

The Influence of Swelling Capacity of Superdisintegrants in Different pH Media on the Dissolution of Hydrochlorothiazide From Directly Compressed Tablets

Submitted: November 16, 2004; Accepted: January 28, 2005; Published: September 20, 2005

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ABSTRACT

The purpose of this study was to investigate the efficiency of superdisintegrants in promoting tablet disintegration and drug dissolution under varied media pH. Significant reductions in the rate and extent of water uptake and swelling were observed for both sodium starch glycolate (Primojel) and croscarmellose sodium (Ac-Di-Sol) in an acidic medium (0.1 N HCl) but not for crospovidone NF (Polyplasdone XL10), a nonionic polymer. When Primojel and Ac-Di-Sol were incorporated in model formulations, a significant increase in tablet disintegration time was observed for slowly disintegrating tablets (lactose-based tablets) but not for the rapidly disintegrating tablets (dicalcium phosphate-based tablets). The dissolution rate of the model drug, hydrochlorothiazide, was found highly dependent on both tablet disintegration efficiency and the solubility of base material(s) in the testing medium. A laser diffraction particle size analyzer proved to be an effective tool for determining the intrinsic swelling of disintegrant particles in different media. Water uptake and swelling were confirmed as 2 important functions of superdisintegrants. The reduced water uptake and swelling capacity of disintegrants containing ionizable substituents in an acidic medium can potentially jeopardize their efficiency in promoting tablet disintegration and the drug dissolution rate.

KEYWORDS: superdisintegrants, particle swelling, liquid uptake, disintegration medium pH, dissolution medium pH, hydrochlorothiazide

INTRODUCTION

Tablet disintegration is a prerequisite to fast release of active ingredients from solid oral dosage forms. The disintegrant is routinely integrated into a formulation to speed the process of disintegration. Despite all the theories proposed, however, there is still a lack of a full understanding

of the mechanism of disintegration. Proposed mechanisms for the action of disintegrants include water uptake through wicking, swelling, deformation (shape) recovery, particle repulsion, and heat of wetting, though the latter 2 are not well supported by research.¹

Water penetration is an indispensable preprocessing step for disintegration. The sorption properties of various disintegrants are found essential for efficient disintegration and dissolution.^{2,3} If the wetting of the disintegrant particles is slowed, for example by coating the disintegrants with a hydrophobic substance (magnesium stearate), disintegration of the tablets is also slowed.⁴ These researchers have not only implicated that the extent of water uptake is important but also have conclusively demonstrated that the rate of water uptake is of critical importance for a number of tablet disintegrants.

The swelling of disintegrant particles is perhaps the most widely accepted mechanism for tablet disintegration. Primarily, this is because almost all disintegrants swell to some extent. Two types of swelling are of particular interest, intrinsic swelling and bulk swelling. There are primarily 2 methods cited for determining the intrinsic swelling of particles, optical microscopy,^{5,6} and size analysis using the Coulter Counter (Beckman Coulter Inc, Fullerton, CA).⁷ Both methods have been very informative. Nevertheless, the optical microscopy technique requires assumptions about the particle geometry since all measurements are in 2 dimensions, whereas swelling is a volumetric change and an electrolyte solution has to be used in the Coulter Counter method. Because the ionic strength can alter the swelling capacity, this may not be a very reliable method to determine intrinsic swelling. The advent of new techniques in particle size analysis, which uses laser diffraction as used in the present study, makes possible the measuring of the volume particle size distribution of disintegrant powders, both dry and after dispersion in a liquid vehicle. The percent increase in diameters can be taken as a measure of the intrinsic swelling capacity of superdisintegrants in the specific dispersing medium.

Bulk swelling of superdisintegrants has also been widely studied. Sophisticated devices are now available that measure the dynamic processes of the swelling of disintegrant particles during water uptake.⁸ A positive correlation was generally found between the rate of swelling and the tablet

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disintegration time. A similar apparatus has been built in our laboratory and has been successfully applied in previous studies.⁹

The 3 main classes of superdisintegrants represented by Primojel, Ac-Di-Sol, and Polyplasdone XL10 reportedly exhibit a broad range of intrinsic swelling capacity (Primojel > Ac-Di-Sol >> Polyplasdone XL10), yet all 3 are clearly very effective disintegrants. Furthermore, the swelling of some disintegrant particles is also dependent on the pH of the medium.^{5,10} Shangraw et al observed that the sedimentation volumes of anionic cross-linked starches and celluloses were significantly reduced in acidic medium, whereas Polyplasdone XL and Starch 1500 remained unchanged.

