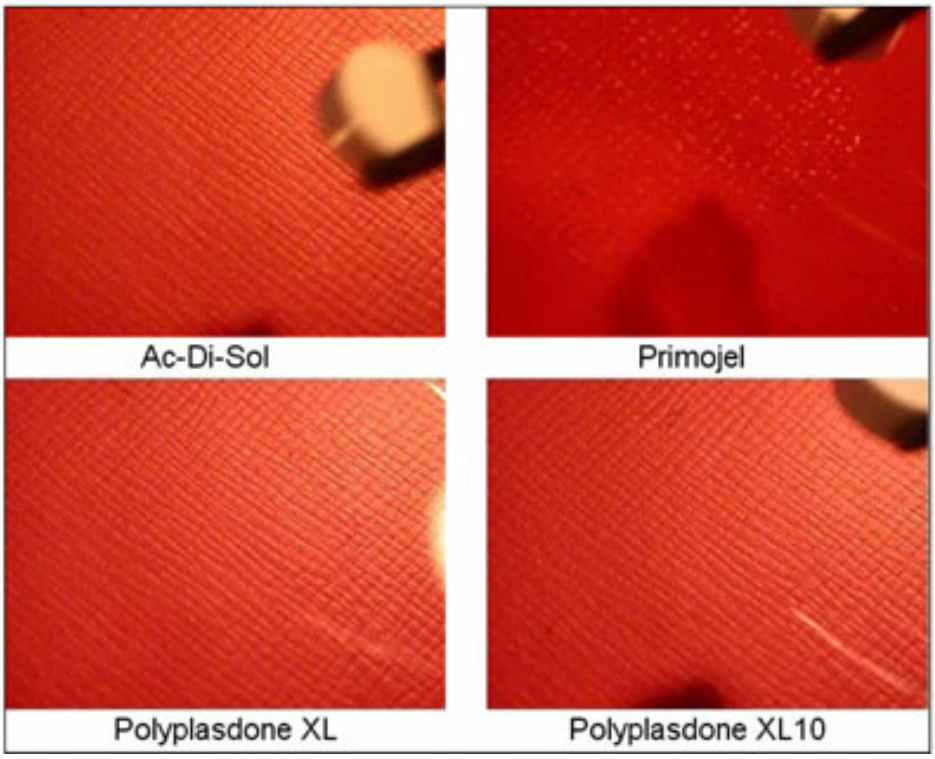

Figure 1. Disintegration of dicalcium phosphate tablets with 1% superdisintegrant in purified water at zero degree of agitation. View Video.

liquid holder was read from the electronic balance. The readings were automatically transferred to a PC and collected by a program written in C++ language. Data were collected every second until saturation was reached. Experiments were performed in triplicates at room temperature. All tablets were saturated with water rapidly within

