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The effect of aging on the dissolution of wet granulated tablets containing super disintegrants

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Summary

The effect of aging at various storage conditions on the dissolution efficiency of tablets containing three 'super disintegrants' (croscarmellose sodium, crospovidone, and sodium starch glycolate) was investigated utilizing wet granulated tablets. The super disintegrants were incorporated via three methods: extragranularly, intragranularly, or distributed equally between the two phases. The solubility of the tablets was varied by using lactose, dibasic calcium phosphate, or naproxen as the main tablet component. The granulation moisture content was varied to investigate its impact on tablet dissolution after aging. The results indicated that aging decreased the dissolution efficiency of super disintegrants in wet granulated tablets. Generally, the formulations that initially exhibited the fastest dissolution showed the largest decreases in dissolution after storage. Croscarmellose sodium was affected to a greater extent after storage than crospovidone or sodium starch glycolate. Tablets that contained lactose were more affected by storage at the various conditions than were tablets that contained naproxen or dibasic calcium phosphate. Tablet dissolution after aging was unaffected by both the mode of super disintegrant incorporation and the granulation moisture content. No significant correlation was observed between changes in tablet hardness and alterations in dissolution rate after storage. Monitoring tablet dimensions showed that there was no substantial swelling in tablets after aging at elevated humidity and temperature, except for a slight increase in thickness for tablets that contained crospovidone.

Introduction

In the development of tablets, it is generally recognized that aging may cause chemical and physical changes that may modify the dissolution of drugs from compressed tablets. These changes in dissolution may alter the bioavailability of the active drug substance. 'Super disintegrants' (Shangraw et al., 1980) such as croscarmellose sodium, sodium starch glycolate, and crospovidone are now frequently used to enhance the dissolution rates of drugs in tablet formulations. Therefore, it is important to know the effect of aging on the effectiveness of super disintegrants in promoting drug dissolution from tablets.

Several investigators have described the effect of aging on tablets containing super disintegrants with respect to tablet disintegration time (Bavitz

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et al., 1974; Guyot-Hermann et al., 1985; Muti and Othman, 1989; Sheen and Kim, 1989). Although tablet disintegration is often a necessary precursor for drug dissolution, it does not ensure that the drug substance will dissolve, and hence have the potential to be systemically absorbed. Therefore, it is therapeutically more appropriate to examine the stability properties of super disintegrants in the context of how the dissolution rate of model tablet systems are affected by storage. The three reports that have investigated the performance of super disintegrants in terms of dissolution after tablet storage have all utilized direct compression formulations (Bolhuis et al., 1979; Horhota et al., 1976; Gordon and Chowhan, 1990). However, the wet granulation technique is frequently employed to manufacture tablets. There are no reports in the literature that describe the behavior of super disintegrants in terms of dissolution for wet granulated tablet systems that have undergone aging.

The purpose of this study was to determine whether tablet aging affected the performance of the super disintegrants in wet granulated tablet formulations in terms of dissolution. Three commonly used super disintegrants were employed: croscarmellose sodium, sodium starch glycolate, and crospovidone. With the wet granulation technique, the disintegrant may be incorporated during manufacture by one of three methods: intragranularly, extragranularly, or distributed in both phases. This study examined whether the mode of inclusion had an impact on the stability characteristics of the tablets. The tablet base solubility was varied by utilizing three different excipients as the main component of the tablet: dibasic calcium phosphate (which, with less than 1 mg/ml solubility, was insoluble in the dissolution medium at 37°C), naproxen (which, at 6 mg/ml, was poorly soluble), and lactose (which, at 203 mg/ml, was highly soluble). Each granulation was dried to three different moisture levels. The finished tablets were stored for 8 months at room temperature, and then stored at 37°C/80% RH for 2 and 8 weeks. In order to further study the effect of environmental changes (i.e., cycling), after storage at 37°C/80% RH for 8 weeks the tablets were stored at room temperature for 24 h. Dissolution and hardness testing were performed at each time point. Tablet dimensions were measured before and after exposure for 2 and 8 weeks to 37°C/80% RH to examine if some of the super disintegrants caused substantial tablet swelling upon prolonged exposure to high humidity.

It is important to determine whether after tablet aging the super disintegrants maintain their original ability to promote rapid tablet dissolution in wet granulated tablet systems, and further, to examine if variables such as the mode of disintegrant incorporation, granulation moisture content, and tablet composite solubility have an impact. Increased understanding of these factors should help in developing better tablet formulations that will maximize dissolution over the life of the tablet, and thereby maximize the potential bioavailability of the medicament throughout the shelf life of the tablet.

Materials and Methods

Materials

Croscarmellose sodium (Ac-Di-Sol®, FMC Corp.), crospovidone (Polyplasdone XL®, GAF Corp.), sodium starch glycolate (Explotab®, Edward Mendell Co.), unmilled dibasic calcium phosphate, dihydrate (J.T. Baker), regular lactose, monohydrate (Foremost Whey Products), naproxen (Syntex, Inc.), povidone K-29-32 (Plasdone, GAF Corp.), and high purity magnesium stearate (Mallinckrodt, Inc.) were all USP/NF grade. The *p*-aminobenzoic acid (Aldrich Chemical Co.) was at least 99% pure.

Powder blend

The intragranular super disintegrant (if required by the experimental design), *p*-aminobenzoic acid, and main tablet component (lactose, dibasic calcium phosphate dihydrate, or naproxen) were passed through a 30-mesh screen prior to mixing. The super disintegrant and *p*-aminobenzoic acid were geometrically diluted with the main tablet component before dry blending. Dry blending was performed in a high shear mixer (Gral 10, Machines Collette) for 3 min.

Binder preparation

Povidone K-29-32 (5% w/w of the tablet formulation), dissolved in an appropriate amount of delonized water, was the bi ıder for each formulation. The amount of granulating water used (as a percent of the total dry weight of the formulation) was 14% (lactose formulations), 17% (naproxen formulations), and 18% (dibasic calcium phosphate formulations). Since the mixing time was held constant for all formulations, it was necessary to vary the percentage of water to achieve similar granulations.