Most immediate release tablets are intended to disintegrate in the stomach, where the pH is acidic. The purpose of this article is to study the influence of the altered swelling capacity of superdisintegrants in different pH media on their water uptake capacity and their efficiency in promoting disintegration and dissolution of active ingredients from directly compressed tablets. Hydrochlorothiazide (HCTZ) was chosen as the model drug. Its low solubility makes its dissolution more likely controlled by disintegration. HCTZ (50 mg) was incorporated in each tablet with either lactose or dicalcium phosphate as the filler, which represented the "soluble" and "insoluble" tablet matrices, respectively. Tablets were evaluated for weight variation, breaking force, disintegration time, and dissolution rate.

MATERIALS AND METHODS

Materials

The materials used in this study were unmilled dibasic calcium phosphate dihydrate, USP/FCC (Emcompress; JRS Pharma LP, Patterson, NY), lactose monohydrate (spray-dried NF, Fast Flo; Foremost Farms, Baraboo, WI), hydrochlorothiazide USP (Ciba Specialty Chemicals Inc, Basel, Switzerland), croscarmellose sodium (Ac-Di-Sol; FMC BioPolymer, Philadelphia, PA), sodium starch glycolate (Primojel; DMV International, Veghel, The Netherlands), Crospovidone NF (Polyplasdone XL10; ISP Technologies Inc, Ashland, KY), and magnesium stearate (Mallinckrodt Inc, Hazelwood, MO).

Methods

Particle Size Analysis

The Malvern Mastersizer S (S/N 32913-99; Malvern Instruments, Bethlehem, PA), using a laser diffraction technique, was used to test the particle size distribution of superdisintegrants. The particle size distribution of dry powders was analyzed by feeding the disintegrant powders directly into

the system through a dry powder feeder (Malvern Instruments). An external vacuum was connected to the other side to disperse and, at the same time, remove the particles from the system. To test the swelling of superdisintegrants in water or 0.1 N hydrochloric acid solution (HCl), disintegrant powders were first dispersed in a small volume of liquid and then ultrasonicated for 10 minutes. The suspension was transferred with a pipette to a small volume sample dispersion unit (Malvern Instruments), which was connected to a circulating cell, to achieve an optimal obscuration of 10% to 30%. The stirrer speed was set at 2000 rpm. The volume median diameter was recorded as the average of 3 to 9 measurements. The ratio of particle diameters in the dispersing medium to the dry powders was used as an indicator of the intrinsic swelling capacity of superdisintegrants in the test medium.

Liquid Uptake Study

The liquid uptake characteristic of the loose disintegrant powders allows an evaluation of both the intrinsic swelling and the wettability of the studied superdisintegrants. A modified gravimetric liquid uptake apparatus^{9,11} was developed in our laboratory to facilitate the measuring of liquid uptake by the disintegrant powders or tablet. Liquid uptake was performed with both water and 0.1 N HCl at room temperature.

The apparatus consists of a Buchner funnel with a fritted disk to hold the sample and a liquid holding vessel resting on an electronic balance. The 2 parts were adjusted at the same horizontal level and connected by a plastic tube so that the water can flow freely from 1 side to the other. During the measurement, either 200 mg of disintegrant powder or a tablet was placed on a piece of filter paper inside the sample holder. The water or 0.1 N HCl was then passively drawn into the sample from the feeder. The loss of weight from the liquid holder was read from the electronic balance. The reading was automatically transferred to a personal computer and collected by a program written in C++ language. Data were collected every second until saturation was reached. Experiments were performed in triple for both the neat disintegrant powders and the tablets, and the average was reported.

Blending and Tableting

The formulations of HCTZ (mesh -60) tablets are given in Table 1. The weight of the dicalcium phosphate tablets was selected to achieve the same true volume as lactose based on its true density. Superdisintegrant (2% wt/wt) was used in the lactose tablets, which corresponded to a 1.4% wt/wt of superdisintegrant in the dicalcium phosphate tablets. Drug and excipients without lubricant were first

Table 1. Direct Compression Formulations

Ingredients	Quantity (mg/tablet)	
	Lactose	Dicalcium Phosphate
Hydrochlorothiazide (active)	50.00	50.00
Spray-dried lactose or	388.75	
Dicalcium phosphate (filler)		586.75
Super disintegrant	9.00	9.00
Magnesium stearate (lubricant)	2.25	2.25
Total tablet weight	450	648

mixed for 15 minutes in a twin shell blender (Patterson Kelly Twin Shell V-Blender, model LB-331; The Patterson-Kelly Co Inc, E Stoudsburg, PA). After the addition of magnesium stearate (mesh -45), the mixing procedure continued for 5 minutes.

