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Effect of Superdisintegrants on Dissolution of Cationic Drugs

J. Balasubramaniam[1,4], K. Bindu[1], V. U. Rao[1], D. Ray[2], R. Haldar[2], and A. W. Brzeczko[3]

e-mail: jbalasubramaniam@ispcorp.com

[1] *International Specialty Products (India) Pvt. Ltd., H. No 6-3-1090/A, Bhupal Towers, Rajbhavan Road, Somajiguda, Hyderabad – 500 082, INDIA*

[2] *International Specialty Products, 1361 Alps Road, Wayne, NJ 07470*

[3] *ISP Pharma Systems LLC, 9176 Red Branch Road, Columbia, MD 21045*

ABSTRACT

The effects of selected superdisintegrants on the dissolution behavior of several cationic drugs with varying water solubility were evaluated. All formulations were made with fixed disintegrant concentration and equal drug load using a model formulation. Tablets were made by direct compression and were compressed to equal hardness. Dissolution studies were carried out in dissolution media specified in the compendium (*USP*) or in media recommended by the U.S. Food and Drug Administration (FDA) for the respective actives. The effect of media pH on the dissolution of drugs was also evaluated.

The use of crospovidone significantly improved the dissolution of the cationic drugs in the model formulation when compared with the other superdisintegrants studied. The compendial or the FDA recommended media, in most cases, was able to discriminate among the tablets containing different superdisintegrants.

Crospovidone can be effectively used as a tablet disintegrant to improve the dissolution of either soluble or poorly soluble cationic drugs.

INTRODUCTION

In spite of the increased focus and interest generated in the area of controlled release and targeted drug delivery system in recent years, tablet dosage forms that are intended to be swallowed whole, disintegrate, and release their medicaments rapidly in the gastrointestinal tract still remain the formulation of choice from both a manufacturing as well as a patient acceptability point of view. Thus, a drug given in the form of a tablet must undergo dissolution before being absorbed and eventually transported into systemic circulation. For most of the tablet dosage forms, disintegration precedes drug dissolution. Superdisintegrants (*1*) such as croscarmellose sodium, sodium starch glycolate (SSG), and crospovidone are now frequently used in tablet formulations to improve the rate and extent of tablet disintegration and thus improve the rate of drug dissolution.

The behavior of superdisintegrants in various tablet formulations has been investigated by many researchers (*2–6*). The majority of this research has been directed at the function-related properties of the superdisintegrants with special emphasis on correlating these properties to disintegrant efficiency and drug release.

The research focus in recent years has shifted to the formulation of both fast dissolving or disintegrating tablets that are swallowed and tablets that are intended to dissolve in the oral cavity (*7–9*). However, some research has also focused on using substantially higher amounts of superdisintegrants with the aim of either improving the dissolution or stabilizing the formulations (*10*, *11*).

The choice of superdisintegrant for a tablet formulation depends largely on the nature of the drug being used. For example, the solubility of the drug component could affect the rate and mechanism of tablet disintegration. Water-soluble materials tend to dissolve rather than disintegrate, while insoluble materials generally tend to disintegrate if an appropriate amount of disintegrant is included in the formulation (*6*).

Furthermore, the ionic nature of the drug and superdisintegrants and their potential interactions have been reported to affect the dissolution of tablet formulations (*12–14*). Of the commonly used superdisintegrants, crospovidone is nonionic, while SSG and croscarmellose sodium are anionic. It has been proposed that any weakly basic (cationic) drug, when present in an environment where the pH is >2 and near or below the pK_a of the cationic drug, should be expected to interact with ionized polymers like croscarmellose sodium and SSG (*13*). Further, in an in vitro dissolution test conducted by using a fixed amount of distilled water, the drug-excipient interaction could result in a decreased or apparent incomplete drug release from the dosage form. In an earlier study (*14*), it was reported that dissolution of phenylpropanolamine HCl from tablets containing croscarmellose sodium showed only 60% of apparent amount of drug released, while the release from the corresponding control tablet (without any disintegrant) and a tablet with pregelatinized starch as the disintegrant showed almost complete release. However, this interaction did not adversely influence the bioavailability of phenylpropanolamine in human subjects.