Granulation

After the 3 min of dry blending in the high shear mixer, the binder solution was added to the mixing bowl during the initial 15 s of a 5 min mixing period. To ensure even and complete granulation, the mixing blades and the bowl were scraped well with a spatula before allowing the granulation to mix for an additional 5 min. The granulations were then tray-dried at 60°C to a moisture content of 0.5% (±0.2%), 1.25% (±0.25%), or 2.25% (±0.25%). The moisture content was determined by the loss on drying method at 105°C utilizing a Compu-Trac® moisture analyzer (model MA-5A, Arizona Instrument Corp.). The dibasic calcium phosphate batches were not compressible at 0.5% loss on drying (LOD), so in order to maintain three moisture content levels, these batches were also dried to 3.25% (±0.25%) LOD. The dried granulation was passed through a 16-mesh screen using an oscillator (Erweka AR400) and stored in a tightly closed polyethylene bag.

Final blending

The milled granulations were mixed with the required amount of super disintegrant (when incorporated extragranularly or distributed equally between both phases) in the high shear mixer for 3 min. Batches that did not require addition of super disintegrant during the final blend were also mixed for 3 min. The final blend was then mixed with magnesium stearate for 2 min and stored in a tightly closed polyethylene bag.

Compression

The moisture content of the granulations was retested just prior to compression to ensure that it had not changed during processing. The tablets were compressed with a single punch machine (Stokes F-4) to a targeted hardness of 8 kp (±1 kp), except for the 0.5% LOD naproxen formulations, which could be compressed only to a hardness of 6 kp (±1 kp). The tablets were manufactured to a targeted weight of 500 mg (±25 mg). A 1.11 cm standard concave punch and die set was used. The tablets were double-bagged in tightly closed polyethylene bags for storage.

Dimensions

The tablet dimensions (thickness and diameter) were determined using a vernier caliper (Model 120M, Starret). 10 tablets were tested after storage at room temperature for 8 months, and after 2 and 8 weeks at 37°C/80% RH.

Hardness

The tablet hardness was determined immediately after compression using an instrument (Model HT-300, Key International) that utilizes the principle of strain-gauge linear force to ascertain the degree of tablet hardness. 20 tablets were tested at the initial time point for each batch and the mean and standard deviation were calculated. 10 tablets were tested at each time point thereafter, except during the cycling time point, where only six tablets were tested due to the number of tablets remaining after storage. Hardness was measured in kp (1 kp = 1.4 Strong-Cobb units = 9.8 N).

Storage

The tablets were packaged in tightly closed polyethylene bags and stored at room temperature for 8 months. Then an appropriate number of tablets from each of the 90 batches were placed in open Petri dishes (with the tablets not touching each other) and exposed to 37°C/80% RH for 2 and 8 weeks. After the 8 week time point, the remaining tablets were removed and stored at room temperature for 24 h.

TABLE 1

Generalized tablet formulation for all batches

Component	% (w/w)
p-Aminobenzoic acid	1.00
Intragranular super disintegrant (crospovidone, sodium starch glycolate, or croscarmellose sodium)	0, 1.00, or 2.00 [a]
Extragranular super disintegrant (crospovidone, sodium starch glycolate, or croscarmellose sodium)	0, 1.00, or 2.00 [a]
Povidone K-29-32	5.00
Main tablet component (lactose, naproxen, or dibasic calcium phosphate)	91.50
Magnesium stearate	0.50

[a] Except for control formulations, the quantity of super disintegrant always totalled 2.00%. Control formulations substituted 2% additional 'main tablet component' for the super disintegrant.

TABLE 2

Tablet dissolution results at 15 min for tablets with a moisture content of 0.5 ± 0.2% (sorted by main tablet component, type of disintegrant, and storage conditions)

Main component	Disintegrant	Mode of incorporation	% dissolved ± SD after compression	% dissolved ± SD after 8 months at RT	% dissolved ± SD after 2 weeks at 37°C/80% RH	% dissolved ± SD after 8 weeks at 37°C/80% RH	% dissolved ± SD after cycling
Lactose	cros povidone	control	47.6 ± 0.6	45.0 ± 2.2	38.4 ± 2.2	34.0 ± 2.3	37.0 ± 1.4
		intragranular	64.0 ± 1.2	52.0 ± 2.9	51.6 ± 2.2	46.5 ± 2.4	47.0 ± 2.0
		intra + extra	101.8 ± 1.6	95.8 ± 1.6	90.9 ± 1.1	76.2 ± 5.6	70.8 ± 4.6
		extragranular	105.2 ± 0.7	102.3 ± 0.6	97.5 ± 0.5	92.8 ± 0.9	96.6 ± 1.1
	sodium starch glycolate	control	47.6 ± 0.6	45.0 ± 2.2	38.4 ± 2.2	34.0 ± 2.3	37.0 ± 1.4
		intragranular	54.7 ± 1.5	47.1 ± 1.1	41.3 ± 0.9	38.9 ± 2.8	40.8 ± 2.0
		intra + extra	63.5 ± 0.8	56.6 ± 1.6	51.6 ± 0.7	49.3 ± 2.3	48.7 ± 2.8
		extragranular	100.7 ± 2.9	91.8 ± 1.4	79.4 ± 1.1	67.3 ± 4.3	69.1 ± 3.1
	cros-carmellose sodium	control	47.7 ± 0.6	45.0 ± 2.2	38.4 ± 2.2	34.0 ± 2.3	37.0 ± 1.4
		intragranular	99.8 ± 2.2	92.1 ± 3.6	98.3 ± 0.8	63.9 ± 4.3	64.3 ± 2.6
		intra + extra	106.9 ± 0.9	101.5 ± 1.1	78.2 ± 3.1	59.7 ± 2.7	59.1 ± 3.0
		extragranular	105.7 ± 1.2	102.8 ± 0.9	96.4 ± 0.6	68.9 ± 4.6	65.2 ± 3.5
Naproxen	cros-povidone	control	6.1 ± 0.2	6.0 ± 0.5	5.7 ± 0.3	5.1 ± 0.4	5.0 ± 0.2
		intragranular	6.3 ± 0.2	6.4 ± 0.3	5.9 ± 0.2	5.7 ± 0.4	6.2 ± 0.4
		intra + extra	16.3 ± 0.9	18.1 ± 0.8	14.8 ± 0.9	13.5 ± 1.5	14.2 ± 1.3
		extragranular	85.9 ± 7.0	87.5 ± 3.4	75.6 ± 6.2	77.4 ± 7.3	76.2 ± 4.3
	sodium starch glycolate	control	6.1 ± 0.0	6.0 ± 0.5	5.7 ± 0.3	5.1 ± 0.4	5.0 ± 0.2
		intragranular	15.7 ± 0.7	10.4 ± 1.7	5.5 ± 0.3	4.8 ± 0.3	4.8 + 0.2
		intra + extra	53.9 + 6.3	44.0 + 2.6	34.4 ± 1.7	24.7 + 1.4	23.5 ± 1.6
		extragranular	89.9 ± 2.1	87.8 ± 1.3	86.3 ± 1.9	87.5 ± 5.4	80.3 ± 7.8
	cros-carmellose sodium	control	6.1 ± 0.2	6.0 ± 0.5	5.7 ± 0.3	5.1 ± 0.4	5.0 ± 0.2
		intragranular	98.4 ± 0.8	96.7 ± 3.6	89.6 ± 1.0	78.0 ± 6.7	77.0 ± 4.5
		intra + extra	85.9 ± 2.5	90.6 ± 4.0	83.6 ± 2.1	70.2 ± 7.7	69.4 ± 5.9
		extragranular	93.9 ± 1.2	95.7 ± 0.5	89.7 ± 1.6	86.9 ± 5.1	83.8 ± 5.8