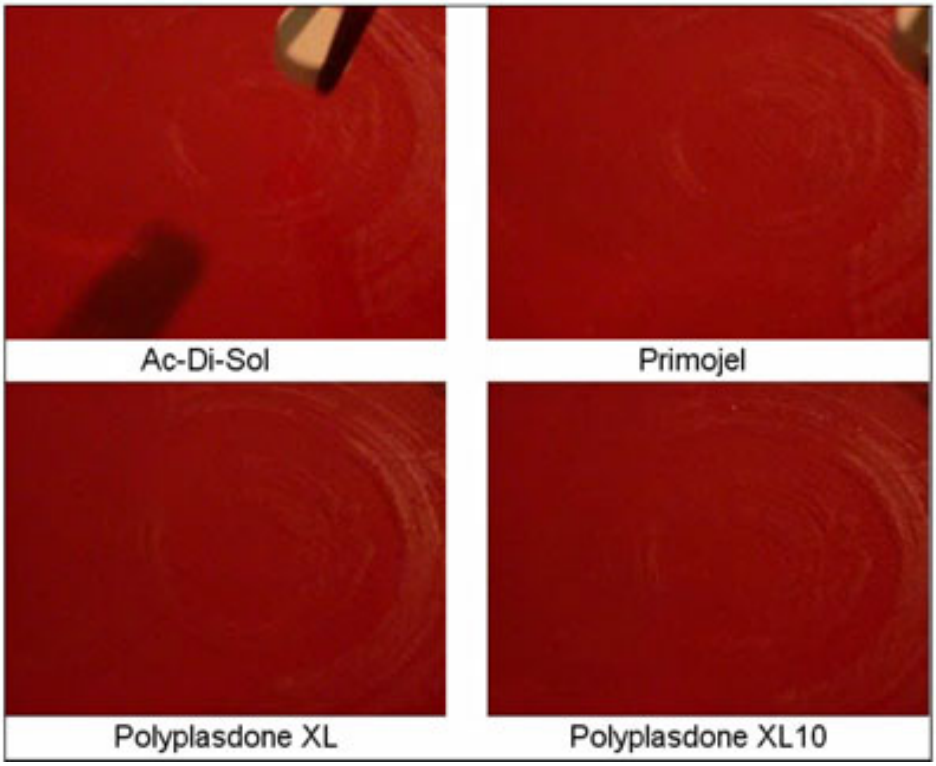

Figure 2. Disintegration of dicalcium phosphate tablets with 2% super disintegration in purified water at zero degree of agitation. View Video.

Table 1. Dicalcium Phosphate Tablets Properties*

Superdisintegrant	Weight (mg)	Hardness (kp)	Disintegration Time (seconds)
1% Disintegrant			
Ac-Di-Sol	446 (1)	19.7 (1.0)	15 (0)
Primojel	445 (1)	20.0 (0.8)	132 (65)
Polyplasdone XL	446 (1)	17.9 (1.9)	716 (355)
Polyplasdone XL10	446 (1)	17.6 (1.7)	185 (67)
2% Disintegrant			
Ac-Di-Sol	446 (1)	15.2 (1.1)	7 (0)
Primojel	447 (1)	14.6 (0.4)	38 (24)
Polyplasdone XL	442 (1)	15.0 (1.2)	78 (18)
Polyplasdone XL10	442 (1)	15.5 (1.0)	10 (3)

*All values are mean ± SD, n = 6.

0.5 to 2 minutes. Therefore, only the tablet maximal water uptake amount was reported.

Results and Discussion

Dicalcium Phosphate Tablets

Tablet weight, hardness, and disintegration time are presented in Table 1. All tablets were found uniform in weight and hardness.

All tablets disintegrated rapidly in the *USP* test. However, the relatively larger fragments generated by tablets containing Primojel and Polyplasdone XL were not small enough to pass through the screen of the disintegration vessels. Accordingly a longer disintegration time and a larger variation were observed for both formulations, especially when the disintegrants were used at the lower concentration (1%). Ac-Di-Sol and Polyplasdone XL10 disintegrated tablets more rapidly. Tablets formulated with 2% of those 2 disintegrants disintegrated nearly immediately, even when tested at room temperature.

With the aid of a video camera, the dynamic process of tablet disintegration was further investigated. The videos (Figures 1 and 2) clearly demonstrated the distinctly different behavior of these superdisintegrants in promoting tablet disintegration. Visually, tablets formulated with Ac-Di-Sol can be seen to rapidly disintegrate into more or less uniform fine particles, while tablets formulated with Primojel appeared to disintegrate much more slowly into more or less uniform coarser particles. Tablets containing Polyplasdone (both XL and XL10) seemed to swell immediately despite the limited swelling capacity of this class of superdisintegrants. Polyplasdone was reported to exhibit a high capacity to retain deformation during postcompression.[18] The rapid swelling of these tablets upon wetting may partly be attributed to the recovery of deformation. However, those tablets formulated with 1% disintegrant did not obviously disintegrate into particles; rather, they tended to separate axially into upper and lower sections. When used at 2% concentration, tablets with this class of superdisintegrants disintegrated further into large irregularly shaped fragments. Considering the short disintegration times measured by the *USP* disintegration apparatus, these fragments must be weakly held particle associations that apparently persist under the conditions of this test (ie, passive disintegration with no applied agitation). The videos (Figures 1 and 2) are consistent with the results from the *USP* disintegration apparatus to the extent that Ac-Di-Sol disintegrated tablets rapidly into relatively fine particles, Primojel disintegrated tablets more slowly into relatively larger fragments, and Polyplasdone XL and XL10 disintegrated tablets into relatively large fragments of loosely associated particles, which