In these earlier studies demonstrating drug–excipient interactions in dissolution media, many of the cationic

[4]*Corresponding author.*

drugs were of moderate to high aqueous solubility. However, many new or recently discovered cationic drugs are poorly water soluble. Thus in the present study, an attempt has been made to investigate the effect of various tablet superdisintegrants on the dissolution behavior of some model cationic drugs having varying degrees of aqueous solubility. For convenience, the drugs used were classified broadly as soluble drugs (cetirizine HCl, ranitidine HCl, venlafaxine HCl, and chlorpromazine HCl) and poorly soluble drugs (ciprofloxacin HCl, fexofenadine HCl, terbinafine HCl, and clopidogrel bisulfate).

MATERIALS AND METHODS

Cetirizine HCl (Glochem Industries Ltd., Hyderabad, India), fexofenadine HCl and terbinafine (Aurobindo Pharma Ltd., Hyderabad, India), ciprofloxacin HCl (Dr. Reddy's Laboratories, Hyderabad, India), ranitidine HCl (Orchev Pharma Pvt. Ltd., Rajkot, India), chlorpromazine HCl and clopidogrel bisulfate (Emco Industries, Hyderabad), and venlafaxine HCl (Amoli Organics Pvt. Ltd., Vapi, India) were purchased from the sources indicated. Croscarmellose sodium (Ac-di-sol®, FMC Biopolymer) and SSG (GLYCOLYS®, Roquette) were purchased from Signet (India). Polyplasdone® XL crospovidone was provided by International Specialty Products (ISP). All other reagents were of analytical grade.

Preparation of Tablets

The general formula of the tablets is given in Table 1. The required quantities of the ingredients were weighed and blended to form a homogenous powder mix. The blends were then compressed on 12.5-mm flat-faced, beveled-edged punch set on a Rotary Compression machine (Cadmach, 16-station, Ahmedabad, India) at 550 mg theoretical weight and at approximately equal hardness. AIM software (MCC, NJ) was used to determine the compression force required to yield tablets of approximately equal hardness for the various drugs used in the study.

Breaking Force Determination

The breaking force of the prepared tablets was determined 24 h after compression using Erweka hardness tester (Erweka TBH 310 MD), which also measures the diameter of the tablets. Ten tablets from each batch were tested for tablet strength, and the mean and standard deviation were calculated.

Table 1. General Formula of the Prepared Tablets.

Ingredient	Weight % per tablet	mg per tablet
Active drug	18	100
Superdisintegrant	2	10
Magnesium stearate	0.5	2.5
Talc	0.5	2.5
Avicel pH 102	q.s. 100	435

Disintegration Time

Disintegration times of the prepared tablets were measured in 900 mL of purified water with disc at 37 °C using Erweka TAR series tester. Disintegration times of six individual tablets were recorded.

In Vitro Dissolution Studies

The dissolution studies of the prepared tablets were carried out using USP Apparatus 2 (Vankel VK). A peristaltic pump was coupled to a Cary 50 UV–vis spectrophotometer to provide a continuous flow of drug solution through 1-cm cuvettes. Dissolution was performed in 0.1 N HCl (pH 1.2), pH 4.5 acetate buffer, and pH 7.2 phosphate buffer (900 mL each) at 37 ± 0.5 °C at the paddle speed recommended for each drug in the compendium. In addition, the profiling was performed using the compendial or FDA recommended medium of the respective drugs if it was different from the ones already used. Furthermore, if the pH of the compendial or recommended medium was within ±1.5 pH units of the above-mentioned three media, then dissolution was only carried out in the compendial or FDA recommended medium for that particular pH range. Samples were programmed to be analyzed at 5, 10, 15, 30, 45, and 60 min at the λ_{max} of the respective drugs. The time required for 80% of drug to be released (t_{80}) was considered for comparing the dissolution results. The t_{80} was determined by fitting the dissolution data to a four-parametric logistic model using the Marquardt–Levenberg algorithm (Sigmaplot 9.0 SPSS Inc., Chicago, IL).

$$y = min + \frac{max - min}{1 + 10^{[logEC_{50} - x] \times hillslope}}$$

In this equation, y represents the Cumulative % drug released, x is the time in minutes, *min* is the baseline of % drug released at 0 min, *max* is the plateau of % drug released at 60 min, and *hillslope* is the slope of the curve at transition center EC_{50}.