In vitro dissolution

Dissolution of the tablets was performed at each time point, as per USP XXI, using Apparatus 1. The medium was 900 ml of deaerated phosphate buffer maintained at 37.0 ± 0.5°C. The baskets rotated at 100 rpm. Automated sampling equipment removed the samples through a filter and analyzed them spectrophotometrically at 266 nm, sampling every 5 min for 60 min. The lactose and dibasic calcium phosphate tablets were examined for the amount of *p*-aminobenzoic acid released, whereas tablets containing naproxen were monitored for the combined naproxen and *p*-aminobenzoic acid that was liberated from the

TABLE 3

Tablet dissolution results at 15 min for tablets with a moisture content of 1.25 ± 0.25% (sorted by main tablet component, type of disintegrant, and storage conditions)

Main component	Disintegrant	Mode of incorporation	% dissolved ± SD after compression	% dissolved ± SD after 8 months at RT	% dissolved ± SD after 2 weeks at 37°C/80% RH	% dissolved ± SD after 8 weeks at 37°C/80% RH	% dissolved ± SD after cycling
Lactose	cros-	control	42.4 ± 2.4	38.3 ± 1.5	34.8 ± 0.8	41.5 ± 2.0	36.0 ± 2.6
	povidone	intragranular	63.4 ± 4.0	58.8 ± 3.3	50.0 ± 1.4	52.1 ± 3.9	50.3 ± 2.1
		intra + extra	103.3 ± 1.3	98.6 ± 2.0	90.2 ± 1.9	80.0 ± 2.4	78.6 ± 1.6
		extragranular	105.1 ± 0.4	103.7 ± 0.6	97.8 ± 0.8	95.4 ± 0.2	96.7 ± 0.3
	sodium	control	42.4 ± 2.4	38.3 ± 1.5	34.8 ± 0.8	41.5 ± 2.0	36.0 ± 2.6
	starch	intragranular	50.7 ± 1.6	45.2 ± 0.9	47.0 ± 0.6	37.9 ± 1.9	41.1 ± 1.5
	glycolate	intra + extra	61.8 ± 1.5	56.1 ± 1.6	57.9 ± 1.9	48.1 ± 1.9	50.8 ± 1.1
		extragranular	98.5 ± 2.9	98.3 ± 2.3	90.0 ± 9.8	71.4 ± 1.8	80.6 ± 6.3
	cros-	control	42.4 ± 2.4	38.3 ± 1.1	34.8 ± 0.8	41.5 ± 2.0	36.0 ± 2.6
	carmellose	intragranular	97.5 ± 1.6	90.2 ± 2.7	81.4 ± 3.0	52.1 ± 1.5	56.6 ± 0.7
	sodium	intra + extra	104.0 ± 0.8	99.2 ± 2.3	79.0 ± 1.3	56.6 ± 1.1	59.4 ± 0.4
		extragranular	103.8 ± 4.1	99.8 ± 2.1	90.1 ± 3.3	60.2 ± 3.3	60.1 ± 3.5
Naproxen	cros-	control	6.0 ± 0.2	5.9 ± 0.2	5.6 ± 0.2	6.9 ± 0.4	6.1 ± 0.3
	povidone	intragranular	6.6 ± 0.3	8.8 ± 0.4	6.8 ± 0.4	11.0 ± 0.5	7.3 ± 0.2
		intra + extra	31.8 ± 2.5	29.9 ± 2.2	27.0 ± 1.3	25.2 ± 2.3	24.1 ± 2.0
		extragranular	43.5 ± 3.3	43.7 ± 2.4	43.0 ± 5.6	43.7 ± 8.0	40.3 ± 4.8
	sodium	control	6.0 ± 0.2	5.9 ± 0.2	5.6 ± 0.2	6.9 ± 0.4	6.1 ± 0.3
	starch	intragranular	17.6 ± 1.0	10.5 ± 0.6	8.1 ± 1.4	6.2 ± 0.4	6.6 ± 0.4
	glycolate	intra + extra	56.8 ± 0.9	50.9 ± 1.5	47.4 ± 2.4	34.2 ± 2.1	36.7 ± 3.1
		extragranular	54.2 ± 2.5	50.0 ± 2.6	58.4 ± 1.7	50.0 ± 3.8	50.6 ± 1.2
	cros-	control	6.6 ± 0.2	5.9 ± 0.2	5.6 ± 0.2	6.9 ± 0.4	6.6 ± 0.3
	carmellose	intragranular	66.1 ± 1.5	60.3 ± 1.9	61.0 ± 2.2	48.6 ± 1.5	49.5 ± 0.6
	sodium	intra + extra	85.0 ± 7.2	94.4 ± 3.2	91.4 ± 6.4	67.5 ± 11.7	81.2 ± 4.7
		extragranular	83.6 ± 5.4	72.5 ± 7.2	75.8 ± 9.8	62.2 ± 3.5	52.5 ± 4.3
Dibasic calcium phosphate	cros-	control	22.0 ± 0.3	16.5 ± 0.6	19.0 ± 0.7	17.5 ± 1.3	18.3 ± 0.7
	povidone	intragranular	24.8 ± 1.3	21.9 ± 0.9	19.9 ± 1.4	18.7 ± 1.0	19.2 ± 0.9
		intra + extra	29.9 ± 4.5	31.4 ± 2.6	21.2 ± 6.4	18.6 ± 1.3	18.8 ± 0.8
		extragranular	62.7 ± 4.2	37.2 ± 7.1	29.3 ± 6.1	24.3 ± 7.0	21.7 ± 2.6
	sodium	control	22.0 ± 0.3	16.5 ± 0.6	19.0 ± 0.7	17.5 ± 1.3	18.3 ± 0.7
	starch	intragranular	31.1 ± 0.7	26.2 ± 1.4	25.8 ± 1.9	25.6 ± 1.6	26.4 ± 1.3
	glycolate	intra + extra	39.0 ± 2.8	32.3 ± 1.9	37.9 ± 2.0	38.1 ± 2.3	37.5 ± 3.4
		extragranular	49.2 ± 5.2	37.4 ± 1.6	44.1 ± 2.7	44.1 ± 2.7	42.4 ± 2.2
	cros-	control	22.0 ± 0.3	16.5 ± 0.6	19.0 ± 0.7	17.5 ± 1.3	18.3 ± 0.6
	carmellose	intragranular	60.9 ± 1.3	58.7 ± 3.5	53.0 ± 4.3	48.2 ± 4.2	52.6 ± 4.5
	sodium	intra + extra	98.8 ± 1.1	51.1 ± 3.3	50.0 ± 4.2	51.2 ± 3.4	52.2 ± 4.1
		extragranular	64.8 ± 3.8	47.5 ± 2.6	48.3 ± 4.0	51.1 ± 2.5	50.4 ± 2.5