Table 2. Aspirin Tablet Properties*

Superdisintegrant	Disintegration Time (seconds)	Q_{15} (%)	Q_{30} (%)	Q_{45} (%)	Maximal Water Uptake (mg/tablet)
0% Disintegrant					
Control	N/A†	2.2 (0.4)	4.2 (0.6)	6.1 (1.0)	0.02 (0.00)
1% Disintegrant					
Ac-Di-Sol	23 (2)	45.7 (6.4)	82.6 (6.8)	103.7 (6.4)	260 (7)
Primojel	1262 (302)	5.3 (0.8)	10.4 (1.6)	15.3 (2.4)	84 (3)
Polyplasdone XL10	68 (30)	13.8 (2.0)	26.3 (3.4)	38.0 (3.7)	134 (2)
2% Disintegrant					
Ac-Di-Sol	20 (3)	61.2 (4.8)	98.6 (3.3)	110.1 (2.2)	295 (5)
Primojel	74 (24)	29.2 (4.1)	49.5 (5.1)	64.6 (4.9)	230 (6)
Polyplasdone XL10	36 (6)	28.6 (4.7)	46.4 (6.5)	61.4 (3.2)	185 (11)
5% Disintegrant					
Ac-Di-Sol	17 (7)	71.1 (14.2)	100.9 (10.3)	110.2 (9.1)	346 (6)
Primojel	31 (1)	63.1 (7.0)	92.4 (3.6)	100.9 (4.6)	303 (5)
Polyplasdone XL10	19 (2)	41.8 (7.9)	67.8 (9.7)	83.6 (12.9)	269 (4)

*All values are mean ± SD, n = 6.

†N/A indicates not applicable; tablets fail to disintegrate after 45 minutes.

easily dispersed under the oscillating movement of the *USP* disintegration apparatus.

Aspirin Tablets

The disintegration test is not discriminating since all superdisintegrants appear highly efficient, with disintegration times as short as 30 seconds when used at 2% concentration. However, as discussed above, the videos (Figures 1 and 2) demonstrated differences in the particle size generated in the disintegrated tablets. Those differences could affect drug dissolution since breaking tablets into finer fragments may promote drug dissolution by providing larger total surface areas for drug dissolution to take place. The disintegration times and dissolution profiles of aspirin tablets formulated with 1%, 2%, or 5% Ac-Di-Sol, Primojel, or Polyplasdone XL10 are given in Table 2 and Figure 3. Because of its comparably poorer disintegration efficiency, Polyplasdone XL was not included in this part of study.

The disintegration times of the aspirin tablets were consistent with those of the dicalcium phosphate tablets. At the same addition level, Ac-Di-Sol and Polyplasdone XL10 generally disintegrate tablets faster than Primojel. It was found that the disintegration time was comparable for tablets formulated with either 1% Ac-Di-Sol, 2% Polyplasdone XL10, or 5% Primojel. However, the dissolution of aspirin from these tablets varied in the following decreasing order despite the closeness of their disintegration times: Ac-Di-Sol > Primojel > Polyplasdone XL. These