Flat-faced tablets of diameter of 11.1 mm were prepared on an instrumented rotary tablet press (Stokes B2; Stokes Engineering, Pittsburgh, PA). The press was set to achieve the same tablet thickness for both formulations in an attempt to create tablets having the same total porosity. However, the actual thicknesses of the resulting tablets were 3.52 mm for lactose tablets and 3.62 mm for dicalcium phosphate tablets due to the different deformation recovery tendency of the 2 materials in postcompression (Table 2). The compression force was 3 KN for lactose tablets and 4 KN for dicalcium phosphate tablets. Tablets were sealed in a scintillation vial and kept in a desiccator for at least 24 hours before testing. Tablet weight, thickness, and breaking force were similar for both formulations.

Disintegration and Dissolution Study

Disintegration times were measured in 900 mL of Millipore water or 0.1 N HCl at $37 \pm 1^\circ\text{C}$ using the USP

24 method without a disk. Disintegration time was the time taken by each of the 6 tablets to pass completely through the 10-mesh screen. The data were the average of the disintegration times of 6 individual tablets.

Dissolution profiles of the HCTZ tablets were determined using the paddle method of the USP 24 (VanKel VK7000; VanKel Industries Inc, Edison, NJ), set with a paddle speed of 50 rpm. Dissolution was also tested in 2 media, 900 mL of Millipore water and 0.1 N HCl at $37 \pm 1^\circ\text{C}$. A peristaltic pump (Rainin Instrument LLC, Woburn, MA) was coupled to a Shimadzu UV-160U ultraviolet/visible spectrophotometer (Shimadzu Corp, Tokyo, Japan) to provide a continuous flow of drug solution through the 1-mm cuvettes. The absorbance of drug solution at 225 nm was analyzed every 30 seconds for 45 minutes. The data given were the mean of 6 determinations.

RESULTS AND DISCUSSION

Powder Characterization

The volume median diameters of superdisintegrants in different media determined using the Malvern Mastersizer are given in Figure 1. According to the volume median diameters, Primojel swells only to 20% as much in 0.1 N HCl as in water. A significant reduction in swelling capacity is also observed for Ac-Di-Sol in 0.1 N HCl, which swells to half that in water. The strong decrease in swelling capacity of chemically modified starches and celluloses may attribute to the converting of the carboxymethyl sodium moieties to its free acid form in acidic medium for both substances. Since the acid form has less hydration capacity than its salt form, the liquid holding capacity of the disintegrant particles reduces after deionization in the acidic medium. Therefore, the total degree of substitution and the ratio of basic to acidic substituents are potential factors determining the extent of influence of medium pH on the water uptake and swelling properties of disintegrant

Table 2. Properties of Lactose and Dicalcium Phosphate Tablets (Mean \pm 1.96 SE, $n = 6$)

Super Disintegrant	Thickness (mm)	Weight (mg)	Hardness (kg)	Disintegration Time*		Time to Q_{50} (min)	
				Water	0.1 N HCl	Water	0.1 N HCl
<i>Lactose Tablets</i>							
Ac-Di-Sol	3.51 ± 0.01	449 ± 4	18.7 ± 1.5	4.5 ± 0.2	5.2 ± 0.2	4	5
Primojel	3.52 ± 0.03	450 ± 3	17.6 ± 1.6	5.7 ± 0.3	8.9 ± 0.6	4	8
Polyplasdone XL10	3.52 ± 0.02	445 ± 3	19.4 ± 1.0	4.9 ± 0.5	4.5 ± 0.3	5	6
<i>Dicalcium Phosphate Tablets</i>							
Ac-Di-Sol	3.61 ± 0.02	645 ± 5	10.5 ± 0.4	5 ± 0	5 ± 0	19	10
Primojel	3.62 ± 0.02	654 ± 5	11.1 ± 0.7	12 ± 0	14 ± 1	18	16
Polyplasdone XL10	3.63 ± 0.01	649 ± 3	11.0 ± 0.6	6 ± 0	7 ± 0	21	10

*The disintegration time is measured in minutes for lactose tablets and seconds for dicalcium phosphate tablets.