tablet, with most (95%) of the spectrophotometric response being due to naproxen. The dissolution values reported were the mean of six tablets for each formulation.

Statistical analysis

The results obtained were statistically analyzed using the least significant difference method at the $p = 0.05$ level.

TABLE 4

Tablet dissolution results at 15 min for tablets with a moisture content of 2.25 ± 0.25% (sorted by main tablet component, type of disintegrant, and storage conditions)

Main component	Disintegrant	Mode of incorporation	% dissolved ± SD after compression	% dissolved ± SD after 8 months at RT	% dissolved ± SD after 2 weeks at 37°C/80% RH	% dissolved ± SD after 8 weeks at 37°C/80% RH	% dissolved ± SD after cycling
Lactose	cros-	control	42.6 ± 1.4	43.5 ± 2.3	46.7 ± 2.8	41.3 ± 1.3	38.2 ± 2.3
	povidone	intragranular	64.8 ± 2.4	61.3 ± 1.1	60.8 ± 1.4	52.7 ± 1.6	48.7 ± 2.9
		intra + extra	90.8 ± 1.6	87.1 ± 1.6	87.2 ± 2.6	78.1 ± 0.6	67.4 ± 5.0
		extragranular	107.3 ± 0.7	105.6 ± 1.4	103.5 ± 0.4	98.0 ± 0.5	95.5 ± 2.4
	sodium	control	42.6 ± 1.4	43.5 ± 2.3	46.7 ± 2.8	41.3 ± 1.3	38.2 ± 2.3
	starch	intragranular	45.5 ± 1.2	31.3 ± 2.3	45.3 ± 1.4	55.6 ± 2.4	34.7 ± 1.9
	glycolate	intra + extra	57.9 ± 1.1	58.3 ± 2.0	56.2 ± 0.5	58.4 ± 1.7	45.6 ± 3.6
		extragranular	86.6 ± 2.2	78.9 ± 2.7	80.7 ± 1.6	55.1 ± 2.8	64.1 ± 3.7
	cros-	control	42.6 ± 1.4	43.5 ± 2.3	46.7 ± 2.8	41.3 ± 1.3	38.2 ± 2.3
	carmellose	intragranular	87.4 ± 2.2	92.9 ± 2.1	71.7 ± 2.0	55.6 ± 2.4	51.1 ± 3.1
	sodium	intra + extra	99.5 ± 1.2	85.1 ± 2.6	77.9 ± 1.5	56.4 ± 1.7	55.8 ± 3.3
		extragranular	102.8 ± 2.1	88.0 ± 3.8	85.6 ± 4.4	55.1 ± 2.8	53.3 ± 3.7
Naproxen	cros-	control	5.8 ± 0.1	6.3 ± 0.2	6.7 ± 1.0	5.5 ± 0.2	5.4 ± 0.3
	povidone	intragranular	20.9 ± 1.5	19.9 ± 0.6	18.5 ± 1.0	16.2 ± 0.6	12.9 ± 0.8
		intra + extra	75.5 ± 1.5	64.8 ± 2.1	60.4 ± 3.5	50.5 ± 2.7	49.2 ± 4.7
		extragranular	89.6 ± 3.6	69.1 ± 6.5	82.5 ± 5.8	69.9 ± 8.0	60.1 ± 5.8
	sodium	control	5.8 ± 0.1	6.3 ± 0.2	6.7 ± 1.0	5.5 ± 0.2	5.4 ± 0.3
	starch	intragranular	18.3 ± 1.1	9.3 ± 1.5	7.4 ± 0.5	8.1 ± 0.4	7.6 ± 0.7
	glycolate	intra + extra	51.0 ± 3.3	49.1 ± 3.1	42.5 ± 0.9	34.3 ± 1.5	30.7 ± 2.6
		extragranular	59.9 ± 0.8	53.5 ± 2.2	50.9 ± 2.9	42.6 ± 3.4	37.4 ± 2.7
	cros-	control	5.8 ± 0.1	6.3 ± 0.2	6.7 ± 1.0	5.5 ± 0.2	5.4 ± 0.3
	carmellose	intragranular	72.0 ± 0.7	74.6 ± 1.7	71.1 ± 1.6	55.1 ± 1.5	48.5 ± 3.4
	sodium	intra + extra	81.5 ± 0.9	102.0 ± 0.9	100.2 ± 0.5	83.9 ± 3.7	78.4 ± 5.6
		extragranular	84.7 ± 2.1	92.7 ± 4.9	80.2 ± 5.4	59.0 ± 2.7	53.0 ± 3.8
Dibasic calcium phosphate	cros-	control	21.7 ± 0.5	20.1 ± 0.4	21.4 ± 0.4	19.2 ± 0.3	19.0 ± 0.4
	povidone	intragranular	29.5 ± 1.4	33.9 ± 2.1	34.1 ± 4.5	26.1 ± 2.3	22.2 ± 2.1
		intra + extra	33.6 ± 1.7	35.6 ± 3.2	26.2 ± 1.6	33.4 ± 3.1	29.5 ± 5.9
		extragranular	50.7 ± 10.0	40.9 ± 2.1	23.4 ± 1.6	37.8 ± 9.1	26.7 ± 4.5
	sodium	control	21.7 ± 0.5	20.1 ± 0.4	21.4 ± 0.4	19.2 ± 0.3	19.0 ± 0.4
	starch	intragranular	32.7 ± 1.3	33.8 ± 0.8	31.5 ± 0.6	28.4 ± 0.4	22.2 ± 1.2
	glycolate	intra + extra	51.3 ± 2.7	53.1 ± 1.5	52.1 ± 2.0	47.9 ± 2.1	33.8 ± 2.9
		extragranular	62.1 ± 1.5	61.1 ± 1.1	60.5 ± 3.0	52.1 ± 2.8	42.5 ± 2.9
	cros-	control	21.7 ± 0.5	20.1 ± 0.4	21.4 ± 0.4	19.2 ± 0.3	19.0 ± 0.4
	carmellose	intragranular	67.0 ± 1.1	68.5 ± 3.5	72.5 ± 3.0	65.1 ± 1.6	55.2 ± 5.6
	sodium	intra + extra	74.4 ± 4.5	71.6 ± 4.3	74.4 ± 5.2	67.5 ± 6.2	58.3 ± 7.4
		extragranular	67.7 ± 3.0	72.2 ± 4.7	68.4 ± 3.1	53.7 ± 1.8	52.6 ± 3.2