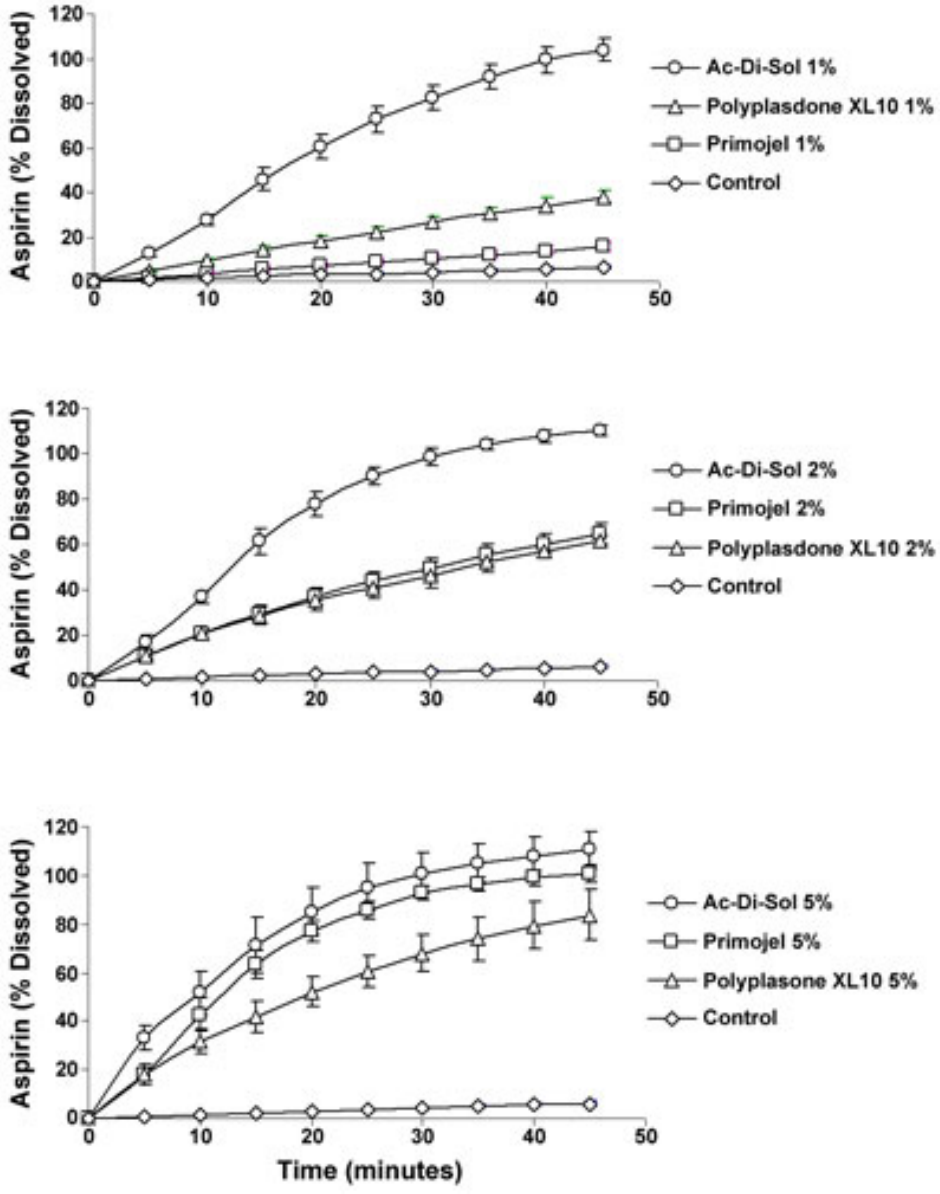

Figure 3. Dissolution of Aspirin from tablets with different concentration of superdisintegrants (mean ± SD, n = 6).