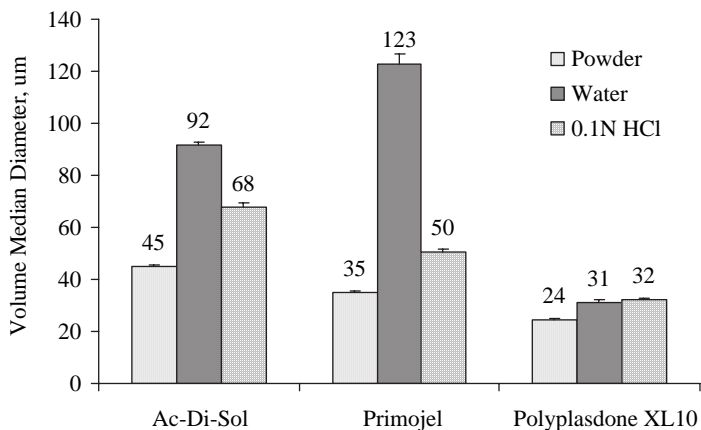


Figure 1. Volume median diameter of superdisintegrants in different media (mean \pm 1.96 SE, $n = 3$ for air; $n = 9$ for water and 0.1 N HCl).

particles. Unlike the other 2 superdisintegrants, there is no apparent change in the swelling capability of the nonionic polymer Polyplasdne XL10 in both media. The percentage of increase in diameter for Ac-Di-Sol, Primojel, and Polyplasdne XL10 is 104%, 251%, and 29% in water and 51%, 43%, and 33% in 0.1 N HCl, respectively. Therefore, the large difference in swelling capacity between superdisintegrants in water is less significant in acidic medium.

The liquid uptake study of superdisintegrant powders describes the dynamic process of particle swelling upon wetting. The liquid uptake of the 3 superdisintegrants

powder in both media is given in Figure 2. Similar to the particle size analysis, major difference in liquid uptake between 2 pH media is observed for Primojel and Ac-Di-Sol but absent for Polyplasdne XL10. The dramatic decrease in both the rate and the extent of liquid uptake of Primojel demonstrates its reduced hydration capacity and wettability in acidic medium. This result is consistent with the particle size distribution analysis (Figure 1). Nevertheless, the reduced swelling of Ac-Di-Sol in acidic medium results in only a minor change to the liquid uptake rate. This is probably due to the unique fiber-shaped characteristic of Ac-Di-Sol because individual fibers can act as hydrophilic channels to absorb water deeply into the system¹² and transfer water immediately to its adjacent particles. The generally spherical-shaped Primojel particles more likely absorb water and retain it rather than transfer it to the next particle. In other words, the water-transferring rate between Primojel particles is slower than the swelling rate of individual particles. In addition, Primojel swells in 3 dimensions, whereas Ac-Di-Sol swells preferentially in 2 dimensions only. Assuming the degree of swelling in diameter were reduced to the same extent for both materials in acidic medium, the decrease in volume would be more profound for the former (cubic to diameter) compared with that of the latter (quadratic to diameter). This also partially explains the marked decrease in total water uptake volume by Primojel from acidic medium. Polyplasdne XL10 behaves the same in both media during liquid uptake, which is consistent with the particle size distribution analysis.