Results and Discussion

Table 1 gives the generalized tablet formulation used in this study. The formulation consisted of 1% *p*-aminobenzoic acid as a tracer, 2% super disintegrant, 5% povidone as the binder, 0.5% magnesium stearate as a lubricant, and 91.5% filler. Each formulation contained one of the three main tablet components, thereby varying the solubility of the formulation, along with one of the three super disintegrants incorporated in one of the three different methods. The control batches did not contain any super disintegrant. Each formulation was dried to three different granulation moisture contents prior to compression. Dissolution results at the 15 min time point for the 90 tablet batches after aging under various conditions are presented In Tables 2–5. The 15 min time point was chosen for presentation because it was the last time point at which trends in dissolution could be completely identified (most of the formulations had not yet reached the upper limit of 100% dissolved). However, the trends seen at 15 min were also evident at later time points, although to a lesser extent.

Fig. 1 exemplifies the type of dissolution profile determined in this study. In all cases, the general form of the curve was the same; lag times

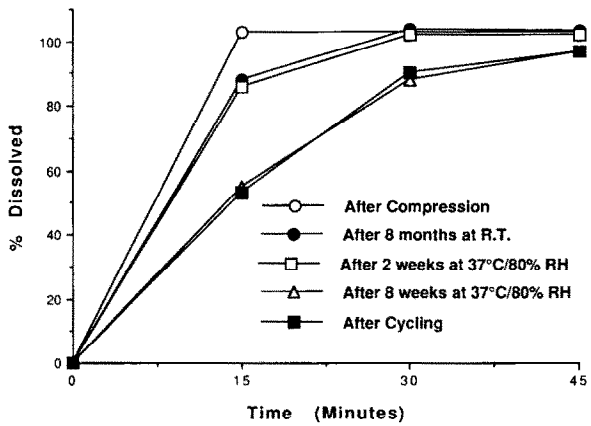

Fig. 1. Typical dissolution profiles of tablets upon aging (2.25% moisture content, lactose, croscarmellose sodium, extragranular).

(as are often seen in capsule dissolution) were never observed. Therefore, the 15 min time point provided a convenient and precise way of characterizing dissolution. Tables 2–5 show that storage at room temperature and subsequent storage at elevated conditions (37°C/80% RH) slowed the rate at which the super disintegrants promoted in vitro dissolution in most of the tablet formulations used. After storage at room temperature for 8 months, 62% (50/81) of the tablet batches

TABLE 5

Tablet dissolution results at 15 min for tablets with a moisture content of 3.25 ± 0.25% (sorted by main tablet component, type of disintegrant, and storage conditions)

Main component	Disintegrant	Mode of incorporation	% dissolved ± SD after compression	% dissolved ± SD after 8 months at RT	% dissolved ± SD after 2 weeks at 37°C/80% RH	% dissolved ± SD after 8 weeks at 37°C/80% RH	% dissolved ± SD after cycling
Dibasic calcium phosphate	cros-povidone	control	21.4 ± 1.1	20.6 ± 0.3	19.1 ± 0.5	19.0 ± 0.4	19.3 ± 0.6
		intragranular	35.5 ± 2.3	36.2 ± 2.8	36.7 ± 6.0	29.0 ± 1.7	29.2 ± 2.4
		intra + extra	52.8 ± 4.0	50.7 ± 3.8	50.8 ± 5.1	37.3 ± 1.6	36.6 ± 2.3
		extragranular	56.4 ± 2.9	51.7 ± 4.5	44.9 ± 1.7	40.8 ± 2.5	39.6 ± 1.6
	sodium starch glycolate	control	21.4 ± 1.1	20.6 ± 0.3	19.1 ± 0.5	19.1 ± 0.4	19.3 ± 0.6
		intragranular	35.7 ± 2.0	31.1 ± 1.1	32.0 ± 0.4	30.8 ± 1.2	27.2 ± 1.7
		intra + extra	36.7 ± 2.3	33.2 ± 1.3	32.0 ± 1.6	32.1 ± 1.1	28.8 ± 1.0
		extragranular	69.7 ± 2.1	60.6 ± 4.5	60.1 ± 4.8	53.0 ± 1.9	51.1 ± 4.5
	cros-carmellose sodium	control	21.4 ± 1.1	20.6 ± 0.3	19.1 ± 0.5	19.1 ± 0.4	19.3 ± 0.6
		intragranular	75.0 ± 5.4	59.7 ± 2.3	62.1 ± 3.8	55.5 ± 3.0	52.5 ± 2.7
		intra + extra	80.4 ± 3.4	74.2 ± 3.8	69.4 ± 2.1	64.9 ± 4.4	60.8 ± 2.2
		extragranular	81.1 ± 2.2	70.8 ± 5.4	66.1 ± 4.2	57.5 ± 2.9	53.8 ± 3.3