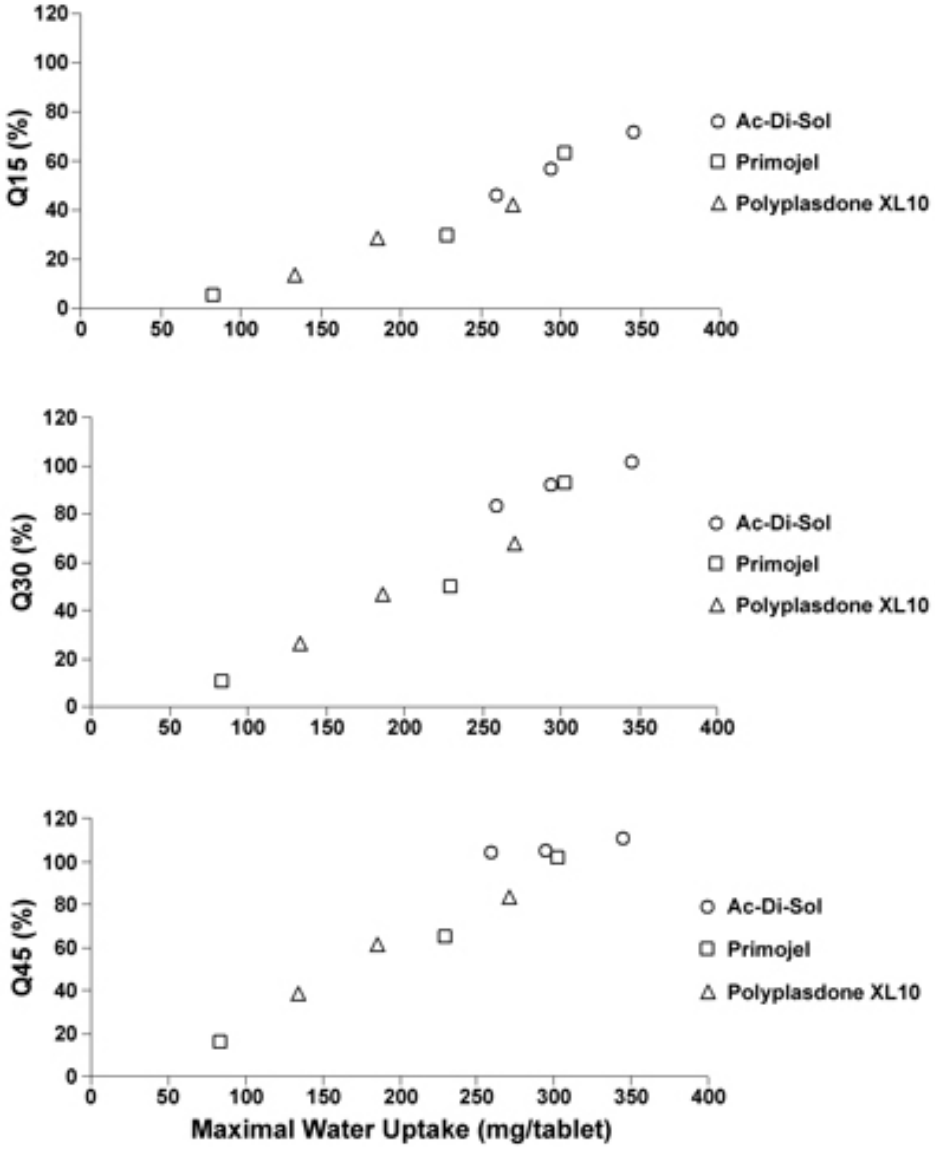

Figure 4. Correlation between the maximal water uptake by Aspirin tablets and the cumulative percentage of drug dissolved after different period of time.

results correlate with the apparent differences in particle size generated in the disintegrated tablets as observed in the videos (Figures 1 and 2). Unlike the up and down movement of the disintegration apparatus, the mild agitation force exerted by the dissolution paddles (50 rpm) apparently was not strong enough to cause a complete breakdown of the larger fragments that resulted from the disintegration of tablets containing Polyplasdone XL10. The drug dissolution rate comparison is presented in Figure 3. Partial data are presented for clarification purposes.

To further investigate the importance of the total surface area in promoting drug dissolution, a water uptake study was performed on all aspirin tablets. Since drug has to dissolve from the interface between drug and water, the maximal water uptake volume can be taken as an estimation of the total surface area available for drug dissolution to take place. The maximal water uptake volume was summarized in Table 2. As shown in Figure 4, a positive linear relationship was observed between the maximal water uptake volume and the cumulative percentage of drug dissolved by 15 minutes, 30 minutes, and 45 minutes. The slightly high Q value from tablets containing Ac-Di-Sol is probably due to the fiber-like nature of Ac-Di-Sol. Each fiber can act as a hydrophilic channel to facilitate water uptake into the tablet matrix and help increase the total water contact area with drug.