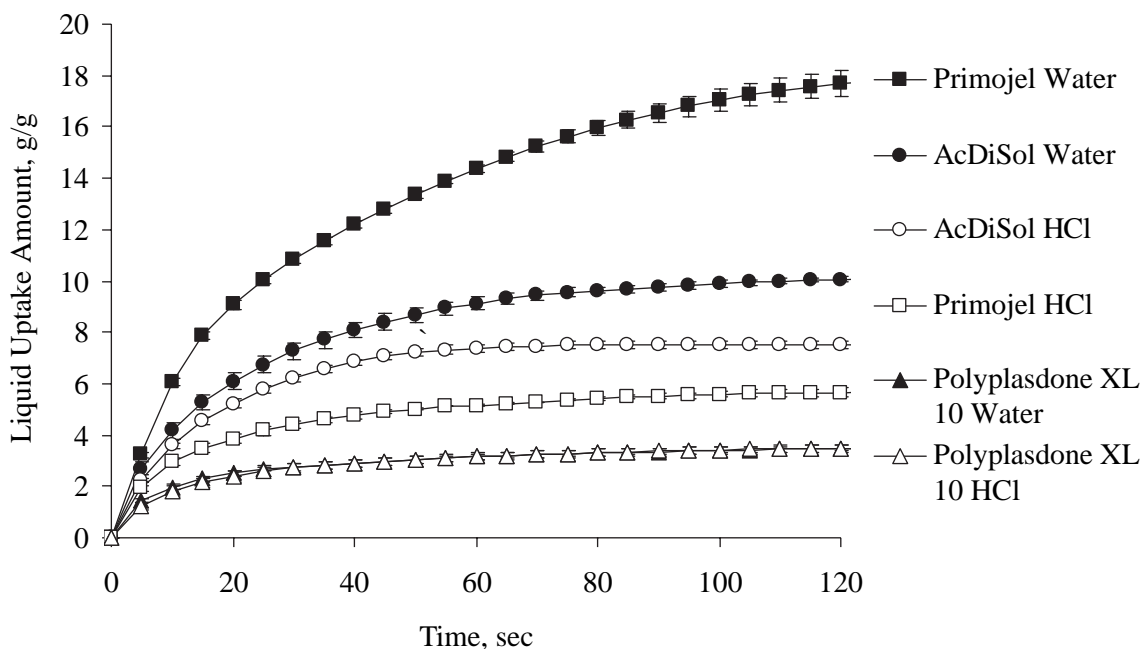


Figure 2. Liquid uptake by superdisintegrants powder from water (solid symbols) and 0.1 N HCl (open symbols) with respect to time (mean \pm 1.96 SE, $n = 3$). Partial data were presented for clarification.

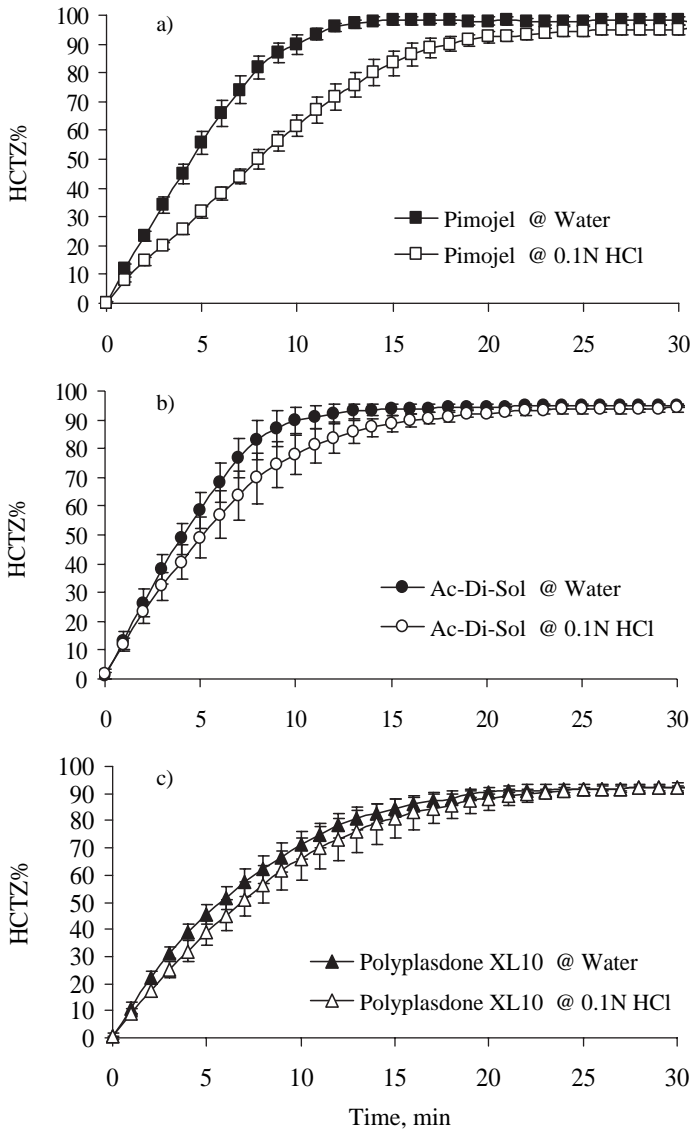


Figure 3. Dissolution of HCTZ from lactose tablets in water (solid symbols) and 0.1 N HCl (open symbols) with respect to time (mean \pm 1.96 SE, $n = 6$). Partial data were presented for clarification.

Tablet Characterization

Lactose Tablets

The physical properties, disintegration times, and the time to reach 50% dissolution (Q_{50}) are presented in Table 2. Tablet thickness, weight, and breaking force are found uniform.

As expected, the reduced swelling capacity and liquid uptake rate of Primojel slow down the disintegration of lactose tablets in acidic medium compared with in water. Tablet disintegration times increase from 6 minutes to 9 minutes. The disintegration times also slightly but significantly increase for Ac-Di-Sol tablets. No significant difference is observed for Polyplasdone XL10 tablets. In Figure 3, it is apparent that HCTZ dissolves rapidly from

all formulations. More than 90% of drug dissolved within 20 minutes, and the time to reach Q_{50} was less than 8 minutes. The dissolution rate of the HCTZ is affected by the efficiency in tablet disintegration. Significant differences are seen in the dissolution rate of HCTZ from the Primojel tablets until 96% of drug is dissolved. The slight increase in disintegration time of Ac-Di-Sol tablets in acidic medium also results in a slightly slower dissolution. But no significant difference is observed until 7 minutes, when more than 65% of drug is dissolved. Again, the dissolution rate of HCTZ from Polyplasdone XL10 tablets remains the same in both media.