showed a statistically significant ($p = 0.05$) slowing of dissolution and 28% (23/81) did not show any statistical difference. After storage for 2 weeks at 37°C/80% RH conditions, 56% (45/81) of the batches showed a significant slowing of dissolution and 36% (29/81) did not change, when compared with dissolution values after 8 months at room temperature. After storage for 8 weeks at 37°C/80% RH, 73% (59/81) of the batches demonstrated slower dissolution compared to the 2 week time point and 78% (63/81) of the batches were affected when compared with the dissolution values after 8 months at room temperature. After the tablets were stored at room temperature for 24 h, 54% (44/81) of the batches showed no effect from cycling, while 36% (29/81) slowed down when compared with the dissolution values at the 8 week time point.

In tablet lots where all the factors were the same except for the main tablet component, the lactose tablet batches exhibited the most significant slowing of dissolution after storage at room temperature (26 of 30 batches slowed significantly), followed by dibasic calcium phosphate (18/30), followed by naproxen (11/30). A number of naproxen (13/30) and dibasic calcium phosphate (10/30) batches were not affected after storage at room temperature. No particular characterizations could be made for the batches that were resistant to changes in dissolution after room temperature storage. The effect of storage conditions on the tablet batches, broken down by

TABLE 6

Average tablet hardness (in kp) after storage at various conditions (sorted by super disintegrant and main tablet component)

Storage condition	Super disintegrant	Main tablet component			
		Lactose	Naproxen	Dibasic calcium phosphate	
0 weeks	none (control)	7.9	6.6	7.7	
	sodium starch glycolate	8.3	7.3	8.2	
	croscarmellose sodium	8.0	7.5	8.0	
	crospovidone	8.0	7.3	7.8	
					grand average: 7.7
8 months at room temperature	none (control)	15.8	14.6	22.5	
	sodium starch glycolate	13.2	12.4	18.4	
	croscarmellose sodium	10.7	10.0	13.2	
	crospovidone	11.8	11.2	18.8	
					grand average: 14.4
2 weeks at 37°C/80% RH	none (control)	18.1	17.0	16.3	
	sodium starch glycolate	19.3	14.3	14.0	
	croscarmellose sodium	12.7	11.5	12.1	
	crospovidone	11.9	13.1	10.9	
					grand average: 14.3
8 weeks at 37°C/80% RH	none (control)	21.2	14.0	21.7	
	sodium starch glycolate	22.9	16.8	17.9	
	croscarmellose sodium	18.4	14.2	13.2	
	crospovidone	13.2	14.6	15.6	
					grand average: 17.0
Cycling	none (control)	23.8	19.5	21.8	
	sodium starch glycolate	27.2	19.1	20.0	
	croscarmellose sodium	17.8	14.8	14.1	
	crospovidone	15.4	16.6	15.3	
					grand average: 18.8

the main tablet component, is shown in Fig. 2. The lactose batches were the most affected, with a decrease in percent dissolved of 17% after storage at 37°C/80% RH for 8 weeks, compared to the 8 month room temperature time point. Naproxen batches showed a decrease of 9% and dicalcium phosphate batches showed only a 5% decrease in dissolution after storage. Subsequent storage of the tablets at room temperature for 24 h did not cause any significant change in terms of dissolution. Although the lactose batches showed the greatest decreases in dissolution after storage, they still exhibited faster dissolution than the tablets that contained naproxen or dibasic calcium phosphate. Representative tablet hardness data are shown in Table 6. The lactose and naproxen tablet batches showed a continuous increase in hardness after storage under all of the conditions. The dibasic calcium phosphate tablets exhibited a greater increase in hardness when stored at room temperature than the naproxen or lactose tablets (10 kp vs 4 kp), but the dibasic calcium phosphate tablets initially softened after exposure to elevated conditions. The dibasic calcium phosphate batches at 1.25% LOD developed cracks in the tablets when exposed to 37°C/80% RH for 2 and 8 weeks.

When the effect of aging on the type of super disintegrant used was examined for all of the

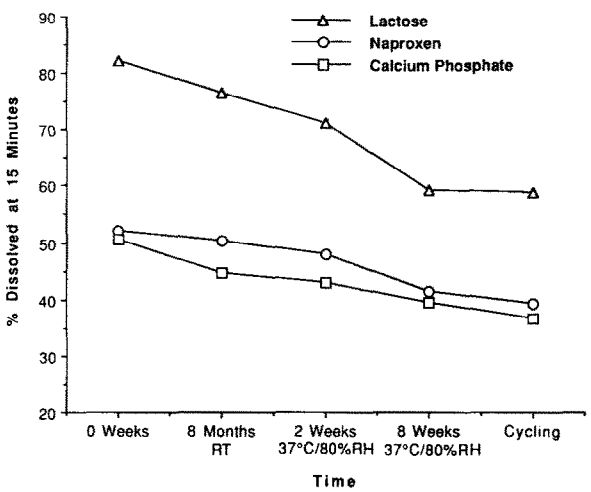

Fig. 2. The influence of the main tablet component on tablet aging.