RESULTS AND DISCUSSION

The objective of the present study was to investigate the effect of nonionic and anionic superdisintegrants on the dissolution behavior of cationic drugs with varying aqueous solubilities. The chemical structures of the superdisintegrants and the different drugs used in the present study are shown in Figures 1–3. Accordingly, crospovidone, specifically Polyplasdone XL, was compared with croscarmellose sodium and SSG.

The breaking force and the disintegration times of the prepared tablets are shown in Table 2. Relatively equal tablet hardness values are shown for all tablets of the model drug with the various superdisintegrants; thus

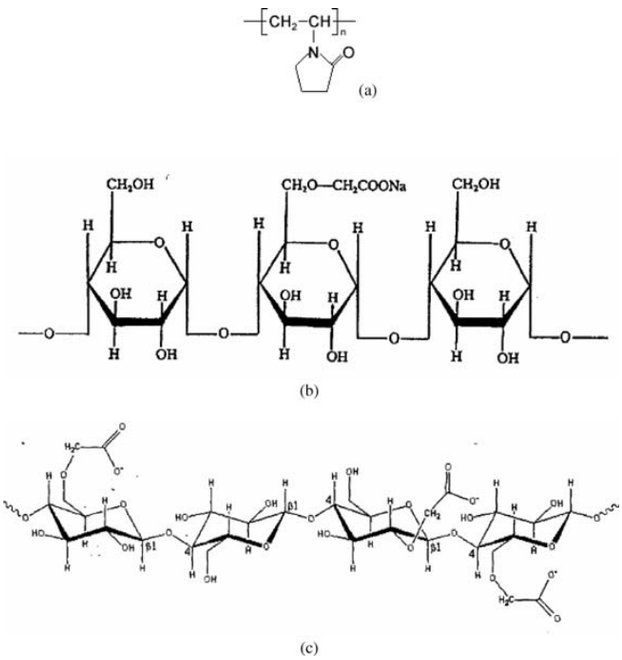

Figure 1. Chemical structures of disintegrants used in the study: (a) Polyplasdone XL crospovidone; (b) sodium starch glycolate; and (c) croscarmellose sodium.

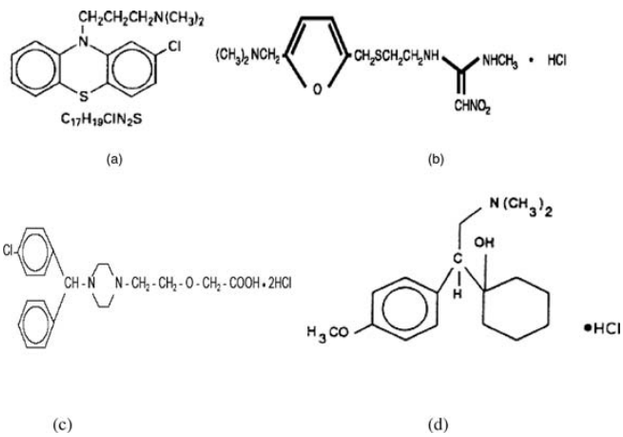

Figure 2. Chemical structures of water-soluble cationic drugs used in the study: (a) chlorpromazine, (b) ranitidine HCl, (c) cetirizine HCl, (d) venlafaxine HCl.

disintegration time variability due to tablet hardness effects was minimal. No differences were observed in the disintegration times of the tablets prepared using the various superdisintegrants for the drugs studied. Based on equal disintegration times, model drug release from the respective tablets should relate solely to the drug dissolution rate and not the rate of tablet disintegration. Notably, the disintegration times of the soluble cationic drugs were higher than those of the poorly soluble cationic drugs, except for cetirizine HCl.