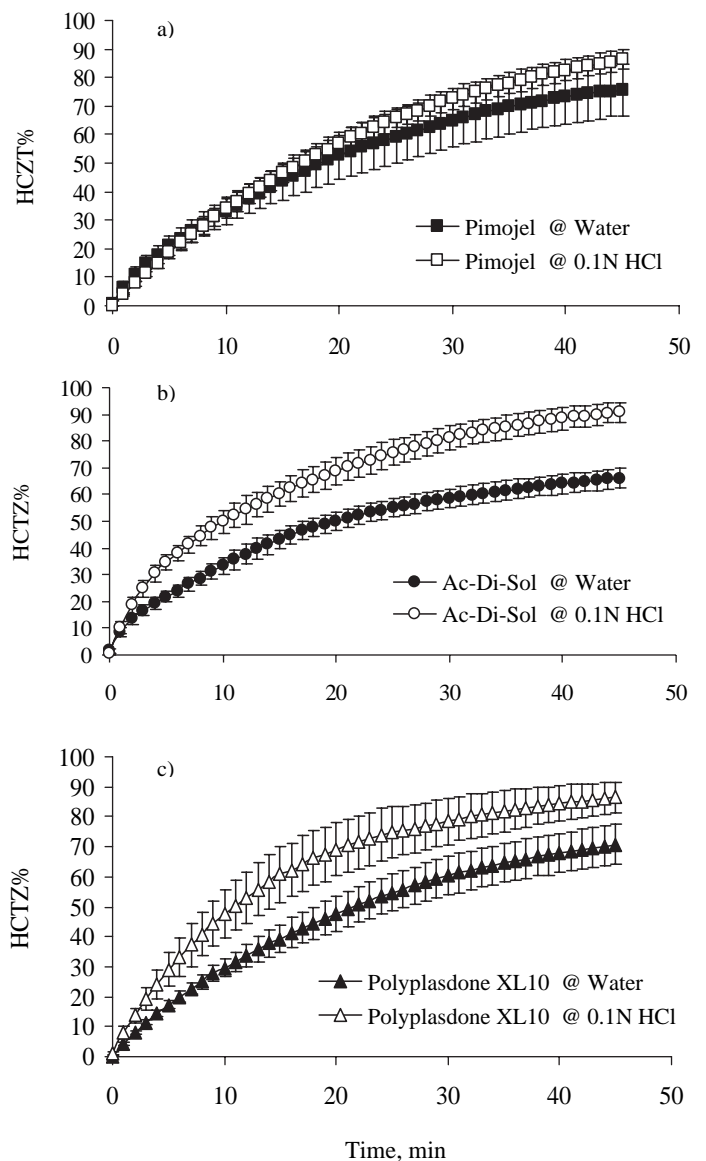


Figure 4. Dissolution of HCTZ from dicalcium phosphate tablets in water (closed symbols) and 0.1 N HCl (open symbols) (mean \pm 1.96 SE, $n = 6$). Partial data were presented for clarification.