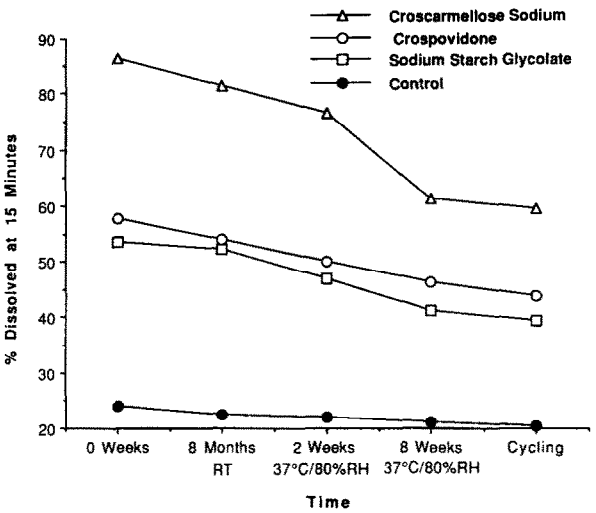

Fig. 3. The impact of tablet aging on the effectiveness of super disintegrants in promoting tablet dissolution.

batches (Fig. 3), it was found that the three super disintegrants (croscarmellose sodium, sodium starch glycolate, and crospovidone) were generally affected in a relatively minor fashion by storage at room temperature for 8 months. After storage at 37°C/80% RH for 2 weeks, the ability of all three super disintegrants to promote dissolution tended to decrease slightly. The effectiveness of the super disintegrants decreased even more after tablet exposure for 8 weeks to 37°C/80% RH, with croscarmellose sodium showing a 20% decrease in dissolution rate, followed by sodium starch glycolate (11%), followed by crospovidone (8%). The tablets that contained croscarmellose sodium usually dissolved significantly faster than the tablets that incorporated crospovidone or sodium starch glycolate, regardless of the main tablet component, the mode of incorporation, or the moisture content of the formulations. When crospovidone was compared with sodium starch glycolate, both initially and after storage, crospovidone caused faster dissolution than did sodium starch glycolate in the lactose formulations, whereas sodium starch glycolate caused faster dissolution in the naproxen and dibasic calcium phosphate formulations. The control batches (which contained no super disintegrant) were not significantly affected by the

37°C/80% RH storage condition. Storing the batches for 24 h at room temperature after aging at 37°C/80% RH usually did not influence the dissolution characteristics of any of the tablet batches. When examined for the increase in hardness of tablets based on the type of super disintegrant used, batches containing the three super disintegrants as well as the control batches increased in hardness after storage at room temperature for 8 months. The hardness increase was higher in control and sodium starch glycolate batches than in crospovidone and croscarmellose sodium batches. In most instances, there was no significant change in hardness after storage at elevated conditions for 2 and 8 weeks, although tablets containing sodium starch glycolate and croscarmellose sodium showed a tendency to increase in hardness by the 8 week time point. There were no major changes in hardness in batches after storage at room temperature for 24 h. It is interesting to note that the control batches almost tripled in hardness over time while dissolution did not change. However, tablets with super disintegrants, which had no greater hardness increases than the controls, demonstrated slower dissolution after storage. This indicates that the decrease in dissolution was due to a change in the effectiveness of the disintegrant and was not correlated to increased hardness.

TABLE 7

Average tablet hardness (in kp) after storage at various conditions, sorted by mode of incorporation

Storage condition	Mode of super disintegrant incorporation		
	Intra-granular	Intra- and extragranular	Extra-granular
0 weeks	7.7	8.0	7.7
8 months at room temperature	14.4	13.9	11.6
2 weeks at 37°C/80% RH	14.4	14.0	11.6
8 weeks at 37°C/80% RH	17.2	17.9	13.9
Cycling	19.6	19.9	14.7

Fig. 4 shows that aging uniformly decreased the in vitro dissolution of tablets that had super disintegrants incorporated in different methods. Extragranular incorporation continued to result in faster dissolution after aging, when compared to distributing the disintegrant equally in both phases, which caused faster dissolution than did intragranular inclusion. With respect to hardness (Table 7), the mode of incorporation did not impact the general curve of the increase over time. However, extragranular inclusion resulted in less hardening (7 kp) over the total length of

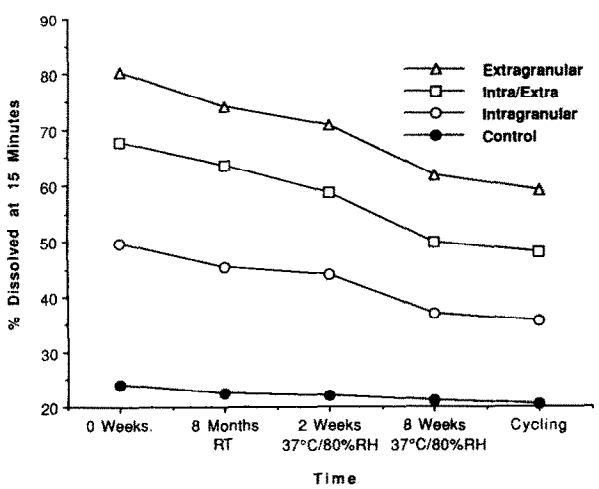

Fig. 4. The influence of the mode of super disintegrant incorporation on tablet aging.

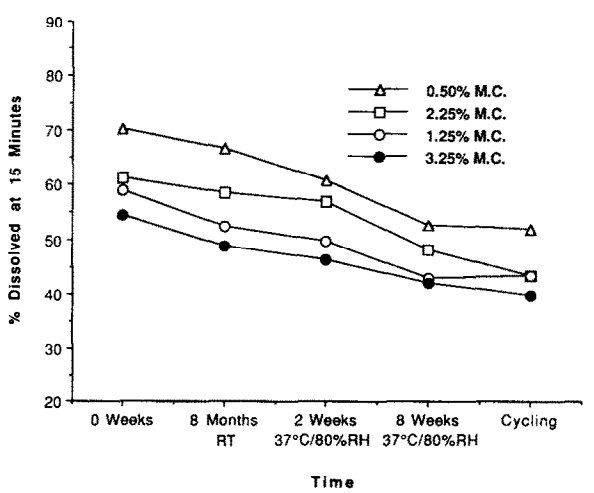

Fig. 5. The influence of moisture content (M.C.) on tablet aging.

storage than did the two other modes and the controls (which exhibited increases of about 12 kp).

Fig. 5 indicates that, regardless of the moisture content level, aging decreased tablet dissolution in an overall similar manner. However, Table 8 shows that there was a notable correlation between higher moisture content and greater increases in hardness after aging for 8 months at room temperature, again showing a lack of correlation between changes in hardness and dissolution. The 3.25% LOD batches exhibited an average increase in hardness of 19 kp, the 2.25% LOD batches increased 11 kp, whereas the tablet batches with lower granulation moisture contents (1.25 and 0.5%) did not show significant changes in hardness after room temperature storage. The tablets with higher moisture content decreased in hardness after storage at 37°C/80% RH at the 2 week time point (8 kp for the 3.25% LOD batches and 4 kp for the 2.25% batches) and then increased in hardness about 4 kp at the 8 week time point. The lower moisture content tablet batches increased by approx. 6 kp in hardness at elevated conditions. Small additional increases in hardness were generally observed after tablets were stored at room temperature for an additional 24 h.