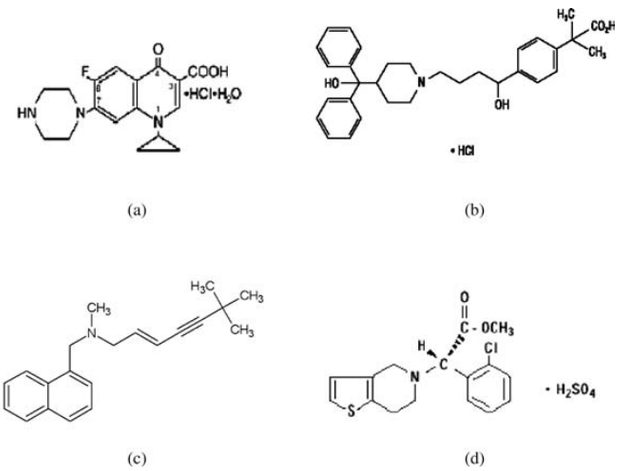

Figure 3. Chemical structures of poorly soluble cationic drugs used in the study: (a) ciprofloxacin HCl, (b) fexofenadine HCl, (c) terbinafine, (d) clopidogrel bisulfate.

Table 2. Hardness and Disintegration Time (DT) for the Prepared Tablets.

Drug	Superdisintegrant	Hardness (N)	DT (min)
Ciprofloxacin	Croscarmellose sodium	182 ± 4	4.5 ± 0.3
	SSG	187 ± 6	3.5 ± 0.3
	Polyplasdone XL	190 ± 4	4.0 ± 0.4
Fexofenadine	Croscarmellose sodium	180 ± 5	4.5 ± 0.3
	SSG	176 ± 6	3.5 ± 0.3
	Polyplasdone XL	181 ± 6	4.0 ± 0.3
Terbinafine	Croscarmellose sodium	158 ± 5	3.5 ± 0.4
	SSG	149 ± 5	4.0 ± 0.4
	Polyplasdone XL	163 ± 5	4.5 ± 0.4
Clopidogrel bisulfate	Croscarmellose sodium	156 ± 6	4.0 ± 0.6
	SSG	160 ± 5	4.5 ± 0.5
	Polyplasdone XL	161 ± 5	3.5 ± 0.5
Chlorpromazine	Croscarmellose sodium	158 ± 5	9.0 ± 0.5
	SSG	149 ± 6	9.5 ± 0.5
	Polyplasdone XL	163 ± 6	10.0 ± 0.4
Ranitidine	Croscarmellose sodium	183 ± 5	10.0 ± 0.5
	SSG	178 ± 5	11.0 ± 0.6
	Polyplasdone XL	189 ± 5	10.5 ± 0.5
Cetirizine	Croscarmellose sodium	180 ± 5	4.0 ± 0.5
	SSG	179 ± 6	3.0 ± 0.6
	Polyplasdone XL	182 ± 6	3.5 ± 0.5
Venlafaxine	Croscarmellose sodium	174 ± 6	8.5 ± 0.5
	SSG	181 ± 7	8.0 ± 0.4
	Polyplasdone XL	178 ± 6	8.5 ± 0.4

For the water-soluble cationic drugs studied, the compendial dissolution medium for ranitidine (pK_a of 8.2), cetirizine (pK_a of 8.3), and venlafaxine (pK_a of 9.4) is water, while for chlorpromazine (pK_a of 9.3) it is 0.1 N HCl (pH 1.2). The t_{80} data (Table 3 and Figure 4) show that drug release from tablets of ranitidine, cetirizine, and venlafaxine containing croscarmellose sodium and SSG was slower than from the corresponding tablets containing Polyplasdone XL. This is consistent with a previous study (*14*) wherein the drug–excipient interaction was observed for the cationic drug phenylpropanolamine and the anionic disintegrant croscarmellose in its compendial dissolution media, which is also water. When water is the dissolution medium, raniditine, cetirizine, and venlafaxine demonstrate a greater interaction with the anionic disintegrants, because fewer counterions are present in water. A similar trend was also observed for chlorpromazine; drug release in pH 1.2 (compendial medium) from tablets containing croscarmellose sodium and SSG was slower than from corresponding tablets containing Polyplasdone XL. For these drugs, perhaps a higher affinity for the anionic disintegrants is favored even in the presence of competing ions.