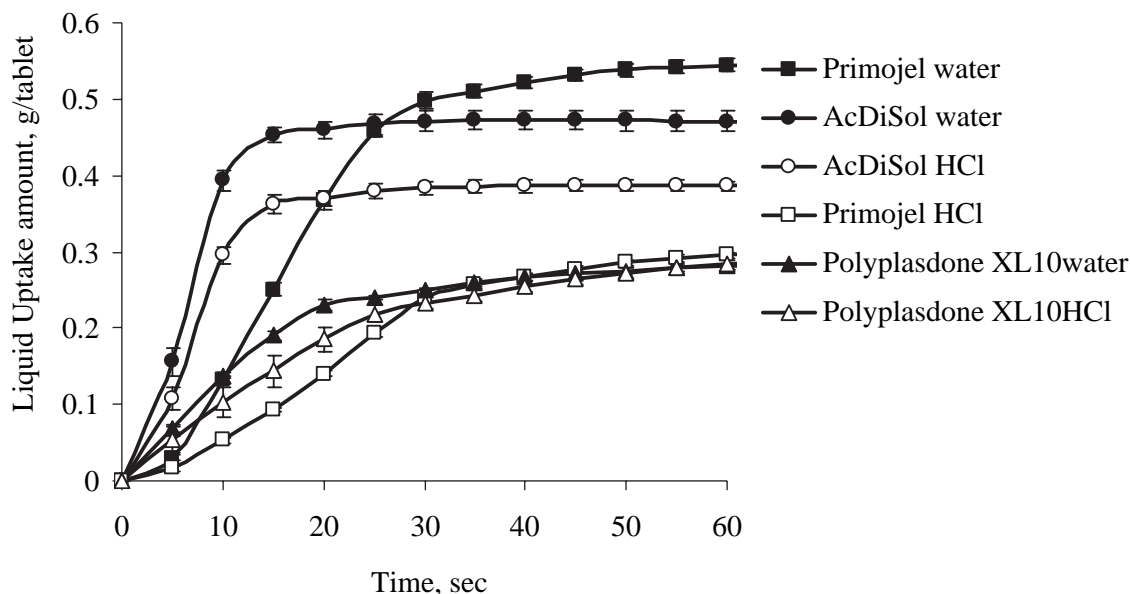


Figure 5. Liquid uptake by dicalcium phosphate tablets from water (closed symbols) and 0.1 N HCl (open symbols) (mean \pm 1.96 SE, $n = 3$). Partial data were presented for clarification.

Dicalcium Phosphate Tablets

The physical properties, disintegration times, and the time to reach Q_{50} are reported in Table 2. Tablet dimensions, weight, and breaking force have no significant difference between tablets with different disintegrants.

Unlike the lactose tablets, all dicalcium phosphate tablets disintegrated within 15 seconds regardless of the test medium and/or superdisintegrants used. This result is consistent with the findings of other investigators, who confirmed that the dicalcium phosphate tablets usually disintegrated within a minute even when superdisintegrants were used at very low concentration.^{8,13}

The dissolution profile of HCTZ is presented in Figure 4. None of the formulations dissolves completely after 45 minutes. The dissolution of HCTZ from dicalcium phosphate tablets is significantly slower than the corresponding lactose tablets despite their fast disintegration. The dissolution rate of HCTZ is apparently filler-solubility controlled. Because dicalcium phosphate has a higher solu-

bility in acidic medium, the drug dissolution rate from Ac-Di-Sol and Polyplasdone XL10 tablets significantly increases in 0.1 N HCl (Figure 4, b and c), and the time to reach Q_{50} is shortened by half (Table 2) compared with water. However, the enhancing effect is absent from Primojel tablets, which is probably compromised by its reduced disintegration efficiency in acidic medium. The dissolution of HCTZ from this formulation is comparable in both media.

A liquid uptake study was also performed on the dicalcium phosphate tablets in a manner similar to that used to test the liquid uptake of the neat disintegrant powders. Because pure dicalcium phosphate tablets without disintegrants have no apparent liquid uptake, the liquid uptake from the tablets, displayed in Figure 5, is mainly due to the presence of superdisintegrants. The influence of test medium on the rate and extent of liquid uptake for all formulations is similar to those on the neat disintegrants powder, which indicates that disintegrants retain their functionality after incorporation inside a tablet formulation. Assuming that a

Table 3. Liquid Uptake Characteristics of Dicalcium Phosphate Tablets (mean \pm 1.96 SE, $n = 3$)

Amount of Liquid in mg Taken by	Ac-Di-Sol		Primojel		Polyplasdone XL10	
	Water	0.1 N HCl	Water	0.1 N HCl	Water	0.1 N HCl
Each tablet	472.7 (12.9)	386.6 (7.3)	549.8 (9.0)	321.4 (5.2)	299.5 (3.9)	316.0 (5.4)
1 mg SD	10.3 (0.1)	7.5 (0.1)	18.2 (0.6)	5.7 (0.2)	3.8 (0.0)	3.7 (0.1)
9 mg SD/tablet	92.7	67.5	163.8	51.3	34.2	33.3
Amount of liquid in newly opened pores	380.0	319.1	386.0	270.1	265.3	282.7

full extent of swelling is achieved for the incorporated disintegrants, the apparent amount of liquid residing inside the disintegrants can be estimated because there is approximately 9 mg of disintegrants in each tablet. The volume of the total pores, both the original and newly opened, after liquid uptake can be calculated by subtracting the amount of liquid that resided inside the disintegrants from the total amount of liquid absorbed into the tablet. These data are summarized in Table 3. Primojel and Ac-Di-Sol open similar volumes of pores inside the tablets (380 vs 386 g/tablet) during water uptake, although the former is capable of swelling more extensively than the latter in water (Figure 1). These values are reduced for both disintegrants in 0.1 N HCl, with Ac-Di-Sol reducing to 319 g/tablet and Primojel to 270 g/tablet. The volume of pores opened by Primojel in 0.1 N HCl is barely comparable with that achieved by Polyplasdone XL10, which appears to have a limited swelling capacity. This result is consistent to the particle size analysis (Figure 1) in which the intrinsic swelling capability is found rather similar in acidic medium.