Dissolution is a physical phenomenon, not a chemical one. This study raises the question as to why aging might cause a decrease in dissolution rate. The literature indicates that useful hypotheses center on two possibilities. The first hypothesis is related to the major tablet components. Lausier et al. (1977) found that the decrease in dissolution efficiency was due to the loss of water of hydration during storage at high temperature and high humidity, but thought that at 25°C and 50% relative humidity that other factors, such as case hardening, played an important role in the aging process. Case hardening could be due to limited dissolution and recrystallization of major tablet components in the available water in the tablet. The second hypothesis centers on the disintegrant agent. Khan and Rhodes (1975) wrote that tablets containing a disintegrant break up rapidly in water because of a sudden and immediate application of stress, but that when a tablet containing a disintegrant is exposed to water vapor, stress is built up slowly and the tablet absorbs some of the strain. They thought that disintegrants within such exposed tablets lose some of their absorption and swelling ability leading to poorer disintegration and dissolution. Horhota et al. (1976) used directly compressible formulations to demonstrate upon aging a decrease in dissolution without any changes in hardness or tablet size. They speculated that this was partly due to the effect of water vapor on the disintegrant. Chowhan (1980) reported that the large decrease in dissolution rate on aging under high humidity appeared to be caused by the expansion/contraction and general opening of the structure of the disintegrant grains (starch in this case), and their bonding, via water molecules, to the excipient. Recently, Marshall et al. (1991) showed that a disintegrant's water uptake and swelling force generation may be impacted by elevated temperature and/or humidity. The results of the current study suggest that, in fact, both hypotheses are operative in tablet systems. Since the highly soluble tablet base (lactose), which will crystallize more easily, was affected to a greater extent upon aging than were the less soluble main tablet components (naproxen and dibasic calcium phosphate), this indicates that crystallization plays a role in the aging mechanism. However, the three super disintegrants also behaved differently from each other upon aging, suggesting that disintegrant specific mechanisms are also involved.

TABLE 8

Average tablet hardness (in kp) after storage at various conditions, sorted by moisture content

Storage condition	Moisture content			
	0.5%	1.25%	2.25%	3.25%
0 weeks	7.2	7.9	7.9	7.8
8 months at room temperature	6.6	8.7	19.2	26.7
2 weeks at 37°C/80% RH	13.0	10.6	15.6	18.7
8 weeks at 37°C/80% RH	12.4	14.0	19.7	23.6
Cycling	14.0	14.3	22.2	26.5

TABLE 9

Average tablet thickness (in mm) after storage at 37°C / 80% RH sorted by main tablet component, mode of incorporation, and type of super disintegrant (values are the average of the three moisture contents[a])

Storage condition	Main tablet component	Mode of incorporation	Super disintegrant		
			Cros-carmellose sodium	Sodium starch glycolate	Cros-povidone
8 months at room temperature	lactose	intragranular	4.681	4.736	4.857
		intra and extra	4.707	4.702	4.761
		extragranular	4.700	4.798	4.934
	naproxen	intragranular	5.279	5.417	5.401
		intra and extra	5.469	5.439	5.592
		extragranular	5.520	5.478	5.569
	dibasic calcium phosphate	intragranular	3.628	3.695	3.658
		intra and extra	3.681	3.611	3.758
		extragranular	3.720	3.652	3.737
averages:			4.598	4.614	4.696
2 weeks at 37°C/80% RH	lactose	intragranular	4.699	4.742	4.904
		intra and extra	4.731	4.714	4.841
		extragranular	4.728	4.794	5.109
	naproxen	intragranular	5.375	5.417	5.408
		intra and extra	5.458	5.452	5.616
		extragranular	5.525	5.481	5.634
	dibasic calcium phosphate	intragranular	3.655	3.709	3.670
		intra and extra	3.709	3.618	3.765
		extragranular	3.759	3.657	3.818
averages:			4.627	4.620	4.752
8 weeks at 37°C/80% RH	lactose	intragranular	4.703	4.740	4.867
		intra and extra	4.730	4.710	4.846
		extragranular	4.939	4.821	5.147
	naproxen	intragranular	5.380	5.405	5.405
		intra and extra	5.240	5.426	5.609
		extragranular	5.502	5.471	5.637
	dibasic calcium phosphate	intragranular	3.627	3.676	3.665
		intra and extra	3.688	3.616	3.771
		extragranular	3.739	3.629	3.826
averages:			4.616	4.610	4.753

[a] Moisture content did not affect tablet thickness during storage.

Table 9 demonstrates that aging the tablets at elevated humidity and temperature for 8 weeks did not cause any significant swelling of the tablets except for the tablets that contained crospovidone as the super disintegrant; those tablets exhibited an average 1.2% increase in thickness.

Conclusions

The results of this study suggest that tablet aging, at both room temperature and 37°C/80% RH, adversely influenced the effectiveness of super disintegrants in wet granulated tablets. Generally, the formulations that initially exhibited the fastest dissolution also demonstrated the largest decrease in dissolution after aging. The magnitude of the decrease in the effectiveness of the super disintegrants after storage may be slightly dependent on the composite solubility of the formulation. Croscarmellose sodium was the most adversely affected super disintegrant after prolonged storage at 37°C/80% RH. Still, tablets that contained croscarmellose sodium generally

exhibited faster dissolution than tablets that included the other two disintegrants. The mode of super disintegrant incorporation and granulation moisture content did not influence the dissolution characteristics of the tablets during aging.

Aging at room temperature and at 37°C/80% RH affected the hardness of the tablets, with most of the batches increasing in hardness after storage at room temperature. The changes in hardness at 2 and 8 weeks at 37°C/80% RH seemed to be slightly dependent on the granulation moisture content and main tablet component, and independent of the type of disintegrant or the mode of incorporation of the super disintegrant. There were no definable correlations between the changes in the hardnesses and the dissolution rates of the tablets. The only tablets that showed an increase in dimensions during storage at elevated conditions contained crospovidone as the disintegrant, and that increase was relatively small.

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