For poorly soluble drugs, t_{80} release (Table 4 and Figure 5) was not achieved for any of the drugs (except ciprofloxacin HCl) with any of the superdisintegrants in any medium other than the compendial or recommended medium. This could be attributed to the lack of aqueous solubility of these drugs, rather than to the nature of the superdisintegrants used. In the case of clopidogrel, tablets containing Polyplasdone XL showed the fastest release in the compendial medium (pH 2.0). However, the release was only marginally faster than that from tablets containing croscarmellose. In comparison, fexofenadine HCl (pK_a of 9.53) tablets with Polyplasdone XL reached 80% release 1.5–2 times faster than tablets containing other disintegrants.

In the case of terbinafine HCl (pK_a of 7.1), only tablets with Polyplasdone XL were able to achieve 80% release in

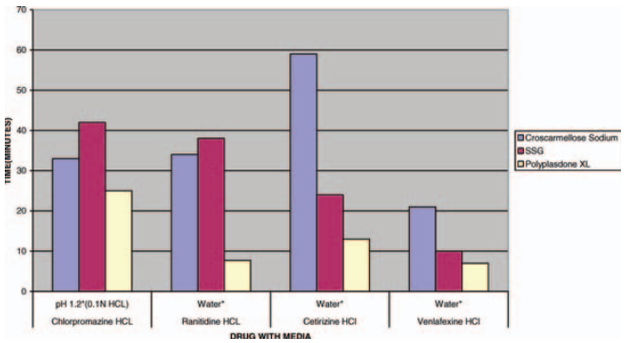

Figure 4. T_{80} of water-soluble cationic drugs in respective compendial media.

Table 3. T_{80} Values of Water-Soluble Cationic Drugs in Different Dissolution Media.

		T_{80} (min)			R^2 values of the fit		
DRUG	**DISSOLUTION MEDIUM**	**Croscarmellose sodium**	**SSG**	**Polyplasdone XL**	**Croscarmellose sodium**	**SSG**	**Polyplasdone XL**
Chlorpromazine HCl	pH 1.2*	32.63 ± 1.4	41.87 ± 2.2	25.04 ± 1.3	0.997	0.995	0.995
	pH 4.5	27.33 ± 1.6	28.72 ± 2.3	25.61 ± 1.6	0.992	0.992	0.997
	pH 7.2	44.75 ± 2.2	54.43 ± 2.1	38.35 ± 1.8	0.991	0.992	0.997
Ranitidine HCl	pH 1.2	1.19 ± 0.5	2.78 ± 0.7	5.41 ± 0.14	0.995	0.994	0.998
	pH 4.5	17.32 ± 2.5	38.79 ± 2.6	1.12 ± 0.1	0.994	0.995	0.997
	pH 7.2	4.53 ± 2.3	6.42 ± 2.8	3.55 ± 0.59	0.993	0.996	0.993
	Water*	33.86 ± 1.2	38.19 ± 2.5	7.67 ± 0.12	0.994	0.994	0.995
Cetirizine HCl	pH 1.2	45.39 ± 2.2	33.94 ± 2.4	12.84 ± 2.2	0.993	0.996	0.995
	pH 4.5	60.65 ± 2.5	43.85 ± 2.5	22.49 ± 2.6	0.991	0.995	0.994
	pH 7.2	52.44 ± 2.3	31.43 ± 1.9	22.54 ± 2.4	0.992	0.995	0.997
	Water*	59.02 ± 2.1	24.31 ± 2.0	12.76 ± 2.5	0.993	0.995	0.996
Venlafaxine HCl	pH 1.2	9.06 ± 0.8	8.83 ± 0.9	7.59 ± 0.56	0.994	0.995	0.995
	pH 4.5	4.89 ± 0.2	2.84 ± 0.4	3.22 ± 0.45	0.996	0.995	0.992
	pH 7.2	11.41 ± 2.3	8.58 ± 0.6	10.64 ± 2.3	0.991	0.995	0.996
	Water*	20.97 ± 2.5	10.37 ± 2.3	6.95 ± 0.25	0.992	0.995	0.994

*Compendial recommended medium

Table 4. T_{80} Values of Poorly Water Soluble Cationic Drugs in Different Dissolution Media.