CONCLUSION

In the present study, 3 disintegrants representing each of the 3 main classes of superdisintegrants differed in their ability to disintegrate model tablets into their primary

particles when used at the same wt/wt percentage concentration. Such a difference can potentially affect drug dissolution. The aspirin tablet matrix appeared to successfully discriminate the ability of these superdisintegrants to promote drug dissolution and is proposed as a model formulation for disintegrant performance testing and quality control purposes.

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REFERENCES

1. Bi YX, Sunada H, Yonezawa Y, Danjo K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. *Drug Dev Ind Pharm.* 1999;25:571–581.

2. Sallam E, Ibrahim H, Abu Dahab R, Shubair M, Khalil E. Evaluation of fast disintegrants in terfenadine tablets containing a gas-evolving disintegrant. *Drug Dev Ind Pharm.* 1998;24:501–507.

3. Bi Y, Sunada H, Yonezawa Y, et al. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oral cavity. *Chem Pharm Bull (Tokyo).* 1996;44:2121–2127.

4. Massimo G, Catellani PL, Santi P, et al. Disintegration propensity of tablets evaluated by means of disintegrating force kinetics. *Pharm Dev Technol.* 2000;5:163–169.

5. Caramella C, Colombo P, Conte U, et al. Water uptake and disintegrating force measurements: towards a general understanding of disintegration mechanisms. *Drug Dev Ind Pharm.* 1986;12:1749–1766.

6. Johnson JR, Wang LH, Gordon MS, Chowhan ZT. Effect of formulation solubility and hygroscopicity on disintegrant efficiency in tablets prepared by wet granulation, in terms of dissolution. *J Pharm Sci.* 1991;80:469–471.

7. Pandit JK, Tripathi MK, Babu RJ. Effect of tablet disintegrants on the dissolution stability of nalidixic acid tablets. *Pharmazie.* 1997; 52:538–540.

8. Sakr A, Bose M, Menon A. Comparative effectiveness of superdisintegrants on the characteristics of directly compressed triamterene hydrochlorothiazide tablets. *Pharm Ind.* 1993;55:953–957.

9. Chen CR, Cho SL, Lin CK, Lin YH, Chiang ST, Wu HL. Dissolution difference between acidic and neutral media of acetaminophen tablets containing a super disintegrant and a soluble excipient. II. *Chem Pharm Bull (Tokyo).* 1998;46:478–481.

10. Zhao N, Augsburger LL. The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS PharmSciTech.* 2005;6:E120–E126.

11. Gordon MS, Rudraraju VS, Dani K, Chowhan ZT. Effect of the mode of super disintegrant incorporation on dissolution in wet granulated tablets. *J Pharm Sci.* 1993;82:220–226.

12. USP. *United States Pharmacopeia, 27th revision.* Rockville, MD: USP Convention, Inc; 2004:2302.

13. Rizk S, Barthelemy C, Duru C, Guyot-Herman AM. Investigation on a new modified USP xanthan with tablet-disintegrating properties. *Drug Dev Ind Pharm.* 1997;23:19–26.

14. Chang RK, Shinwari M, Leonzio M, Wu LS, Hussain MA. Evaluation of the disintegrant properties for an experimental, cross-linked polyalkylammonium polymer. *Int J Pharm.* 1998;173:87–92.

15. Colombo P, Conte U, Caramella C, Geddo M, La Manna A. Disintegrating force as a new formulation parameter. *J Pharm Sci.* 1984;73:701–705.

16. Zhao N, Augsburger LL. On the development of a disintegrating functionality test for superdisintegrants. *AAPS PharmSci.* 2003;5: M1256.

17. Shah U, Augsburger LL. Evaluation of the functional equivalence of crospovidone NF from different sources. 2. Standard performance test. *Pharm Dev Technol.* 2001;6:419–430.

18. Zhao N. *Investigation of Super Disintegrant Functionality and Development of Discriminating Test Methods [dissertation]*. Baltimore, MD: University of Maryland; 2005.