No test was performed on lactose tablets due to the simultaneous dissolution of lactose during liquid uptake. It is reasonable to assume the same functionality of disintegrants in lactose tablets as in dicalcium phosphate tablets, except that this is overshadowed by matrix dissolution effects. Indeed, the order of the capability of superdisintegrants generating fresh pores inside the tablet matrices agrees with the order of the dissolution rate of HCTZ from lactose tablets in which disintegrant is the only variable.

CONCLUSION

In conclusion, a laser diffraction particle size analyzer proved to be an effective tool for determining the intrinsic swelling of disintegrant particles in different media. The results correlated with liquid uptake and swelling measurements made on neat disintegrant powders. An acidic medium significantly reduces the liquid uptake rate and capacity of sodium starch glycolate (Primojel) and croscarmellose sodium (Ac-Di-Sol) but not crospovidone NF (Polyplasdone XL10). In general, tablet disintegration time and the dissolution rate of HCTZ from tablets paralleled this observation, although tablets containing croscarmellose sodium were affected less by acidic medium than those formulated with sodium starch glycolate. Additional insight into the effect of pH was obtained from estimates of the volume of the total pores in tablets, both original and

newly opened after liquid uptake. Disintegrant efficiency must be considered together with matrix solubility effects.

ACKNOWLEDGMENTS

Generous financial support from FMC BioPolymer Inc. (Philadelphia, PA) and United States Pharmacopeia (Rockville, MD) is gratefully acknowledged.

REFERENCES

1. Augsburger LL, Brzecko AW, Shah U, Hahm HA. Characterization and functionality of super disintegrants In: Swarbrick J, Boylan JC, eds. *Encyclopedia of Pharmaceutical Technology*. New York, NY: Marcel Dekker Inc; 2000:269-291.
2. Tagawa M, Chen R, Chen P, et al. Effect of various disintegrants on drug release behavior from tablets. *J Pharm Sci Technol Japan*. 2003;63:238-248.
3. Hahm HA. *Effect of Sorbed Water on the Efficiency of Super Disintegrants: Physical and Mechanistic Considerations*. Baltimore, MD: University of Maryland Press; 2000:6.
4. Bolhuis GK, Smallenbrock AJ, Lerk CF. Interaction of tablet disintegrants and magnesium stearate during mixing. Part 1. Effect on tablet disintegration. *J Pharm Sci*. 1981;70:1328-1330.
5. Shangraw RF, Mitrevej A, Shah M. A new era of tablet disintegrants. *Pharm Technol*. 1980;4:49-57.
6. Mitrevej A, Hollenbeck RG. Photomicrographic analysis of water vapor sorption and swelling of selected super disintegrants. *Pharm Technol*. 1982;6:48-50, 53-54.
7. Caramella C, Colombo P, Conte U, Manna AL. Swelling of disintegrant particles and disintegrating force of tablets. *Labo-Pharma Probl Tech*. 1984;339:115-119. C.A. 101, 60050e.
8. Gissinger D, Stamm A. Comparative evaluation of the properties of some tablet disintegrants. *Drug Dev Ind Pharm*. 1980;6:511-536.
9. Shah U, Augsburger L. Evaluation of the functional equivalence of crospovidone NF from different sources. Part 2. Standard performance test. *Pharm Dev Technol*. 2001;6:419-430.
10. Chen CR, Lin YH, Cho SL, Yen SY, Wu HL. Investigation of the dissolution difference between acidic and neutral media of acetaminophen tablets containing a super disintegrant and a soluble excipient. *Chem Pharm Bull*. 1997;45:509-512.
11. van Kamp HV, Bolhuis GK, de Boer AH, Lerk CF, Lie-A-Huen L. The role of water uptake on tablet disintegration. Design of an improved method for penetration measurements. *Pharm Acta Helv*. 1986;61:22-29.
12. Shangraw RF, Wallace JW, Bowers FM. Morphology and functionality in tablet excipients for direct compression. Part 2. *Pharm Technol*. 1981;5:44, 46, 48, 50, 52, 54, 56, 58, 60.
13. Gissinger D, Stamm A. A comparative study of crosslinked carboxymethylcellulose as a tablet disintegrant. *Pharm Ind*. 1980;42:189-192.