DRUG	DISSOLUTION MEDIUM	T_{80} (min)			R^2 values of the fit		
		Croscarmellose sodium	SSG	Polyplasdone XL	Croscarmellose sodium	SSG	Polyplasdone XL
Ciprofloxacin HCl	pH 1.2*	32.68 ± 1.2	24.69 ± 2.3	21.18 ± 2.2	0.998	0.993	0.994
	pH 4.5	16.45 ± 1.5	22.35 ± 2.5	15.81 ± 2.4	0.993	0.995	0.995
	pH 7.2	19.31 ± 1.6	12.23 ± 1.5	9.89 ± 1.2	0.995	0.991	0.997
	water	59.06 ± 2.0	60.03 ± 2.2	24.32 ± 1.3	0.994	0.995	0.997
Fexofenadine HCl	pH 1.2 (0.001 N HCl)*	28.64 ± 2.6	23.36 ± 2.6	14.1 ± 1.5	0.996	0.993	0.996
Terbinafine HCl	pH 3	NA	11.18 ± 2.8	0.57 ± 0.02	0.992	0.997	0.998
	pH 3 (500 mL)*	NA	NA	32.47 ± 1.7	0.994	0.991	0.994
Clopidogrel bisulfate	pH 2.0*	9.92 ± 0.25	14.64 ± 2.1	9.77 ± 2.2	0.992	0.993	0.995

*Compendial recommended medium.

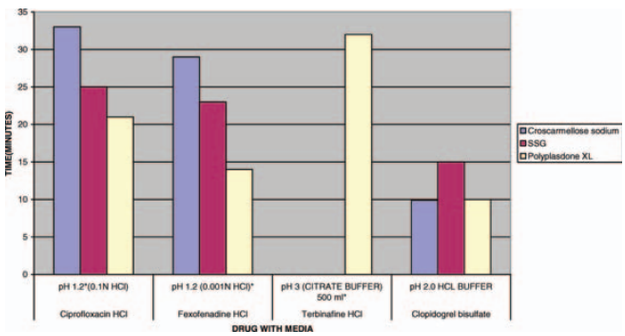

Figure 5. T_{80} of poorly soluble cationic drugs in the respective compendial media.

the compendial medium (pH 3 citrate buffer, 500 mL). When the volume of the dissolution medium was increased to 900 mL, tablets with SSG also managed 80% release. However, tablets with Polyplasdone XL achieved 80% release in less than 1 min. Better sink conditions, owing to the increase in volume of the dissolution media, could be attributed for the faster release. However, the increase in volume did not favor drug release from tablets containing croscarmellose sodium, suggesting that the level of croscarmellose sodium used in the study (2% w/w) may not be adequate to improve the dissolution of terbinafine. Polyplasdone XL gave faster release for ciprofloxacin HCl (pK_a of 8.7) in all the media studied.

The overall results point to the fact that crospovidone is more effective in enhancing the dissolution rate of the drugs studied, irrespective of their aqueous solubilities, and the compendial medium was able to discriminate among the formulations. This trend was even more notable with the poorly soluble drugs. Since it is nonionic, crospovidone does not interact with the cationic drug moiety, unlike the anionic disintegrants croscarmellose sodium and SSG.

CONCLUSION

In this study, a comprehensive evaluation of the dissolution rates of cationic drugs with varying water solubility was performed. The effectiveness of superdisintegrants in model tablet formulations was shown. In general, crospovidone and, more specifically, Polyplasdone XL demonstrated a more rapid dissolution rate for the model cationic drugs, irrespective of their aqueous solubilities. Since Polyplasdone crospovidone is a nonionic disintegrant, no ionic interaction occurs between it and the cationic drugs.

Furthermore, the compendial medium was able to discriminate between the tablets containing different superdisintegrants in most cases studied. In the case of three water-soluble cationic drugs, ranitidine, cetirizine and venlafaxine, where water is the compendial medium, Polyplasdone XL had the fastest t_{80} results. In cases where water provides sink conditions (≤25% maximum drug solubility), water is a preferred compendial medium. However, ionic interaction between cationic drugs and anionic superdisintegrants may delay drug release to such an extent as to fail the Q tolerance of the compendial dissolution method for this product . Although this ionic interaction did not have a biological impact for phenylpropanolamine, this may not be the case for all cationic drugs. In the excipient selection process, formulation screening of superdisintegrants to minimize dissolution retardation from drug-excipient interaction is recommended. In addition, the r^2 values ranged between 0.991 and 0.998 (Tables 3 and 4), suggesting that the four-parameter logistic model provided a reasonably good fit for determining t_{80}.

References

1. Shangraw, R.; Mitrevej, A.; Shah, M. *Pharm. Technol.* **1980**, *4*, 49–57.
2. Gordon, M. S.; Rudraraju, V. S.; Dani, K.; Chowhan, A. T. Effect of mode of superdisintegrant Incorporation on dissolution in wet granulated tablets. *J. Pharm. Sci.* **1993**, *82* (2), 220–226.
3. Zhao, N.; Augsburger, L. L. The influence of swelling capacity of superdisintegrants in different pH media on the dissolution of hydrochlorothiazide from directly compressed tablets. *AAPS PharmSciTech* **2005**, *6* (1), E120–E126.
4. Zhao, N.; Augsburger, L. L. The influence of granulation on superdisintegrant performance. *Pharm. Dev. Technol.* **2006**, *11*, 47–53.
5. Zhao, N.; Augsburger, L. L. Functionality Comparison of 3 Classes of Superdisintegrants in Promoting Aspirin Tablet Disintegration and Dissolution. *AAPS PharmSciTech.* **2005**, *6* (4), E634–E640.
6. Johnson, J. R.; Wang, L. H.; Gordon, M. S.; Chowhan, Z. T. Effect of formulation solubility and hygroscopicity on disintegrating efficiency in tablets prepared by wet granulation. *J. Pharm. Sci.* **1991**, *80*, 469–471.
7. Bi, Y. X.; Sunanda, H.; Yonezawa, Y.; Danjo, K. Evaluation of rapidly disintegrating tablets prepared by a direct compression method. *Drug Dev. Ind. Pharm.* **1999**, *25*, 571–581.
8. 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.* **1999**, *24*, 501–507.
9. Bi, Y.; Sunanda, H.; Yonezawa, Y. Preparation and evaluation of a compressed tablet rapidly disintegrating in the oval cavity. *Chem. Pharm. Bull.* **1996**, *44*, 2121–2127.
10. Dietrich, R.; Ney, H. Oral-administration forms of a medicament containing pantoprazol. U.S. Patent 5,997,903, Dec 7, 1999.
11. Michael, M.; Dorossiev, I. Stable pharmaceutical compositions containing 7-substituted-3,5-dihydroxyheptanoic acids or 7-substituted-3,5-dihydroxyheptenoic acids. U.S. Pat. 6,558,659, May 6, 2003.
12. Chien, Y. W.; Van Nostrand, P.; Hurwitz, A. R.; Shami, E. G. Drug–disintegrant interactions: binding of oxymorphone derivatives. *J. Pharm. Sci.* **1981**, *70*, 709–710.
13. Hollenbeck, R. G.; Mitrevej, K. T.; Fan, A. C. Estimation of the extent of drug–excipient interactions involving croscarmellose sodium. *J. Pharm. Sci.* **1983**, *72*, 325–327.
14. Hollenbeck, R. G. Bioavailability of phenylpropanol-amine HCl from tablet dosage forms containing croscarmellose sodium. *Int. J. Pharm.* **1988**, *47*, 89–93.